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Copper (I) Mediated Radical Cyclisation
Novel Approaches to Nitrogen Heterocycles

by

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Submitted for the Degree of Doctor of Philosophy

Department of Chemistry

University of Warwick

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To Trevor and my parents

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Success and happiness in life are of course so dependent on the people who care for you outside of work. The past three years have been especially happy ones for me since settling down in my home town with my husband Trevor. I have been fortunate to be able to live near to my family, long term friends, and ever increasing numbers of highly entertaining nieces and nephews. The love and support of my husband and my parents have been without limit. They are the people who have made my PhD possible. This thesis is dedicated to them.

Declaration

The work described in this thesis is the original work of the author, except where acknowledgment has been made to results and ideas previously reported. The work was carried out in the Department of Chemistry, University of Warwick between 1st April 2002 and 1st April 2005, and has not been previously submitted for a degree at any other institution.

Joanna V. Geden

Abstract

This thesis describes novel catalysts and methods for the synthesis of nitrogen heterocycles using copper (I) mediated atom transfer radical cyclisation (ATRC). It is divided into six chapters.

The first chapter provides a short review on the use of copper (I) salts in radical cyclisation chemistry.

The second chapter describes the synthesis and copper (I) mediated ATRC of novel α -halo dienamides derived from α,β -unsaturated ketones. A range of multifunctional heterocyclic building blocks were prepared including pyrrolidinones, tetrahydroisoquinolinones and β -lactams by *5-exo*, *6-endo* and *4-exo* cyclisation.

The third chapter extends the methodology discussed in chapter two to the synthesis and cyclisation of further α -halo dienamides derived from α,β -unsaturated aldehydes. This class of radical precursor was found to cyclise exclusively in the *4-exo* mode to give β -lactam products.

The fourth chapter looks at the copper (I) mediated *5-endo* cyclisation of α -halo keto enamides as a potential route to the synthesis of the heterocyclic ring fragment of natural product ZG-1494 α .

The fifth chapter describes the synthesis of novel solid supported copper (I) catalysts and their application to the atom transfer radical cyclisation of α -halo amides. A comparison of the activity of these catalysts to solution ligand/copper (I) halide mixtures is made. The reusability of polystyrene supported catalysts in the cyclisation of one radical precursor is discussed.

The sixth chapter gives the detailed preparative methods and analytical data for the compounds described in chapters two, three, four and five.

Abbreviations

AIBN	azabisisobutyronitrile
Aliph. quat.	aliphatic quaternary carbon
Ar C-H	aromatic carbon – hydrogen bond
Ar quat.	aromatic quaternary carbon
ATRC	atom transfer radical cyclisation
ATRP	atom transfer radical polymerisation
BDE	bond dissociation energy
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridine
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
Bu ₃ SnH	tri- <i>n</i> -butyltin hydride
CAN	cerium (IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
CI	chemical ionisation
d	doublet
DAST	(diethylamino)sulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEA	<i>N,N</i> -diethylaniline
DETA	diethylenetriamine
de	diastereomeric excess
DiPCD	diisopropylcarbodiimide
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	dimethylformamide

DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
EI	electron impact
eq.	equivalents
Et	ethyl
EtOAc	ethyl acetate
g	grams
Hz	hertz
ICP	inductively coupled plasma
IR	infra red
J	coupling constant
JJ-	JandaJel supported
LDA	lithium diisopropylamide
m	multiplet
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Me ₆ -tren	<i>N,N,N',N',N'',N''</i> -hexamethyltriethylenetetramine
mg	milligrams
mol	mole
m.p.	melting point
NA	not applicable
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NPMI	<i>N</i> -alkyl-2-pyridylmethanimine
olef. quat.	olefinic quaternary carbon
petrol	petroleum ether b.p. 40-60°C
PG	protecting group
Ph	phenyl

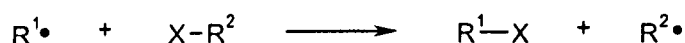
PMB	4-methoxybenzyl
PMDETA	<i>N,N,N',N'',N''</i> -pentamethyldiethylenetriamine
PS-	polystyrene supported
PS(CL)-	polystyrene (with cross-linking) supported
<i>p</i> TSA	<i>para</i> -toluenesulfonic acid
q	quartet
<i>rac</i>	racemic
rt	room temperature
s	singlet
Si-	silica supported
t	triplet
TBAF	tetrabutylammonium fluoride
TEDETA	<i>N,N,N',N'</i> -tetraethyldiethylenetriamine
TFA	trifluoroacetic acid
TBDMS	<i>tert</i> -butyldimethylsilyl
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TPA	<i>tris</i> -pyridin-2-ylmethyl-amine
Ts	4-methyl-benzenesulfonyl
WSC	water soluble carbodiimide

1. INTRODUCTION

1.1 ATOM TRANSFER RADICAL CYCLISATION

Some of the most important synthetic applications of radical chemistry involve intramolecular cyclisation reactions.¹ A variety of radical precursors can be selectively cyclised to give both mono- and polycyclic products, generally in good yields. Radical cyclisations can give high levels of regio- and stereoselectivity, and a number of different methods can be used to carry out the cyclisation reactions. All of these methods involve radical generation (often by atom transfer to a radical initiator or metal ion) and cyclisation (or cyclisations) onto a multiple bond, followed by reaction of the cyclised radical to form the product. Complex heterocyclic systems have been assembled with increasing ingenuity in radical cyclisations. These radical cyclisation methods commonly have several advantages over non-radical methods which require multi-step alternative syntheses.

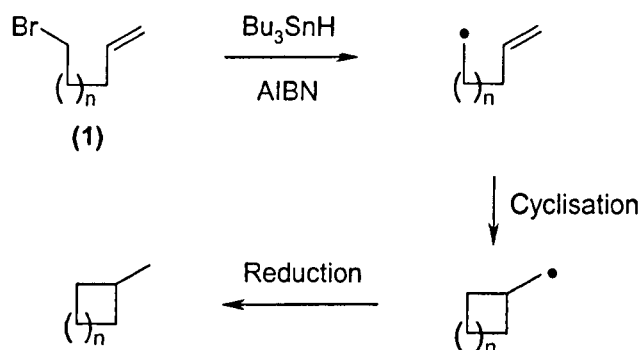
Atom transfer (or radical abstraction) *reactions* involve the removal of an atom X (such as hydrogen or a halogen) from a non-radical precursor (Scheme 1). These reactions can be inter- or intramolecular processes. The mechanism of these reactions involves the attack of a radical R¹• at the σ bond of the atom undergoing abstraction to form a new, more stable, product radical R²•.



Scheme 1

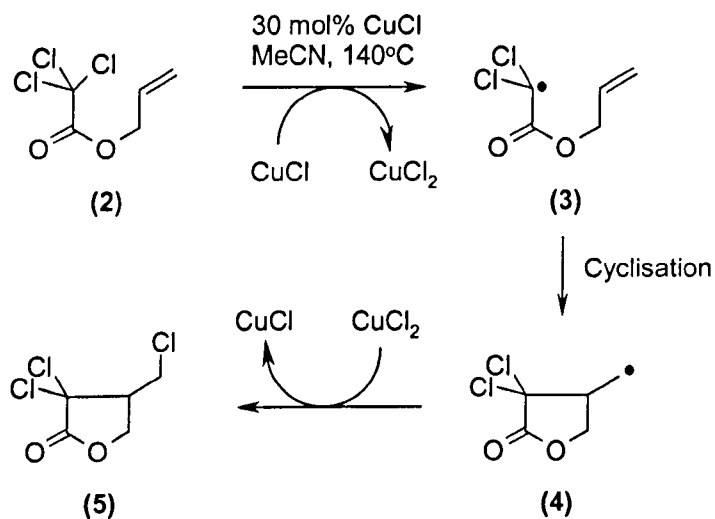
The majority of radical cyclisations are mediated by organostannane or organosilane reagents, such as Bu₃SnH or HSi(SiMe₃)₃.¹ The drawback of these methods is that they are reductive in nature (the cyclised radical may extract a hydrogen atom from the mediating reagent), and lead to the loss of two functional groups. For example, cyclisation of **(1)** with Bu₃SnH leads to the loss of both the radical precursor (halogen) and the radical acceptor (alkene) functionality (Scheme 2). In addition, organostannane reagents are highly toxic, expensive and are difficult to remove from reaction products. For these reasons, the pharmaceutical and agrochemical industries have been reluctant to

employ radical cyclisations to assemble certain heterocyclic ring systems of interest, even though this approach is often the most efficient.



Scheme 2

Transition metals also catalyse inter- and intramolecular addition of halogenated organic molecules to alkenes.² The intramolecular process, known as atom transfer radical cyclisation (ATRC), can be achieved using a range of metal catalysts, such as Ni,³ RuCl₂(PPh₃)₃,² and FeCl₂[P(OEt)₃]₃.² The most effective catalysts are those derived from copper (I) salts.⁴ These atom transfer radical cyclisations involve redox reactions between copper (I) and copper (II) complexes. For example, reaction of trichloroacetate (2) with CuCl generates the initial radical (3) and CuCl₂ (Scheme 3).⁵ After cyclisation, the newly formed and more reactive primary radical (4) reacts with CuCl₂ to regenerate the CuCl catalyst and give the cyclised product (5).



Scheme 3

The use of copper complexes in radical cyclisation reactions has the advantage of (i) the low cost of the copper (I) salts, (ii) the ease of work-up of the reactions (the catalyst is simply removed by filtration through a silica plug), and (iii) the catalytic nature of the process.

1.2 FACTORS GOVERNING THE RATE AND OUTCOME OF COPPER (I) MEDIATED ATRC REACTIONS

The rate and outcome of copper (I) mediated atom transfer radical cyclisations are influenced by a number of factors. These include:

- i) the strength of the C-X σ bond being homolytically broken (X=halogen).
- ii) the stability of the resulting radical intermediate.
- iii) the stereoelectronic effects of ring formation by addition of the intermediate radical to the unsaturated carbon atom.
- iv) conformer populations and their amenability to cyclisation.
- v) the solvent in use.
- vi) additives to the reaction mixture which influence the rate of reaction.

In more detail:

i) The energy required to cleave a C-X bond homolytically to give two radicals is known as the bond dissociation energy (BDE) or bond strength. The size of the BDE is directly related to the thermodynamic stability of the product radicals.⁶ Bond dissociation energies for the homolysis of various C-X bonds are shown in Table 1. The ease of homolytic fission of the C-X bond follows the order C-F < C-Cl < C-Br < C-I as the bond dissociation energy decreases.

Bond	H ₃ C-F	H ₃ C-Cl	H ₃ C-Br	H ₃ C-I
BDE (KJ mol ⁻¹)	460	356	297	239

Table 1

The bonding of additional halogen substituents on the carbon atom weakens the C-X bond and decreases the bond dissociation energy. For example, the C-Cl bond of $-\text{CCl}_3$ is cleaved more readily than that of $-\text{C}(\text{CH}_3)\text{Cl}_2$.

ii) Like carbocations (R_3C^+), carbon centred radicals are stabilised by electron-donating substituents. A tertiary radical ($\text{R}_3\text{C}\cdot$) is therefore more stable than a secondary radical ($\text{R}_2\text{HC}\cdot$) which is in turn more stable than a primary radical ($\text{RH}_2\text{C}\cdot$) (Figure 1). Unlike carbocations, carbon centred radicals may also be stabilised by electron-withdrawing substituents such as halogen atoms or carbonyl groups.

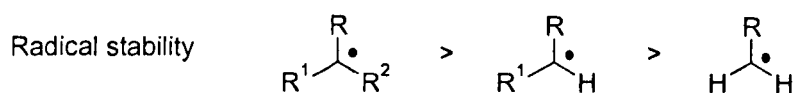
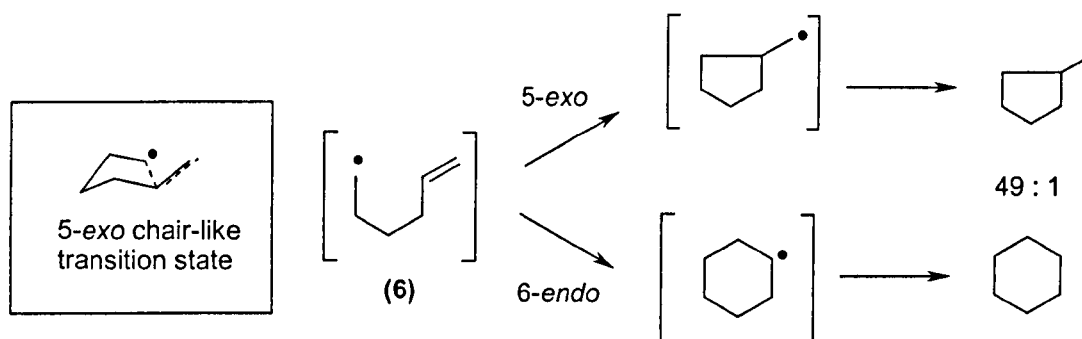


Figure 1

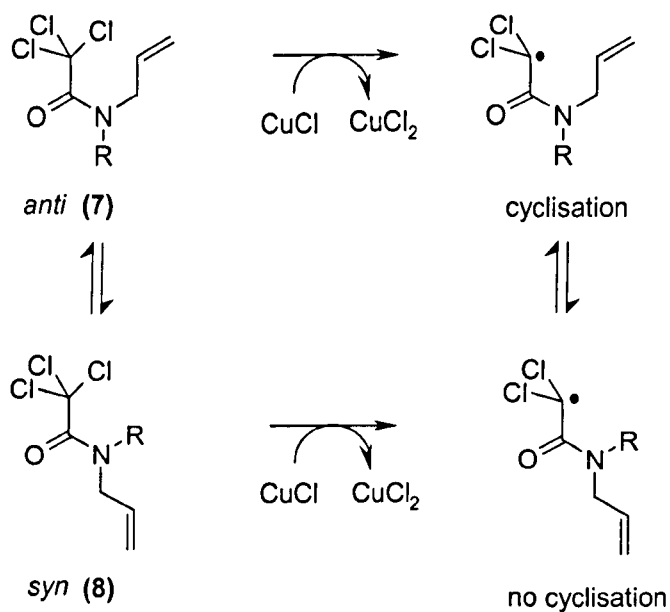
iii) Radical cyclisations are most often applied to the formation of 5- and 6-membered rings. These rings are relatively strain free, and are prepared *via* 5- and 6-membered transition states, which are easy to form. Cyclisations to form 3- and 4-membered rings are reversible, because of ring strain, and the equilibrium usually lies on the side of the acyclic radical precursor. However, cyclopropanes and cyclobutanes can be isolated if the cyclic radical intermediate (produced from a 3- or 4-*exo* cyclisation) is stabilised by substituents.

Cyclopentyl rings are formed very rapidly on 5-*exo* cyclisation of hex-5-en-1-yl radicals (**6**) (Scheme 4). The preference for 5-*exo* rather than 6-*endo* cyclisation (49:1) has been explained by stereoelectronic effects favouring a chair-like transition state (Beckwith model).⁷



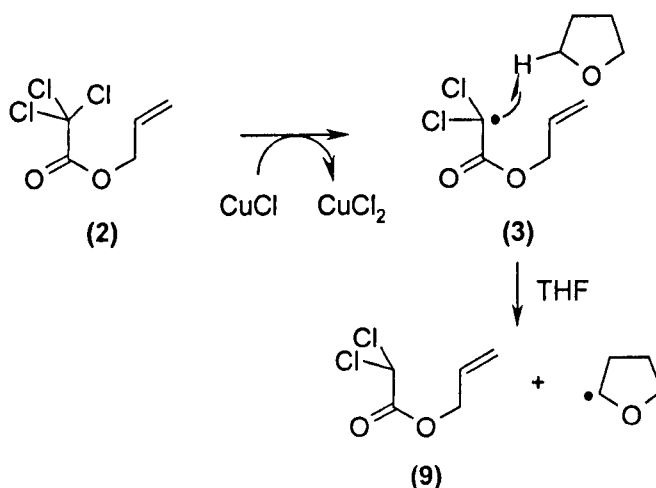
Scheme 4

iv) Certain radical precursors do not cyclise readily since they exist predominantly in a conformation which prevents orbital overlap between the initial attacking radical and the unsaturated carbon atom. For example, the cyclisation of α -*N*-allylcarbamoyl radicals is a difficult process requiring high temperatures, due to the high barrier to rotation which is characteristic of the amide CO-N bond (Scheme 5). If the nitrogen is unprotected (R = H), the least sterically hindered *syn* conformer (**8**) predominates and cyclisation cannot occur. Bulky or electron withdrawing R groups favour cyclisation by shifting the equilibrium towards the *anti* conformer (**7**) which can cyclise.⁸



Scheme 5

v) Solvents or reagents which can readily transfer a hydrogen radical (e.g. THF) may intercept an intermediate radical such as (3) before radical cyclisation takes place to give a product of reduction such as (9) (Scheme 6). For this reason, atom transfer radical cyclisation reactions are usually conducted in solvents which undergo slow atom transfer with intermediate radicals such as DCM or DCE. Acetonitrile has been the solvent of choice for a large number of ATRC reactions since it solubilises the copper (I) complex more than other solvents and hence increases the rate of halogen atom transfer from the radical precursor.



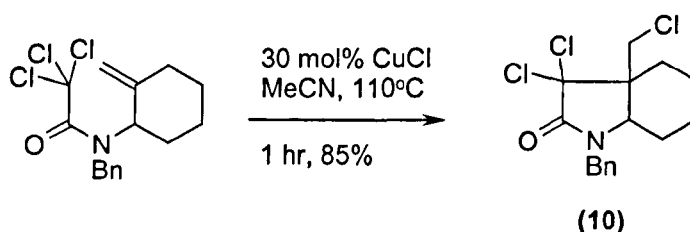
Scheme 6

vi) The addition of certain amine or pyridine ligands to atom transfer reactions has been found to cause an increase in rate for a variety of cyclisation reactions (see Sections 1.3-1.6). The additive is thought to accelerate the atom transfer processes by solubilising the copper (I) halide, or by altering the redox potential of the catalyst system, or by both effects.

1.3 COPPER (I) MEDIATED 5-EXO ATOM TRANSFER RADICAL CYCLISATION

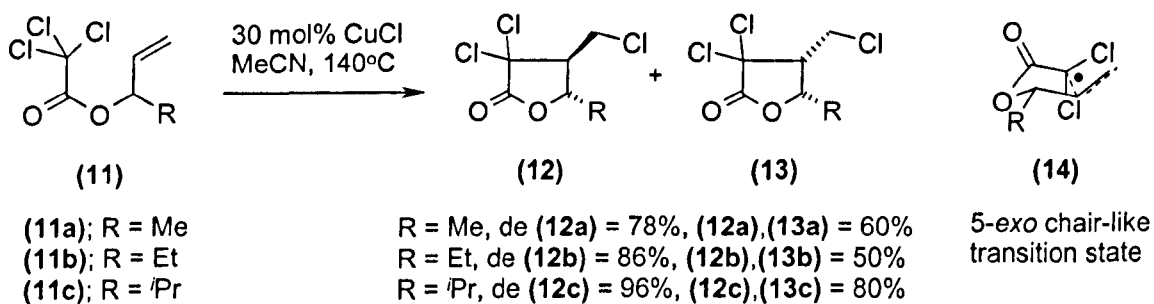
The copper (I) catalysed intermolecular addition of α -halo esters to alkenes was first discovered in 1964,⁹ but it was not until 1983 that Nagashima discovered the intramolecular version of this reaction. γ -Lactone (5) was prepared in 72% yield by the

5-*exo* cyclisation of α -trichloro ester (**2**) using 30 mol% copper (I) chloride in acetonitrile at 140°C in a pressure bottle (Scheme 3).⁵ Soon after this discovery, Nagashima found that he could also prepare γ -lactams from trichloroacetamide derivatives using copper (I) catalysis at high temperatures.¹⁰⁻¹¹ Both secondary and tertiary amides could be cyclised, although tertiary amides were found to cyclise more rapidly. This difference in rate is believed to be due to conformer effects whereby an alkyl nitrogen substituent increases the population of the *anti* conformer which can cyclise. Both mono and bicyclic lactams were prepared in high yield by this approach including hexahydro-oxindole (**10**) which bears an angular chloromethyl group (Scheme 7).¹¹ The formation of a quaternary ring carbon is an accomplishment which is difficult to achieve using non-radical methods.



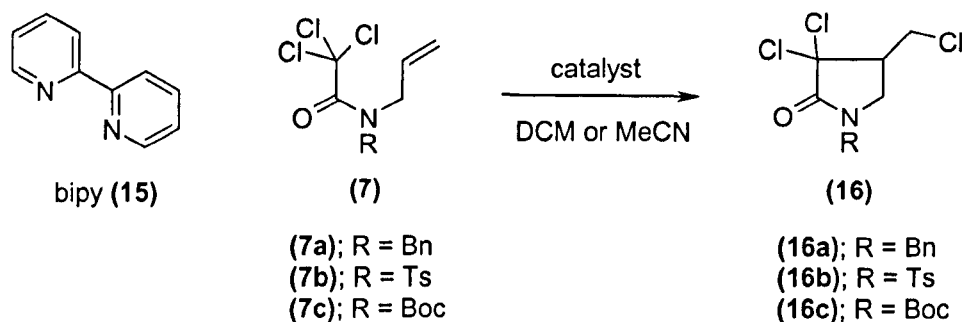
Scheme 7

The cyclisation of trichloroacetates (**11a-c**) derived from secondary alcohols was found to give γ -lactones (**12a-c**) and (**13a-c**) involving diastereoselection reflecting the relative stereochemistry of β - and γ -substituents on the lactone ring (1,2-asymmetric induction) (Scheme 8).¹² The chair-like transition state model for 5-*exo* cyclisation (**14**) provides a rationale for the *trans* stereoselectivity observed in this reaction; in the transition state the alkyl and olefin groups prefer to adopt pseudo-equatorial positions.



Scheme 8

By the late 1980s, the formation of γ -lactones and γ -lactams by copper (I) mediated 5-*exo* cyclisation of α -haloacetates or amides had been established, but the methodology had severe limitations in that only activated radical precursors (trichloro derivatives) had been cyclised, and high temperatures were required to effect cyclisation. This had obvious limitations on the range and usefulness of heterocycles that could be prepared without additional dehalogenation steps. In 1990, however, Nagashima reported an increase in the rate of cyclisation of trichloroacetate (**2**) with catalytic copper (I) chloride by the addition of the ligand 2,2'-bipyridine (bipy) (**15**) to the reaction mixture (Schemes 3 and 9).¹² Substrates (**7a-c**) were all found to cyclise more rapidly with 30 mol% of a 1:1 mixture of CuCl:bipy (in DCM) than with 30 mol% CuCl (in MeCN) (Scheme 9, Table 2).¹³ The increase in rate was sufficient to enable these cyclisation reactions to be achieved at room temperature in a much shorter reaction time and in excellent yield. These results provided encouragement for the potential cyclisation of less activated radical precursors at lower temperatures using nitrogen based ligands.

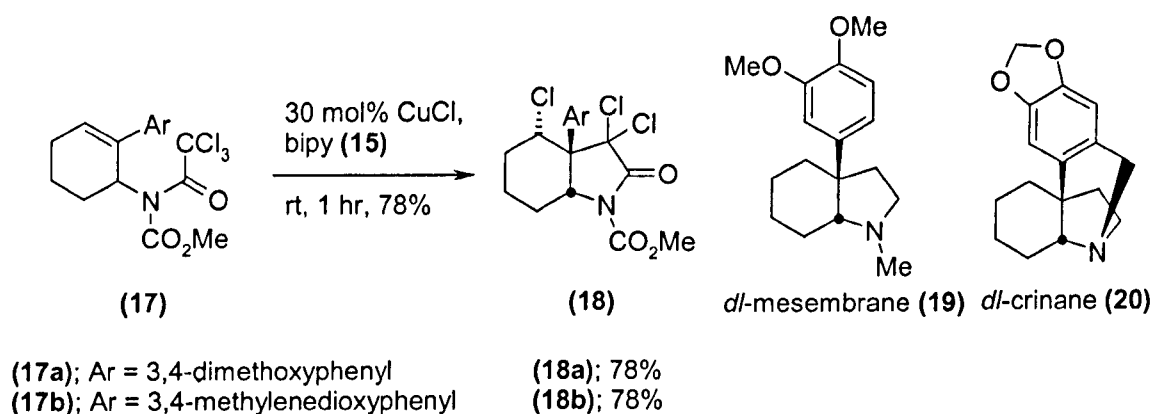


Scheme 9

Substrate	Catalyst	Temp. (°C)	Time (hrs)	Yield (%)
(7a)	CuCl, 30 mol%	80	18	68
(7a)	CuCl, bipy, 30 mol%	rt	1	98
(7b)	CuCl, 30 mol%	rt	24	97
(7b)	CuCl, bipy, 5 mol%	rt	0.2	91
(7c)	CuCl, 30 mol%	80	4	80
(7c)	CuCl, bipy, 30 mol%	rt	2	78

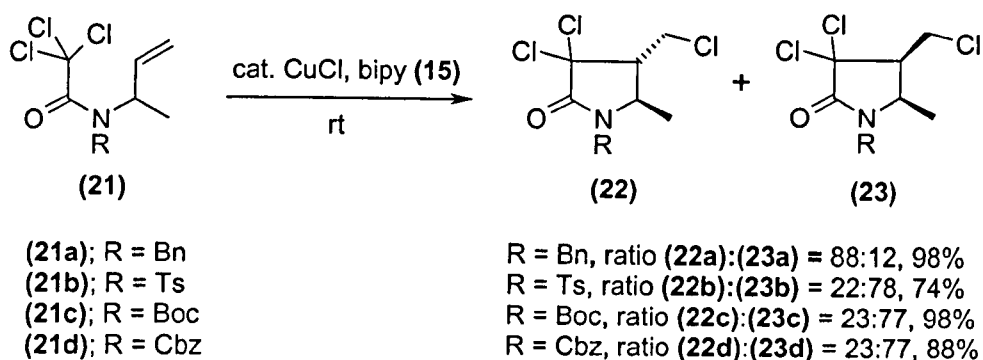
Table 2

The synthesis of *dl*-mesembrane (**19**) and *dl*-crinane (**20**) was achieved from intermediates (**18a**) and (**18b**) which were prepared by the 5-*exo* radical cyclisation of amides (**17a**) and (**17b**) respectively using the activated CuCl/bipy catalytic system (Scheme 10).⁸ The presence of an electron-withdrawing nitrogen protecting group (CO₂Me) was found to aid the cyclisation process by minimising the double bond character of the N-CO bond of the amide, and hence the rotational energy barrier to cyclisation. Attempts to achieve the cyclisation of related *N*-methyl acetamides using the same catalyst system were found to produce only a low yield of the desired bicyclic lactams.⁸ This is believed to be due to the lower population of conformers which can cyclise (due to the small nitrogen substituent) compared with (**17**).



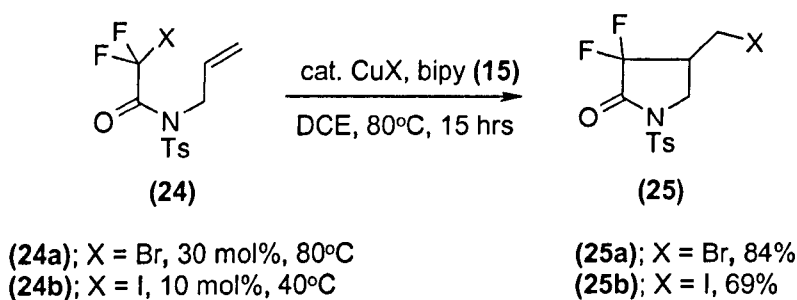
Scheme 10

The nitrogen protecting group was found to affect the selectivity as well as the rate of 5-*exo* cyclisation. *N*-Benzyl compound (**21a**) was found to give largely *trans* product (**22a**) whilst *N*-tosyl compound (**21b**), *N*-Boc derivative (**21c**) and *N*-Cbz derivative (**21d**) all gave predominantly the *cis* products (**23b-d**) (Scheme 11).¹³



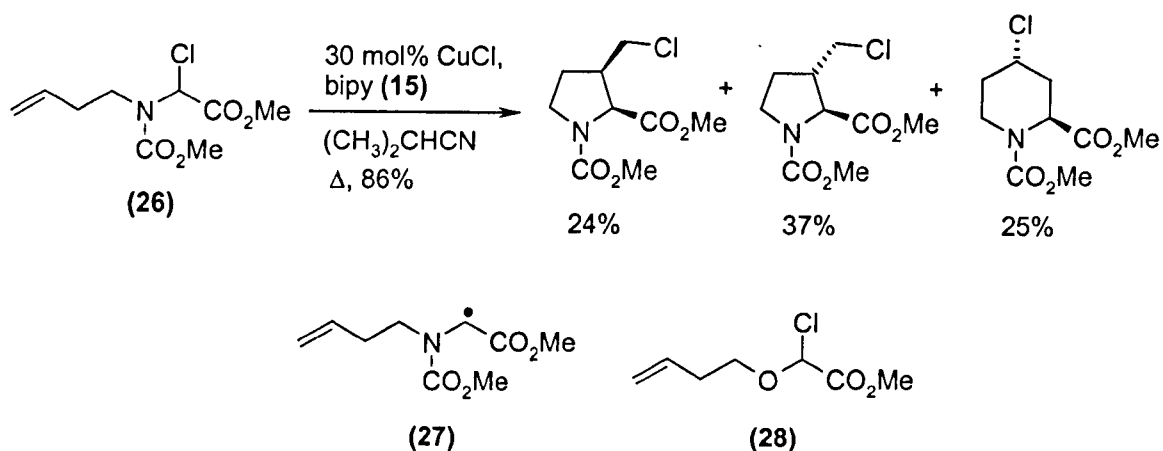
Scheme 11

The combination of the bulky electron-withdrawing *N*-tosyl group and the bipy ligand (15) has also been used to aid the 5-*exo* cyclisation of *N*-allylhalodifluoroacetamides (24a-b) to give fluorinated γ -lactams (25a-b) (Scheme 12).¹⁴ The activation of a carbon-halogen bond in fluorinated hydrocarbons is difficult to achieve compared with that in chlorinated homologues due to a higher C-X bond dissociation energy. In addition, fluorinated amides have a higher rotational energy barrier. The rate of reaction was found to increase from X=Cl to X=I which reflects the decreasing bond dissociation energy of the C-X bond which is homolytically broken in the initial radical generation step.



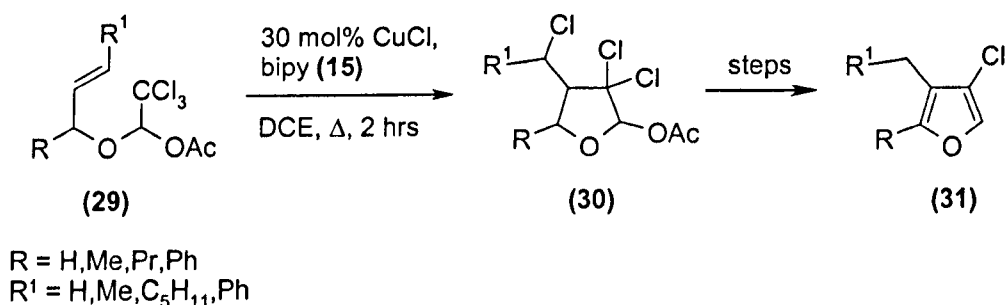
Scheme 12

Copper (I) chloride and 2,2'-bipyridine (15) were also found to effect the cyclisation of mono-halo substrate (26) at 80°C (Scheme 13).¹⁵ This reaction involves the captodatively stabilised radical intermediate (27). The 5-*exo* cyclisation of related ether (28) has also been achieved using the same catalytic system.¹⁶



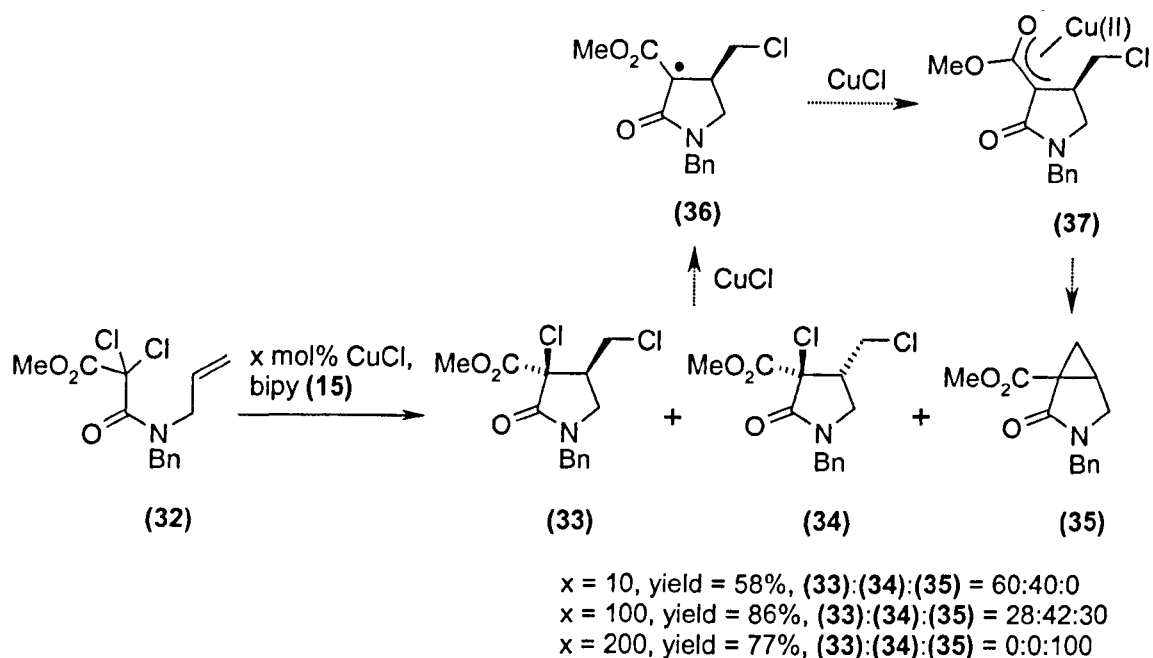
Scheme 13

A 1:1 mixture of copper (I) chloride and 2,2'-bipyridine (15) has been used to synthesise 2,3-disubstituted 4-chlorofurans (31) from β -chloroethyl allyl ethers (29) (Scheme 14).¹⁷ Conversion of the radical cyclisation product (30) to the desired furan (31) was achieved by reductive removal of the ring chlorine and acetoxy groups with zinc, followed by elimination of hydrogen chloride/aromatisation using potassium *tert*-butoxide.



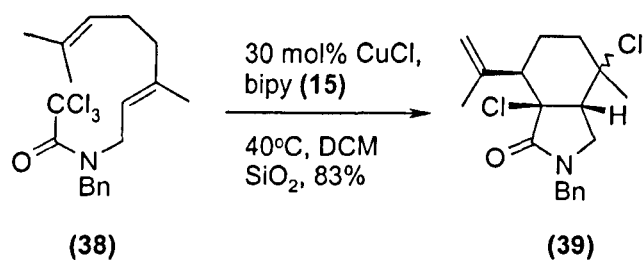
Scheme 14

α,α -Dichloromalonamide (32) was also found to undergo 5-*exo* cyclisation in the presence of CuCl/bipy to give γ -lactam products (33)-(35) (Scheme 15).¹⁸ The product outcome was found to be related to the amount of the CuCl/bipy catalyst used, with bicycle (35) being formed exclusively with two equivalents of copper (I) chloride. Cyclopropanation of (33) and (34) is believed to take place *via* a copper (II) enolate (37) which is formed by the reduction of radical (36).



Scheme 15

Tandem radical cyclisation reactions have been catalysed using copper (I) chloride/bipy.¹⁹ For example, reaction of trichloroamide (38) with this catalyst at 40°C gave the diastereomeric bicyclic lactams (39) in 83% yield (Scheme 16).¹⁹ These products are presumably formed by an initial 5-*exo* cyclisation to give a γ -lactam which generates a further α -carbamoyl radical with copper (I) chloride which then undergoes 6-*exo* cyclisation. The isolated lactam (39) is formed after a final HCl elimination step.



Scheme 16

The rate increase achieved using 2,2'-bipyridine (15) in copper (I) ATRC reactions encouraged a number of groups to discover alternative pyridine and amine ligands which could cyclise less activated mono and dihalo radical precursors. This research effort

resulted in the discovery of new catalytic systems based upon *N*-alkyl-2-pyridylmethanimines (NPMI) (**40**),²¹⁻²⁵ *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (**41**),²⁶⁻³¹ *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA) (**42**),^{20,32-33} and *N,N,N',N',N'',N''*-hexamethyltriethylenetetramine (Me₆-tren) (**43**)^{20,24-25,34} (Figure 2). All of these catalysts have been found to give higher rates of reaction in atom transfer radical cyclisations than those based on 2,2'-bipyridine (**15**).

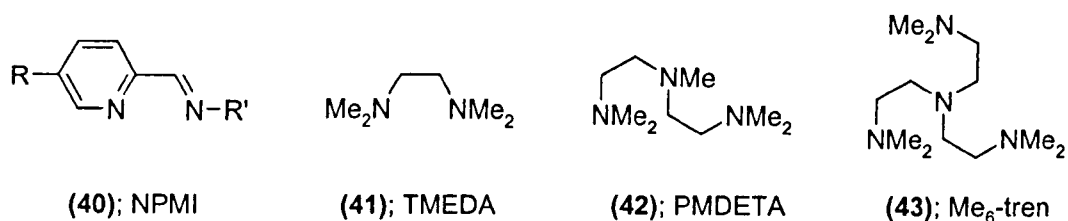
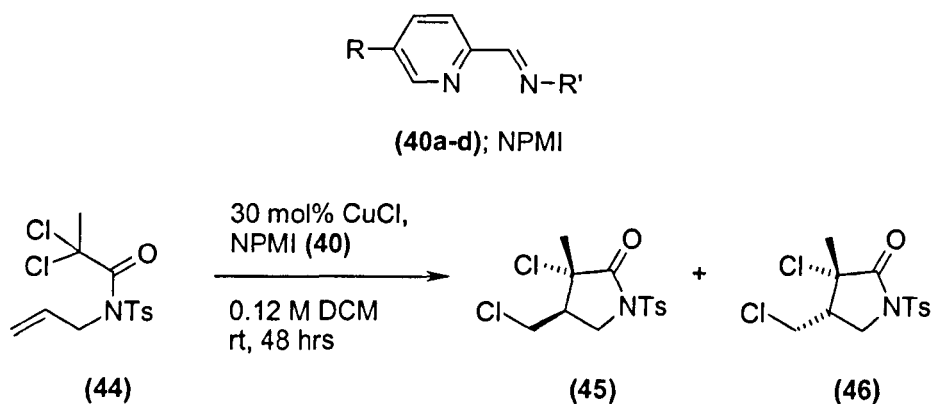


Figure 2

In catalytic systems where copper (I) halides are used with 2,2'-bipyridine (**15**), the ligand is thought to increase the rate of reaction by solubilising the copper (I) as the [Cu(I)(bipy)₂]⁺ complex ion, and by accepting electron density from the metal into its Π^* LUMO thus stabilising the copper (I) oxidation state. NPMI ligands (**40**) (which like bipy (**15**) have low lying Π^* orbitals) have been prepared in the Clark group by the cheap and straightforward condensation of aldehydes with primary amines in the presence of magnesium sulfate.²¹⁻²⁵ The 5-*exo* cyclisation reactions of *N*-allyl- α -haloamides with a range of NPMI ligands (**40**) and copper (I) halide indicated that the rate of reaction was optimal for non-bulky straight chain alkyl R' groups (R' = ⁿBu) and electron donating inductive R groups (R = H, Me) with a 2:1 ratio of the ligand to copper (I) halide (Scheme 17, Table 3).²¹⁻²²



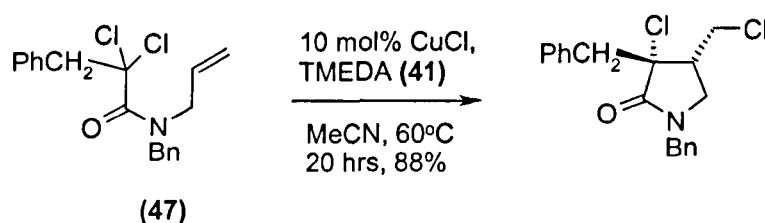
Scheme 17

Ligand	R' group (R=H)	Relative rate ^a	de (45) (%)
(40a)	ⁿ Bu	45	64
(40b)	ⁱ Bu	28	44
(40c)	^s Bu	3	36
(40d)	^t Bu	1	0

^a Relative rate with respect to the reaction of ligand (40d)

Table 3

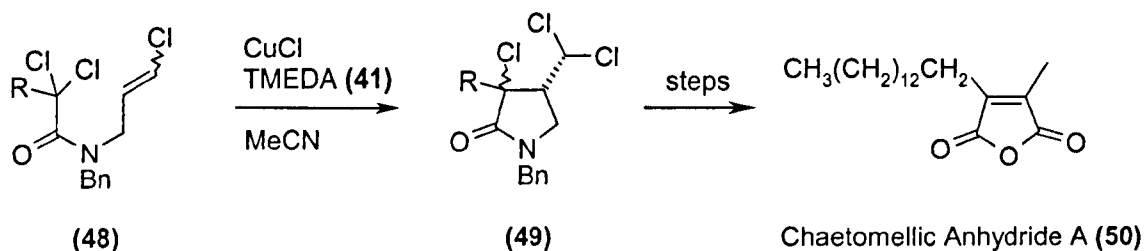
Ghelfi has demonstrated that TMEDA (**41**) is an effective ligand for copper (I) mediated ATRC reactions (Figure 2).²⁶⁻³¹ The inexpensive TMEDA/CuX catalytic system gives improved yields at low catalyst loadings (10 mol%) for a range of 5-*exo* cyclisations including dichloroacetamide derivatives such as (**47**) (Scheme 18).²⁶ As for the bidentate NMPI ligands, the optimum ratio of TMEDA:CuX was found to be 2:1, reflecting the preferred coordination number of four for the copper (I) complex ion.



Scheme 18

More recently, CuCl/TMEDA has been used to achieve the 5-*exo* cyclisation of vinyl chlorides (**48a-b**) (Scheme 19).³⁰ The γ -lactam product (**49b**) was formed in higher

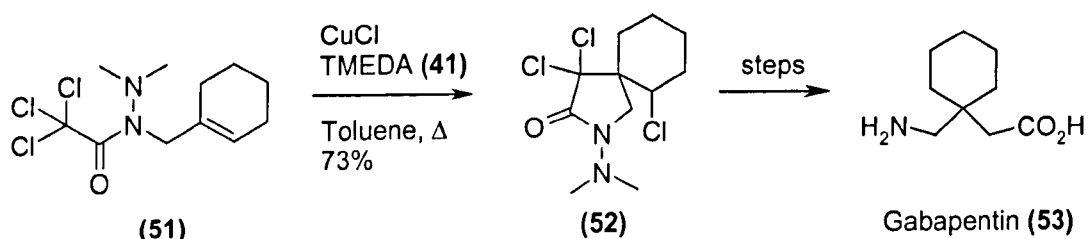
diastereoselectivity than **(49a)** due to the different reaction temperatures (60°C cf. 25°C) under which ring closure was accomplished. The C3 stereo centre is configurationally unstable under the reaction conditions, and the more stable *cis* product is formed by equilibration. Chaetomelic anhydride A (**50**) was prepared from **(49b)** in four steps.



(48a); R = CH₂(CH₂)₄CH₃, 25°C, 20 hr. **(49a)**; 97%, 72:28, *cis:trans*
(48b); R = CH₂(CH₂)₁₂CH₃, 60°C, 20 hr. **(49b)**; 99%, 89:11, *cis:trans*

Scheme 19

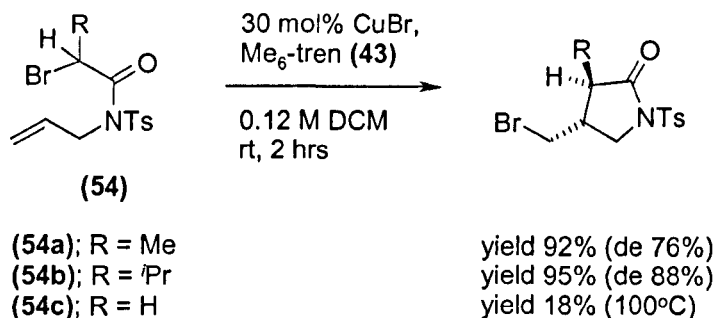
The anti-epileptic drug Gabapentin (**53**) has been prepared by a synthetic sequence which involves the 5-*exo* ATRC of cyclohexene derivative (**51**) using copper (I) chloride and TMEDA (**41**) (Scheme 20).³¹ Spirocycle (**52**) was dehalogenated with Raney nickel prior to efficient protecting group removal and γ -lactam hydrolysis to give target (**53**).



Scheme 20

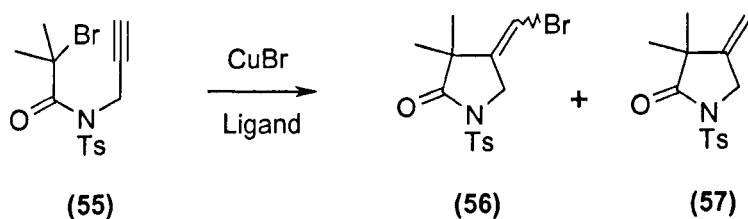
The tetradentate Me₆-tren ligand (**43**) has been shown to be extremely effective in increasing the rate of a number of copper (I) mediated ATRC reactions (Figure 2).^{20,24-25,34} The use of a 1:1 ratio of Me₆-tren:CuX produces a catalyst far more active than those catalysts based on 2,2'-bipyridine (**15**), NPMI (**40**), TMEDA (**41**) or PMDETA (**42**). Cyclisation of a range of monohalo amides was found to be achievable at room

temperature, and even primary bromide (**54c**), which is poorly activated towards radical generation, was found to cyclise albeit at a higher temperature of 100°C (Scheme 21).²⁰



Scheme 21

5-*Exo* cyclisation of α -halo amides onto alkynes has also been reported at room temperature using both NPMI (**40a**) and Me₆-tren (**43**) ligands (Figure 2, Scheme 17, Table 3).^{20,24} Cyclisation of monobromo amide (**55**) was found to give both vinyl bromides (**56**) and also reduced product (**57**) (Scheme 22). The ratio of (**56**) to (**57**) was found to be both ligand and solvent dependent, and reflects the competitive rates of transfer of a bromine or hydrogen radical to the intermediate vinyl radical. Reduction by transfer of a hydrogen radical was found to predominate when Me₆-tren (**43**) was used as the ligand.



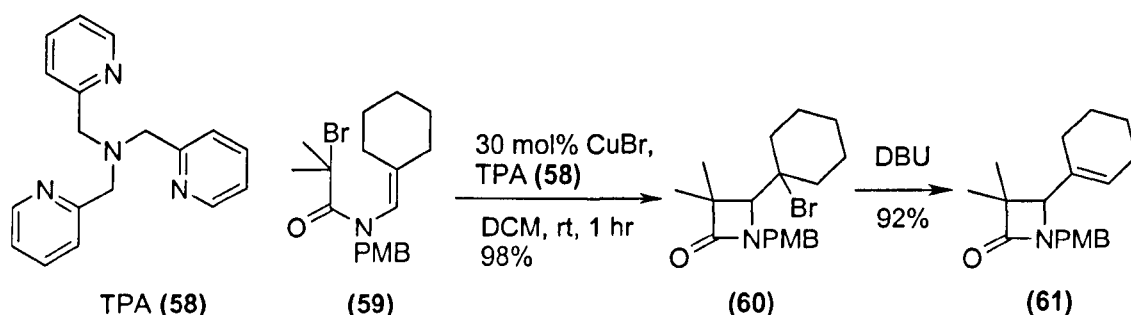
NPMI (**40a**), C₆H₆, yield = 94%, (**56**):(**57**) = 84:1, (**56**) *E*:*Z* = 1:4
 Me₆-tren (**43**), DCM, yield = 95%, (**56**):(**57**) = 1:20, (**56**) *E*:*Z* = 1:4

Scheme 22

Copper (I) mediated 5-*exo* cyclisation of α -halo amides has also been achieved using solid supported catalysts.³⁵ This work is discussed in Chapter 5.

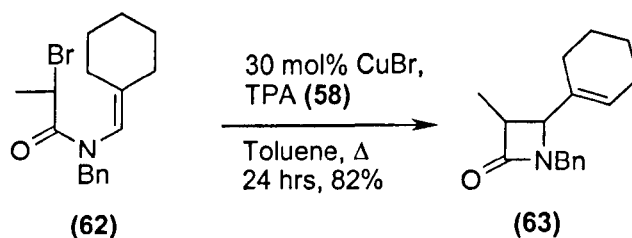
1.4 COPPER (I) MEDIATED 4-EXO ATOM TRANSFER RADICAL CYCLISATION

α -Halo enamides disubstituted at the terminal end of the alkene group undergo 4-*exo* cyclisation with catalytic copper (I) halide in the presence of activating ligands to form β -lactam products.³⁶⁻³⁷ Monobromo enamide (**59**), which has two radical stabilising alkyl substituents at the end of the alkene, was found to form β -lactam (**60**) with 30 mol% copper (I) bromide and the multidentate pyridine ligand (**58**) (TPA) in DCM at room temperature after 1 hour (Scheme 23).³⁶ Elimination of the tertiary bromide (**60**) to give alkene (**61**) was achieved using DBU.



Scheme 23

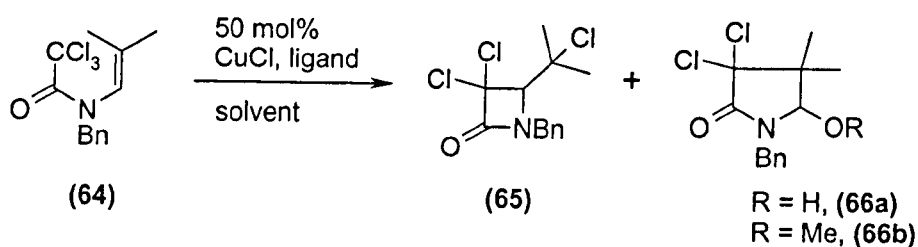
Cyclisation of the less activated secondary monobromide (**62**) was also achieved using the same catalytic system at a higher temperature to give alkene (**63**) directly (Scheme 24).³⁶ TPA (**58**) acts as both a ligand and as a base in this reaction.



Scheme 24

Competing 4-*exo* versus 5-*endo* cyclisation of trichloro enamide (**64**) has been reported (Scheme 25).³⁷ The cyclisation products were found to be solvent dependent. The kinetic

4-*exo* product (**65**) was found to predominate using 2,2'-bipyridine (bipy) (**15**) or TMEDA (**41**) in refluxing acetonitrile, whilst the thermodynamic 5-*endo* products (**66a-b**) were formed preferentially using bipy (**15**) in refluxing toluene.



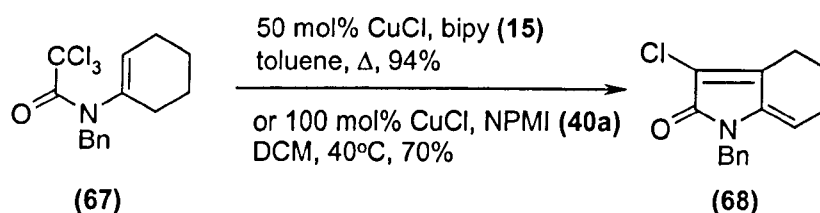
bipy (**15**), Δ , MeCN, or TMEDA (**41**), Δ , MeCN, yield (**65**) = 85-86%

bipy (**15**), Δ , toluene, then MeOH, yield (**65**) = 9%, (**66a**), (**66b**) = 86%, (**66a**):(**66b**) = 1:1

Scheme 25

1.5 COPPER (I) MEDIATED 5-*ENDO* ATOM TRANSFER RADICAL CYCLISATION

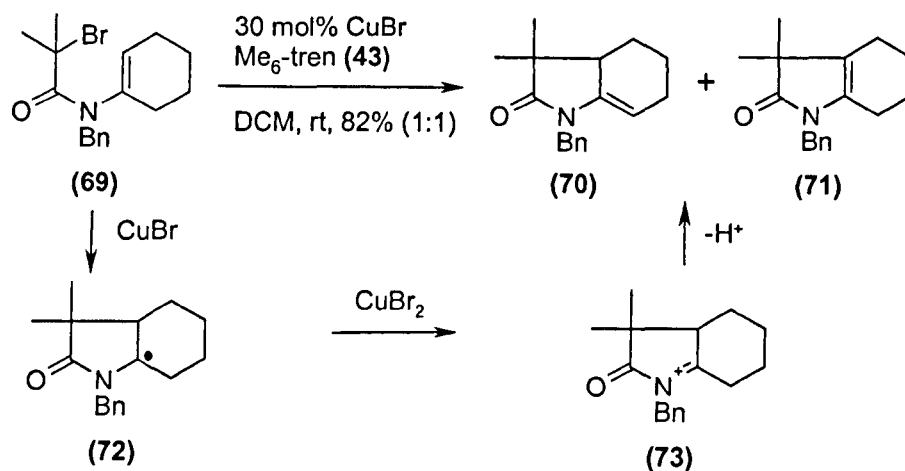
Treatment of trichloro enamide (**67**) with catalytic copper (I) chloride and either bipy (**15**)³⁸⁻³⁹ or NPMI ligand (**40a**)²⁵ has been found to give diene (**68**) which arises from 5-*endo* cyclisation (Scheme 26).



Scheme 26

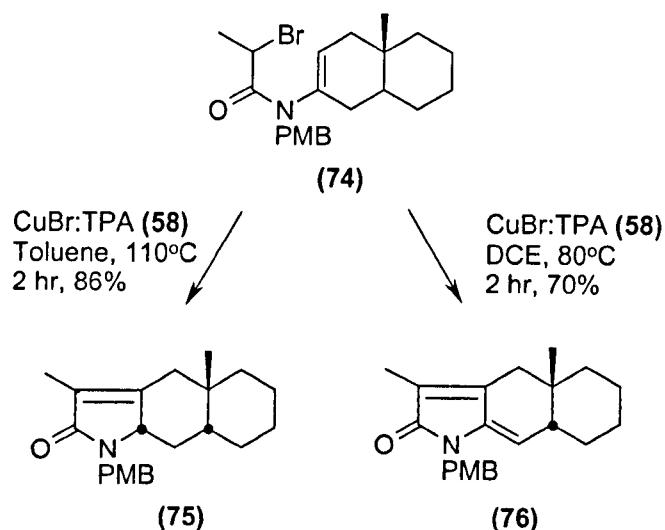
Monobromo derivative (**69**) also undergo 5-*endo* cyclisation when treated with copper (I) bromide and Me₆-tren (**43**) at room temperature in DCM (Scheme 27).²⁵ Alkene products (**70**) and (**71**) are believed to be formed by a radical-polar cross over mechanism in which the initial radical (**72**), generated on 5-*endo* cyclisation, is oxidised by copper (II) to give an *N*-acyliminium ion (**73**) which undergoes proton loss. 5-*Endo* radical cyclisation onto

a number of acyclic and cyclic enamides has been accomplished. A usual criterion for this reaction to occur is that the olefinic carbon of the enamide attached to the nitrogen has an alkyl or aryl substituent which can stabilise the radical intermediate formed on 5-*endo* cyclisation.



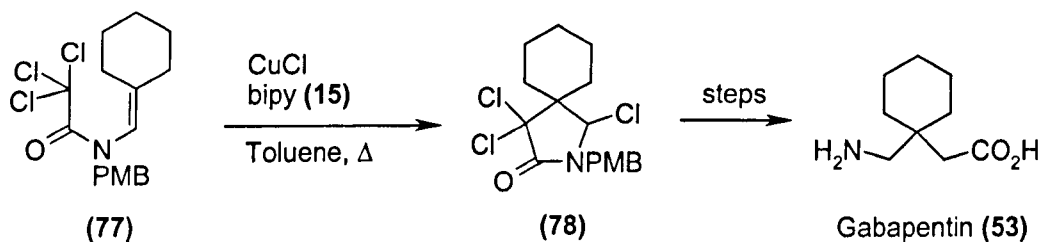
Scheme 27

Although secondary monohalo enamides do not undergo 5-*endo* cyclisation with Me₆-tren (43) and NPMI ligands (40), the TPA ligand (58) is effective in achieving this reaction (Scheme 28).⁴⁰ Reaction of enamide (74) with stoichiometric copper (I) bromide/TPA in refluxing toluene gave α,β -unsaturated lactam (75) in 86% yield. By changing the solvent to DCE, diene (76) was obtained exclusively in 70% yield. Diene (76) is presumably formed by the oxidation of monoene (75) under the reaction conditions. This theory is supported by the observation that a monoene closely related to (75) undergoes oxidation to a diene on treatment with copper (I) in refluxing DCE.⁴⁰



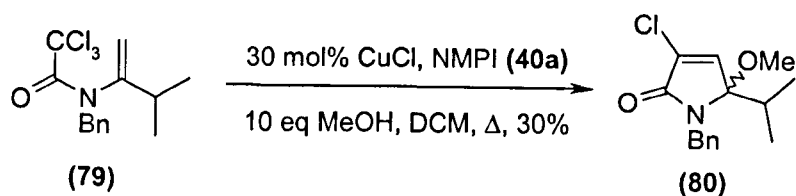
Scheme 28

The synthesis of Gabapentin (**53**) has been achieved from spirocycle (**78**) which was prepared by the *5-endo* cyclisation of trichloro enamide (**77**) using copper (I) chloride and 2,2'-bipyridine (**15**) (Scheme 29).⁴¹ This mode of cyclisation is unusual for an enamide with this substitution pattern; structurally similar enamides (**59**) and (**62**) were found to undergo *4-exo* cyclisation under ATRC conditions (Schemes 23 and 24).



Scheme 29

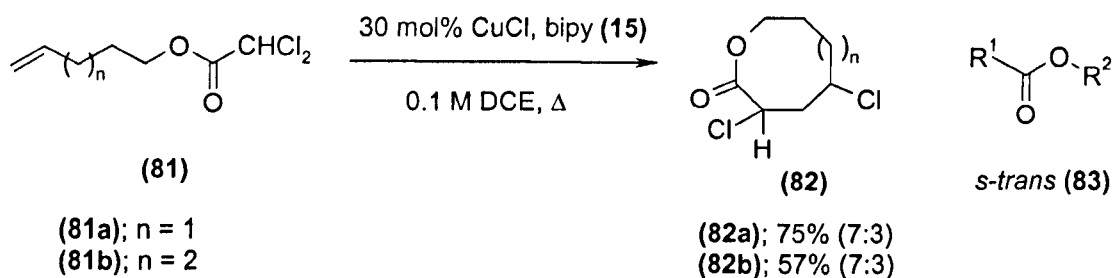
Evidence for the intermediacy of acyliminium ions in *5-endo* cyclisation reactions has been provided by the formation of methoxy lactam (**80**) from trichloro enamide (**79**) when the cyclisation reaction is performed in the presence of methanol (Scheme 30).⁴²



Scheme 30

1.6 SYNTHESIS OF MEDIUM RING HETEROCYCLES

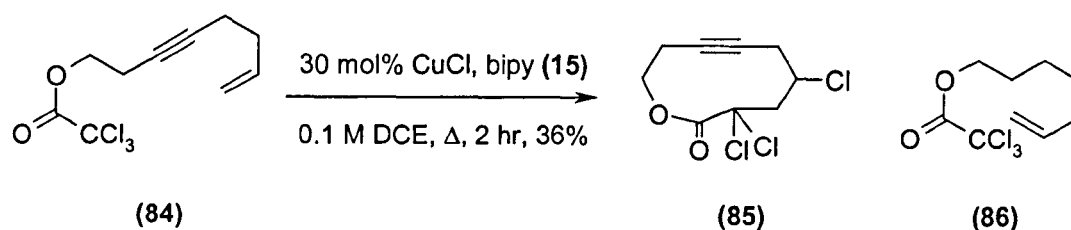
Medium-sized lactones have been prepared by the *endo* radical cyclisation of di- and trichloroacetates using copper (I) chloride and 2,2'-bipyridine (**15**) (Scheme 31).⁴³⁻⁴⁴ For example, reaction of dichloroacetates (**81a-b**) with 30 mol% CuCl/bipy in 0.1 M DCE at reflux for 18 hours gave the desired lactones (**82a-b**) in 75 and 57% yields.⁴³ Since the ring size is 8-membered or more, the most stable *s-trans* conformation of the ester (**83**) does not impede *endo* cyclisation.



Scheme 31

A variety of 8-, 9-, 10- and 11-membered lactones have been prepared using copper (I) mediated ATRC.⁴⁴ The use of 30 mol% copper (I) catalyst was found to be critical for reaction success, together with a low substrate concentration and high reaction temperature (80-190°C). The synthesis of ring sizes of 10 and 11 using 2,2'-bipyridine (**15**) as the activating ligand was found to require an element of rigidity in the cyclisation precursor. For example, cyclisation of trichloroacetate (**84**) (which contains an alkyne) with catalytic CuCl/bipy gave 10-membered lactone (**85**), whilst acetate (**86**) failed to cyclise under the same conditions (Scheme 32).⁴⁵ The flexibility of a long saturated chain

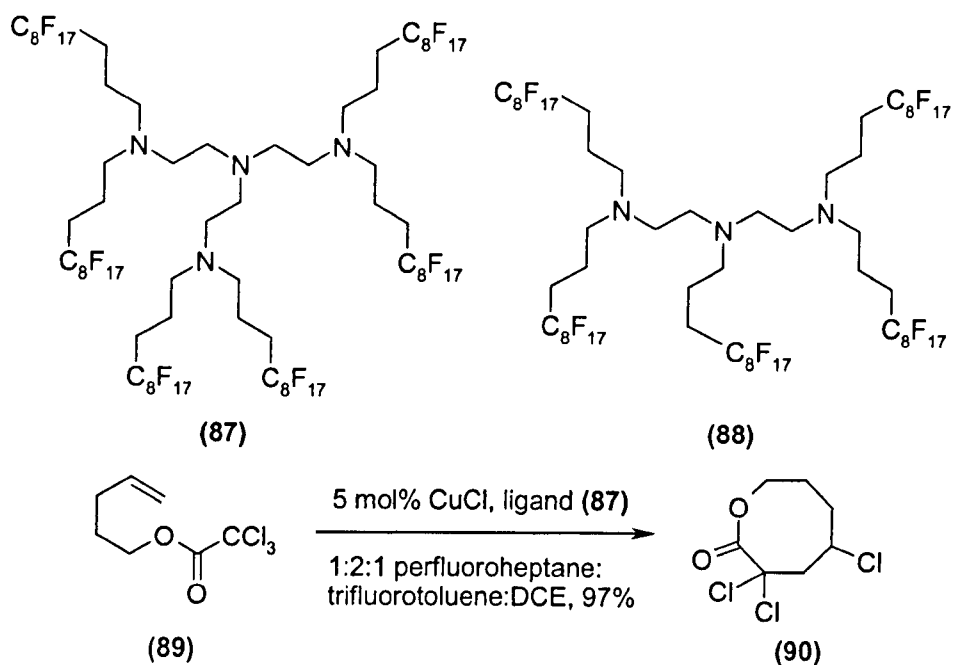
probably favours intermolecular addition (and telomerisation) over intramolecular reaction *via* entropy effects.



Scheme 32

Verlhac has discovered that the use of multidentate pyridine ligands such as TPA (58) facilitates the cyclisation of larger sized lactones with reduced amounts of copper (I) catalyst (Schemes 23 and 32).³² Acetate (86) was found to undergo lactonisation (70% conversion) using 10 mol% CuCl/TPA in 0.1 M DCE at reflux.³² A range of crown ethers (18-*endo* cyclisation)³³ and δ -lactams (6-*exo* cyclisation)²⁰ have also been prepared by the cyclisation of trichloro radical precursors using this catalytic system.

Perfluorinated analogues of Me₆-tren (43) and PMDETA (42) (ligands (87) and (88) respectively) have been used in conjunction with copper (I) chloride to effect the 8-*endo* macrocyclisation of trichloroacetate (89) to give 8-membered lactone (90) (Figure 2, Scheme 33).⁴⁶ The rate and yield of the reaction was found to be greatest with ligand (87). Although cyclisation with ligand (88) was slower and lower yielding than with the related non-fluorinated ligand PMDETA (42), the CuCl/(88) catalyst offers the advantage of recyclability by extraction with perfluorocyclohexane and a simple decantation of the perfluorous layer.



Scheme 33

1.7 SUMMARY

The last twenty years has seen the discovery and development of copper (I) ligand complexes which effect the radical cyclisation of unsaturated α -halo esters and amides. A range of mono- and bicyclic heterocyclic derivatives of varying ring size have been prepared efficiently from the α -carbamoyl radicals which are generated by halogen atom transfer to the copper (I) catalyst. The mode and rate of cyclisation have been found to be dependent on; the spacing of the α -carbamoyl radical from the radical acceptor, the nature of the groups attached to the α -carbon, the substitution pattern of the unsaturated bond, the ligand additive, the nitrogen protecting group (α -halo amides), solvent used and temperature employed. The use of copper (I) complexes to generate radicals has several advantages over other radical initiation methods making it attractive to industrial scale synthesis. Opportunities still exist to explore the cyclisation of novel radical precursors and to develop even more active catalytic systems to increase the structural variety and usefulness of heterocycles prepared by copper (I) mediated atom transfer radical cyclisation.

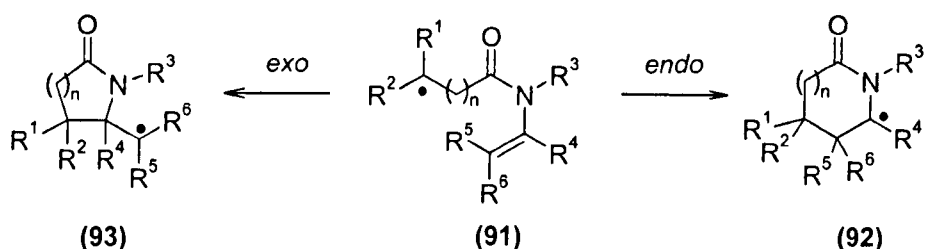
2. COPPER (I) MEDIATED CYCLISATION OF α -HALO DIENAMIDES

DERIVED FROM α,β -UNSATURATED KETONES

2.1 RADICAL CYCLISATION OF ENAMIDES

2.1.1 Introduction

The last decade has seen the development of radical cyclisation procedures which involve the carbon – carbon double bond of an enamide as a radical acceptor (Scheme 34). In these reactions, cyclisation of initial radical (91) can occur either in the “disfavoured” *endo* mode to give the thermodynamic product (92), or in the geometrically more favoured *exo* mode to give the kinetic product (93).



A broad range of methods have been used to generate the initial radical (91) which can cyclise onto the enamide double bond. The most widely used method involves treatment of a halo enamide, or other functionalised enamide, with tributyltin hydride and a radical initiator. α -Halo enamides (94),⁴⁷⁻⁴⁹ β -halo enamides (95),⁵⁰⁻⁵³ γ -halo enamides (96),⁵⁴ halo enamides (97),⁵⁵⁻⁵⁹ halo enamides (98),⁶⁰⁻⁶¹ enamide seleno ester (99)⁶² and α,β -unsaturated enamide (100)⁶³ have all been cyclised using tributyltin hydride (Figure 3).

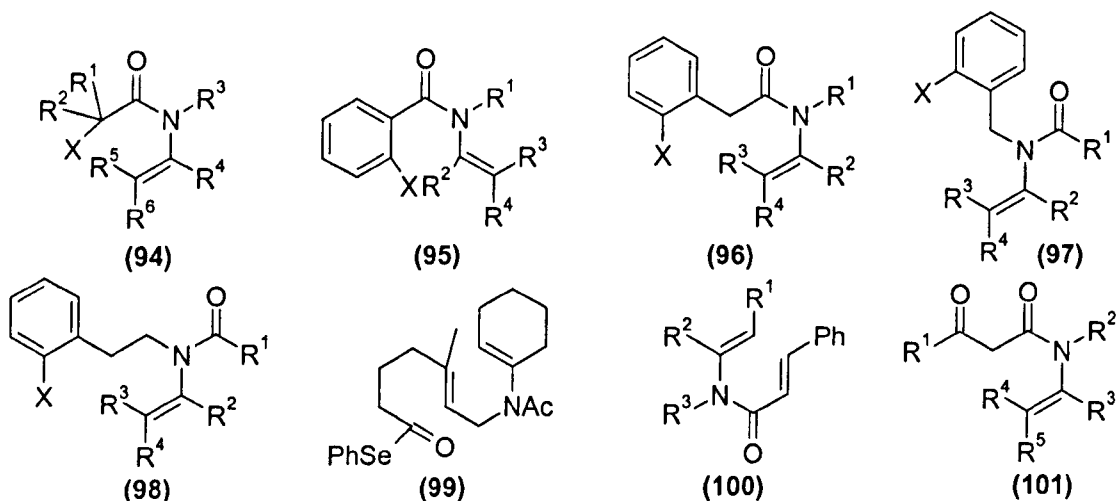
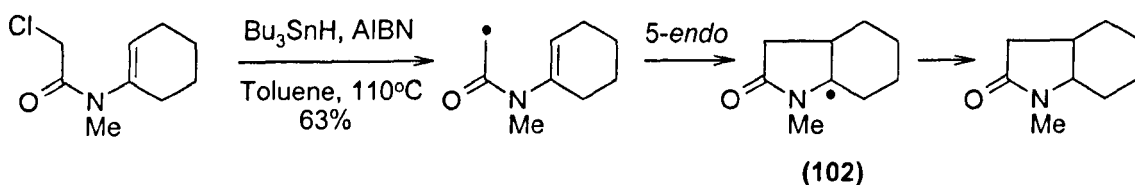


Figure 3

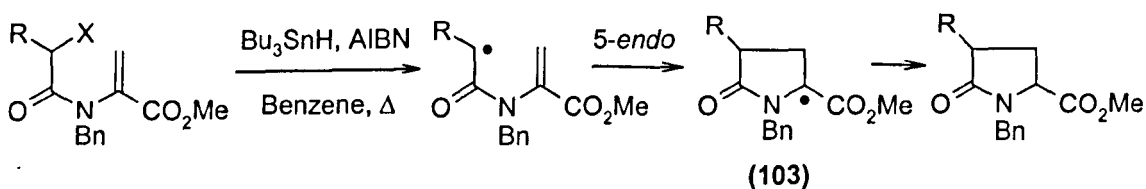
α -Halo enamides (**94**) may also be treated with copper (I) salts,^{25,36-38,40,64} ruthenium (II) complexes³⁷ or nickel⁶⁵ to generate the initial radical by an atom transfer process. Oxidative methods for radical generation have also been developed and involve treatment of β -keto enamides (**101**) with manganese (III)^{39,66-70} or cerium (IV)⁷¹⁻⁷² salts (Figure 3).

2.1.2 *Endo* Cyclisation of Enamides

The presence of radical stabilising groups on the olefinic carbon adjacent to the enamide nitrogen is crucial for the *endo* mode of cyclisation. Enamides with alkyl or aryl substituents on this carbon form tertiary radicals such as (**102**) which are stabilised by three electron donating groups (Scheme 35)⁷³⁻⁷⁵ and those with carbonyl substituents form captodatively stabilised radicals such as (**103**) on radical cyclisation (Scheme 36).⁷⁶⁻⁷⁷

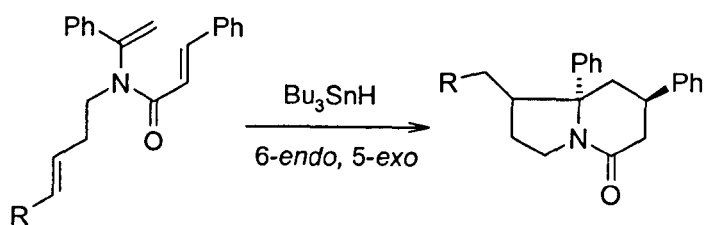


Scheme 35



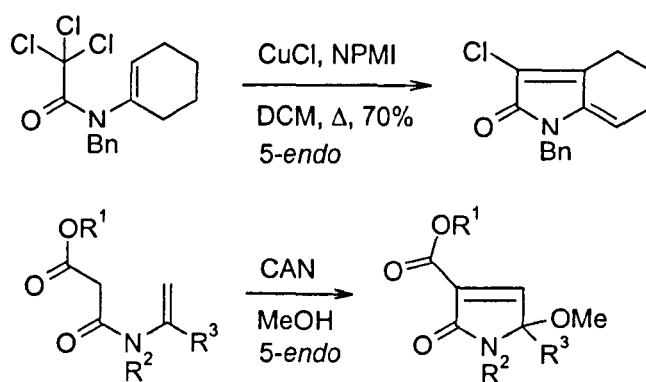
Scheme 36

Endo cyclisation is also promoted if the radical generated on cyclisation can be trapped intra- or inter-molecularly to form new carbon – carbon bonds in tandem reactions (Scheme 37).^{48,63}



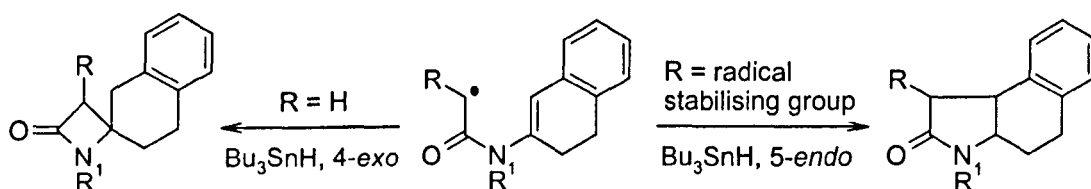
Scheme 37

Alternatively, these intermediate radicals can be oxidised to *N*-acyliminium ions, which can undergo deprotonation²⁵ or reaction with a range of nucleophiles (Scheme 38).⁷²



Scheme 38

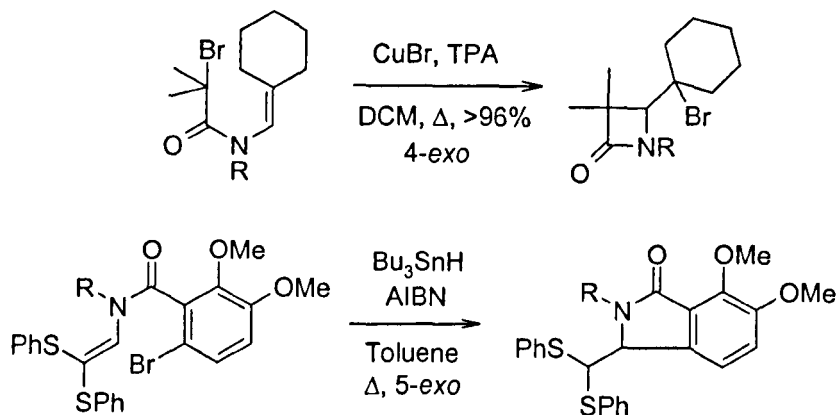
The introduction of radical stabilising groups at the position where the initial radical is generated can also facilitate a reversible *exo* cyclisation promoting the formation of the thermodynamic *endo* product (Scheme 39).⁷⁸



Scheme 39

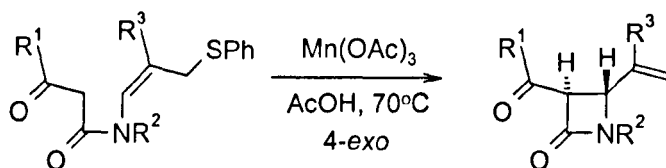
2.1.3 Exo Cyclisation of Enamides

Substitution of the enamide double bond at the β position with bulky, radical stabilising groups (such as *bis* alkyl, aryl or thiophenyl) favours the *exo* mode of cyclisation (Scheme 40).^{36,51}



Scheme 40

Exo cyclisation is also promoted if the radical generated on cyclisation can react with a radical trap, is oxidised and reacted further with a nucleophile,⁷¹ or undergoes a β -fragmentation (Scheme 41).⁶⁸



Scheme 41

2.2 RADICAL CYCLISATION OF α -HALO DIENAMIDES

The radical cyclisation of α -halo enamides (**94**) using tributyltin hydride, copper (I) salts, ruthenium (II) salts and nickel has been explored, and the factors determining *5-endo* versus *4-exo* cyclisation have been established (Sections 2.1.2 and 2.1.3).⁷⁹ α -Halo enamides have two possible modes of cyclisation available to them, and the substrate can

be modified to influence whether a β -lactam (4-*exo*) or γ -lactam (5-*endo*) is formed on cyclisation.

As a development of this research, we decided to explore the synthesis and radical cyclisation of α -halo dienamides (**104**) and (**105**) (Figure 4).

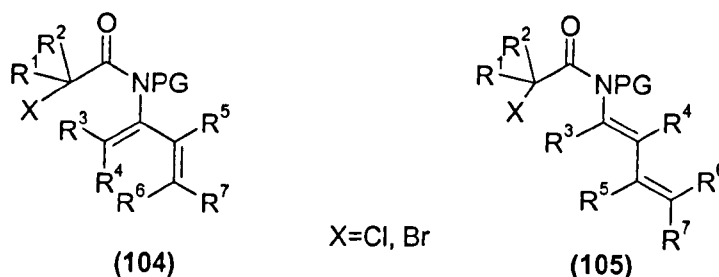


Figure 4

α -Halo dienamides are novel structures with four possible modes of cyclisation available to them. Substrate (**104**) for example, which is substituted at the 2-position of the diene, could potentially undergo 4-*exo*, 5-*endo*, 5-*exo* or 6-*endo* cyclisation. Substrate (**105**) in comparison, which is substituted at the 1-position of the diene, could undergo 4-*exo*, 5-*endo*, 6-*exo* or 7-*endo* cyclisation. Whilst it was unclear to us which would be the preferred mode of cyclisation in each case, we envisaged that a broad range of multifunctional heterocyclic building blocks might be prepared in an efficient manner from these radical precursors. In addition, we hoped to gain an understanding of the factors which determine the preferred cyclisation path for this class of substrate.

2.3 SYNTHETIC APPROACHES TO α -HALO DIENAMIDES

Three approaches to the synthesis of α -halo dienamides (**104**) were considered (Figure 5). Disconnection of the amide bond (**a**) suggests the acylation of an imine derived from an α,β -unsaturated ketone. α -Halo enamides have been routinely synthesised by the acylation of imines in the presence of a base such as pyridine,⁴⁷ *N,N*-diethylaniline,⁴⁸ or

triethylamine,²⁵ so we anticipated that this might be a successful route to our desired radical precursors (**104**).

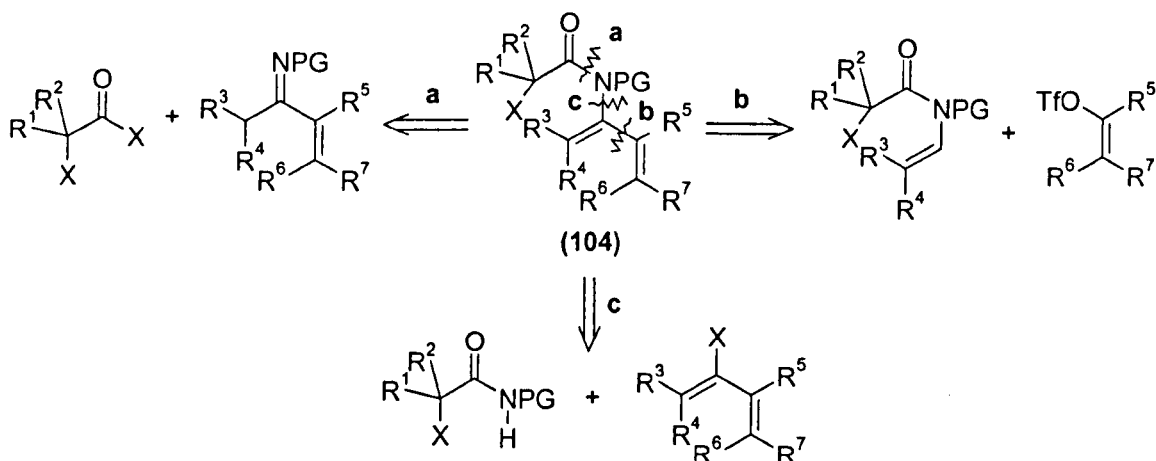
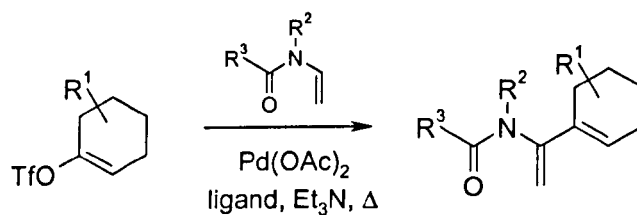


Figure 5

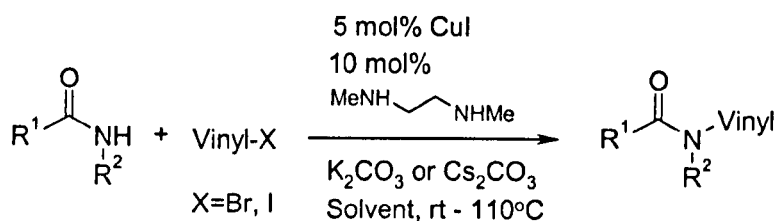
We were keen, however, to explore additional methods to synthesise this class of substrate to broaden the range of dienamides that could be prepared. Curran has recently reported ligand controlled Heck vinylations of enamides with high α -regioselectivity and moderate to good yields of dienamides (disconnection **b**).⁸⁰ He successfully coupled three vinyl triflates with three different *N*-alkylated enamides (Scheme 42). The enamides were reacted in excess with the vinyl triflates with catalytic palladium acetate, bidentate ligand and triethylamine in DMSO. Reactions were heated conventionally to 60-70°C overnight or in the microwave at 90°C for 30 minutes.



Scheme 42

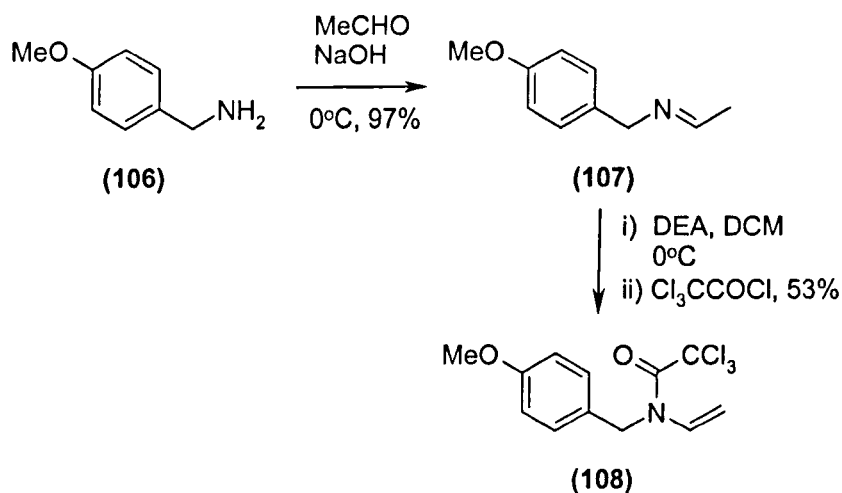
A third possible disconnection (**c**) was suggested by the recent work of Buchwald who has achieved copper catalysed amidation of vinyl bromides and iodides.⁸¹ His protocol uses a combination of catalytic copper (I) iodide and *N,N'*-dimethylethylenediamine

(Scheme 43). Amide substrates bearing ester, silyl ether and amino groups were successfully coupled and the double bond geometry of the vinyl halides was retained under the reaction conditions.



Scheme 43

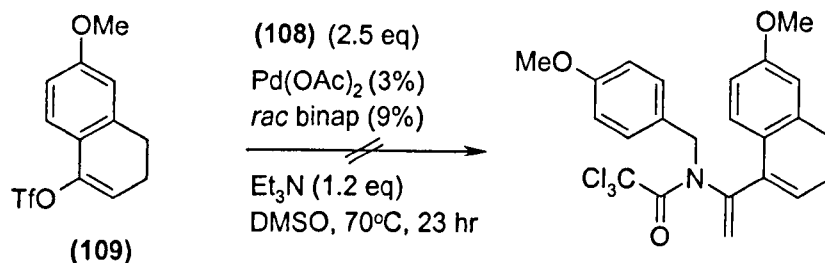
We first decided to attempt the Heck coupling (disconnection **b**) of *N*-vinyl trichloroacetamide (**108**) with the triflates used by Curran under his coupling conditions (Scheme 44). This enamide was synthesised by the condensation of acetaldehyde with 4-methoxybenzylamine (**106**) without solvent,⁸² followed by acylation of imine (**107**) with trichloroacetyl chloride in the presence of *N,N*-diethylaniline. It was found to be essential to conduct the acylation reaction under very dry conditions to avoid significant formation of 2,2,2-trichloro-*N*-(4-methoxy-benzyl)-acetamide. At best, the enamide (**108**) was isolated in 53% yield with 25% conversion to the amide byproduct.



Scheme 44

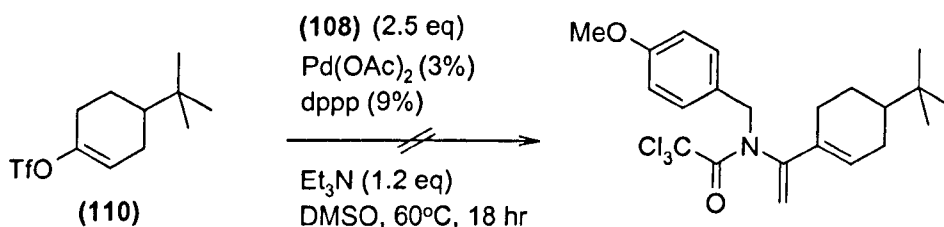
An initial attempt to couple trichloro enamide (**108**) with triflate (**109**)⁸³ using racemic binap as the ligand proved unsuccessful (Scheme 45). After 23 hours at 70°C only

starting materials were recovered together with 2,2-dichloro-*N*-(4-methoxybenzyl)-*N*-vinylacetamide in which the C-Cl bond of the starting material had been reduced, and 2,2,2-trichloro-*N*-vinyl-acetamide in which the 4-methoxybenzyl group had been lost.



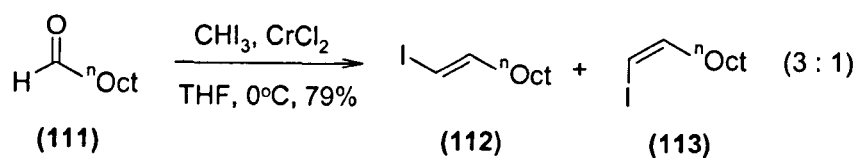
Scheme 45

Similarly, reaction of enamide **(108)** with another of Curran's triflates **(110)**,⁸⁴ this time using dppp as the ligand, gave only recovered starting materials and the previously obtained 2,2-dichloro-*N*-(4-methoxybenzyl)-*N*-vinylacetamide (Scheme 46).



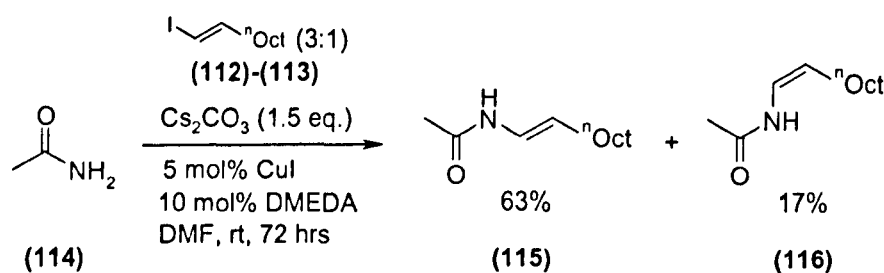
Scheme 46

We next evaluated the copper (I) catalysed amidation approach used by Buchwald (disconnection **c**). Included in Buchwald's results is the successful coupling of acetamide with both *E*- and *Z*-1-iodo-dec-1-ene.⁸¹ In order to evaluate this strategy for the synthesis of α -halo dienamides, we first decided to investigate the coupling of trichloroacetamide with the same vinyl iodides. A 3:1 mixture of *E*- and *Z*-1-iodo-dec-1-ene (**112-113**) was made in good yield from nonyl aldehyde (**111**) using chromium (II) chloride and iodoform (Scheme 47).⁸⁵



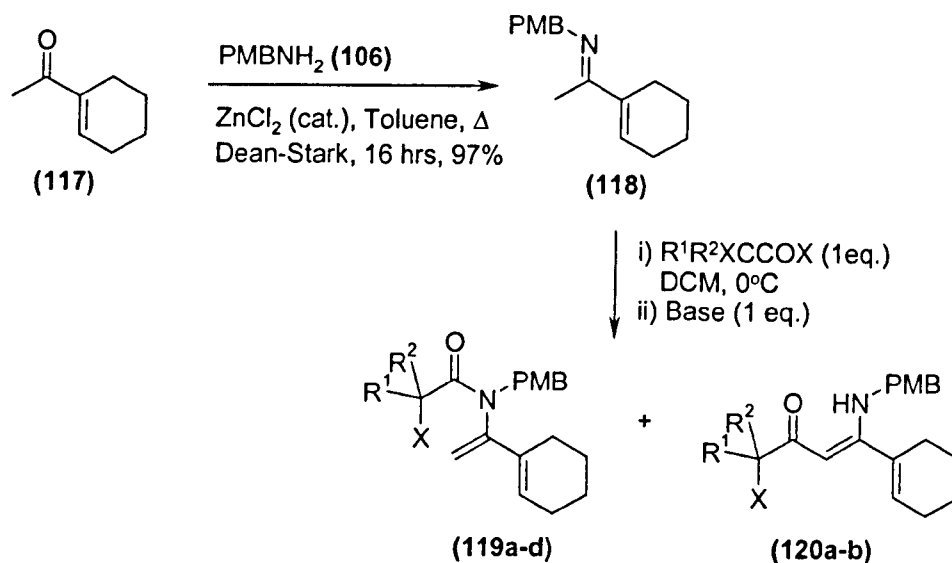
Scheme 47

To verify Buchwald's results, this mixture of vinyl iodides was reacted with acetamide (**114**) following his protocol. The two separable enamides (**115**) and (**116**) were formed in excellent yield confirming his result (Scheme 48). When the reaction was repeated with trichloroacetamide, however, only starting materials were recovered from the reaction mixture, both at room temperature and on heating.



Scheme 48

Keen to achieve the synthesis of a number of α -halo dienamides as quickly as possible, we decided to explore the acylation of α,β -unsaturated imines (disconnection **a**, Figure 5). The first α -halo dienamide substrates were successfully synthesised in two steps from 1-acetyl-1-cyclohexene (**117**) (Scheme 49). Initial benzyl imine formation from the α,β -unsaturated ketone was achieved by refluxing a 1:1 mixture of 4-methoxybenzylamine (**106**) and ketone (**117**) with catalytic zinc chloride in toluene with a Dean-Stark trap. Absence of any catalyst, or use of catalytic *p*TSA gave only starting materials after 1 day. The crude imine (**118**) was then treated with 1 equivalent of acid halide and 1 equivalent of base. Depending on the acid halide used, either the N-acylated compound (**119**) or a mixture of (**119**) and the C-acylated compound (**120**) were isolated from the reaction mixture.



Scheme 49

The results for the acylation of imine (118) with four different acid halides are summarised in Table 4. Trichloroacetyl chloride gave the desired dienamide (119a) in 28% yield and also the C-acylated product (120a) in 18% yield, which could be separated by chromatography. A complex mixture of baseline material accounted for the rest of the mass balance for the reaction.

R ¹	R ²	X	Base	Yield (119) (%)	Yield (120) (%)
Cl	Cl	Cl	DEA	28 (119a)	18 (120a)
Me	Me	Br	DEA	< 5 (119b)	< 5 (120b)
Me	Me	Br	Et ₃ N	23 (119b)	23 (120b)
Me	H	Br	Et ₃ N	47 (119c)	0
Cl	Cl	H	Et ₃ N	40 (119d)	0

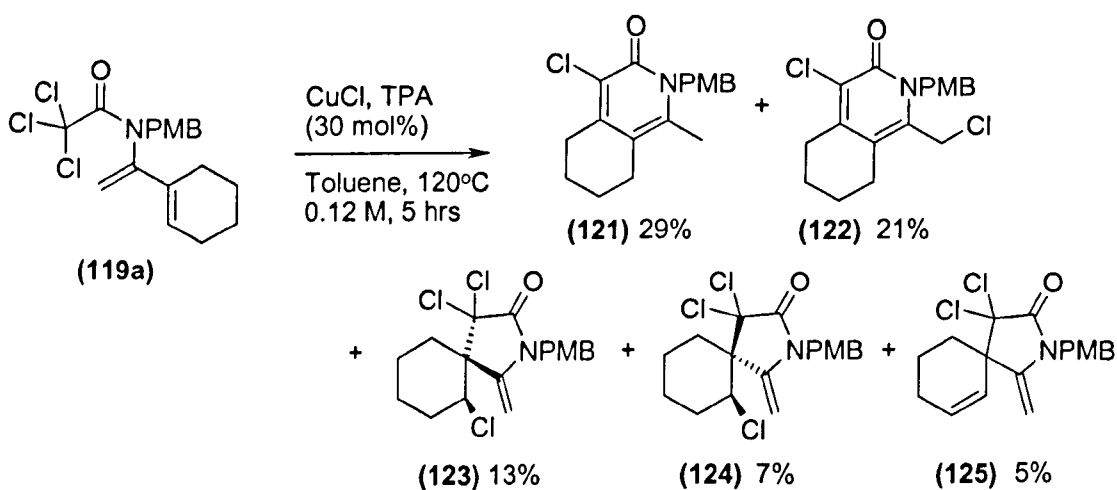
Table 4

2-Bromoisobutyryl bromide in comparison gave an inseparable 1:1 mixture of both N- and C-acylated products, (119b) and (120b) respectively, in extremely low yield using *N,N*-diethylaniline as the base. The yield of each product was found to be increased to 23% by use of the stronger base triethylamine. 2-Bromopropionyl bromide and

dichloroacetyl chloride gave the desired *N*-acylated products (**119c**) and (**119d**) exclusively in modest yield.

2.4 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM 1-ACETYL-1-CYCLOHEXENE

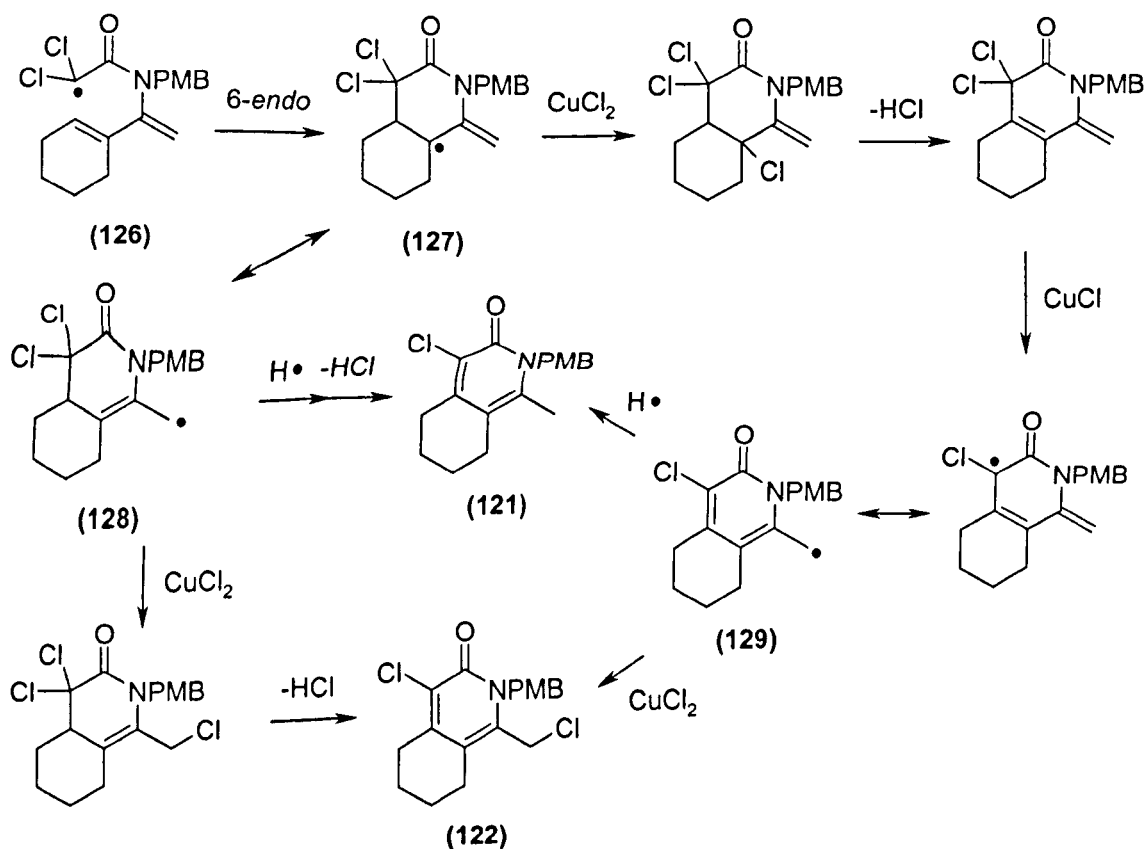
The trichloro dienamide radical precursor (**119a**) was treated with 30 mol% copper (I) chloride and TPA in refluxing toluene (no reaction was observed to take place at room temperature) (Scheme 50). All starting material was found to be consumed after 5 hours and five products (**121**)-(**125**) were isolated from the reaction mixture and characterised. Repeated chromatography (including preparative tlc) was necessary to obtain each of the products in pure form.



Scheme 50

Tetrahydroisoquinolinones (**121**) and (**122**) arise from 6-*endo* cyclisation and the remaining three spirocyclic products (**123**)-(**125**) arise from 5-*exo* cyclisation. Isomer (**123**) was found to predominate over isomer (**124**), however eliminated product (**125**) is probably derived from isomer (**124**). Overall the 6-*endo* mode of cyclisation was found to be preferred over the 5-*exo* mode and no products due to 4-*exo* or 5-*endo* cyclisation were observed. Scheme 51 summarises a possible mechanism for the formation of the

two tetrahydroisoquinolinones (**121**) and (**122**). 6-*Endo* cyclisation of initial radical (**126**) gives a stabilised tertiary allyl radical (**127**) whose resonance structure is (**128**). A chlorine radical may then be captured at either the tertiary or primary carbon positions from copper (II) chloride. If it is captured at the primary position a simple HCl elimination forms observed product (**122**). If it is captured at the tertiary position, elimination of HCl followed by further radical generation with copper (I) chloride eventually leads to same product (**122**). Tetrahydroisoquinolinone (**121**) presumably forms by reduction with a hydrogen atom of either primary radical (**128**) or (**129**), and since (**121**) predominates over (**122**) reduction is evidently more facile than chlorine atom transfer.



Scheme 51

NMR experiments have shown that the major 5-*exo* isomer (**123**) exists as a single conformer in CDCl_3 in which all the bulky groups adopt an equatorial position on the cyclohexane ring (Figure 6). ^1H - ^1H coupling constants of 11.6 Hz and 4.3 Hz for the

double doublet at 4.25 ppm confirm that the hydrogen on the carbon atom bonded to the chlorine (H_{1a}) adopts an axial position. No nOe exists between this axial proton H_{1a} and the olefinic protons, but a nOe does exist between one of the olefinic protons and H_{2a} and H_{4a} , and between H_{1a} and H_{2e} , H_{3a} and H_{5a} . The 1H NMR of the minor isomer (**124**) was found to be extremely broad in $CDCl_3$ and several signals in the ^{13}C NMR were too broad to be seen. By carrying out the NMR spectra of (**124**) in d_8 -toluene at 343K, exchange between the two conformers becomes rapid on the NMR timescale and sharper spectra are seen. The signal in the 1H NMR due to H_1 shows average coupling constants of 8.5 Hz and 4.7 Hz. Low temperature 1H NMR experiments in d_8 -toluene indicate the two conformers due to slow interconversion on the NMR timescale.

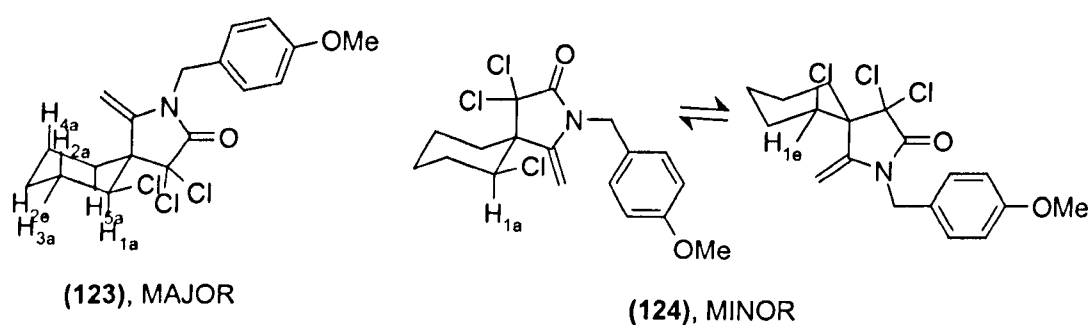
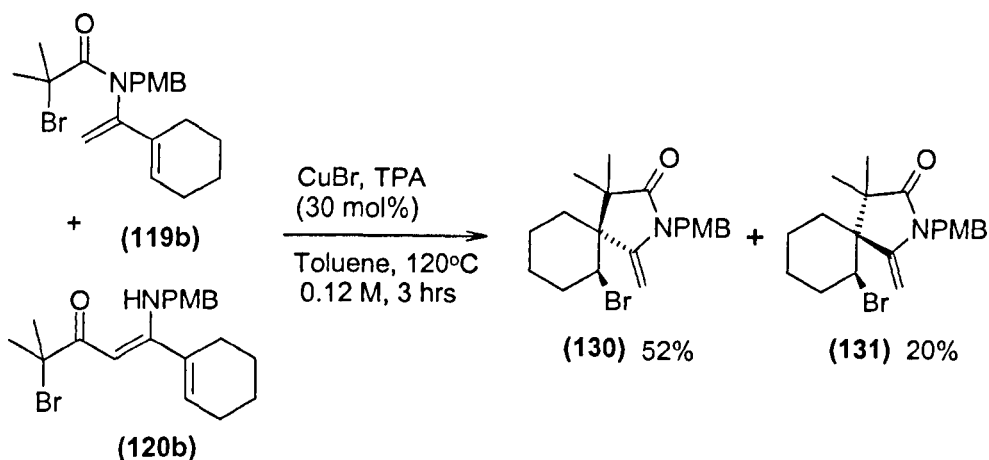


Figure 6

Next we turned our attention to the cyclisation of analogous compound (**119b**). Since the acylated products (**119b**) and (**120b**) could not be separated by chromatography, the 1:1 mixture of compounds was treated with catalytic copper (I) bromide and TPA (30 mol%) in refluxing toluene (Scheme 52). We hoped that the C-acylated compound (**120b**) would not cyclise or react intermolecularly with the N-acylated substrate (**119b**), and that all new products would be derived from dienamide (**119b**). Fortunately, this was found to be the case. After 3 hours, all radical precursor (**119b**) had reacted to form 5-*exo* cyclisation products (**130**) and (**131**) exclusively in a 2.6:1 ratio and overall yield of 72%. Pure unreacted C-acylated compound (**120b**) was isolated from the reaction mixture and fully characterised. Unlike in the cyclisation of the trichloro dienamide (**119a**), the predominant stereoisomer (**130**) was found to have the two most sterically demanding groups arranged *cis* to one another on the cyclohexane ring. No products due to 6-*endo* cyclisation were

observed, presumably due to the inability of this precursor to form a thermodynamically stable aromatic product.



Scheme 52

This time the major 5-*exo* isomer (**130**) was found to have extremely broad signals in its NMR spectra at room temperature in CDCl₃, presumably due to the slow interconversion of the two conformers on the NMR timescale (Figure 7). When the NMR spectra were carried out in d₈-toluene at 343K, however, the signals were seen to sharpen as interconversion of the conformers became fast on the NMR timescale. As for (**124**), low temperature ¹H NMR experiments in d₈-toluene indicated both conformers of (**130**). The minor isomer (**131**) was found to exist as a single conformer at room temperature in CDCl₃ in which the bromine and CMe₂ groups adopt an equatorial position on the cyclohexane ring. ¹H-¹H coupling constants of 11.6 Hz and 4.3 Hz for the double doublet at 4.24 ppm confirm that the hydrogen on the carbon atom bonded to the bromine (H_{1a}) adopts an axial position. No nOe exists between this axial proton (H_{1a}) and the olefinic protons, but a nOe does exist between one of the olefinic protons and H_{2a} and H_{4a}, and between H_{1a} and H_{2e}, H_{3a}, H_{5a} and Me_a.

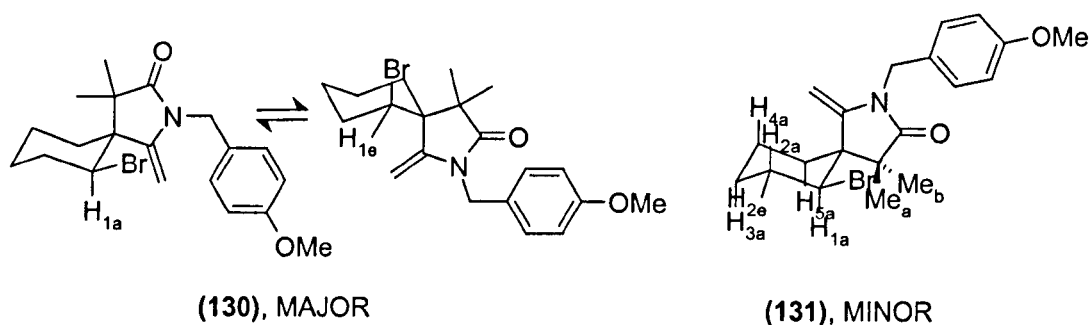
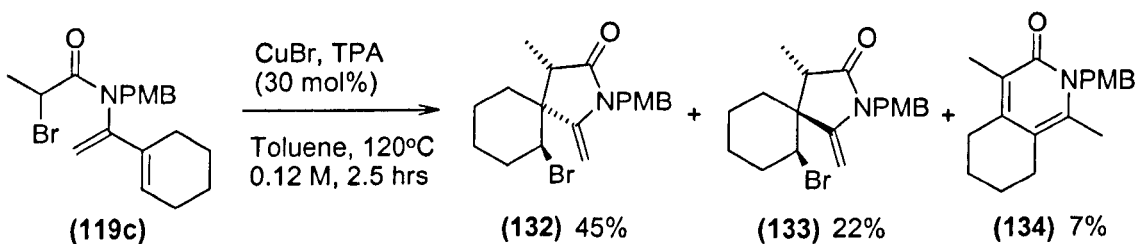


Figure 7

We next investigated the radical cyclisation of bromo dienamide (**119c**) under the same conditions. 5-*Exo* cyclisation was found to predominate to give two of four possible diastereoisomeric γ -lactams (**132**) and (**133**) in a 2:1 ratio and an overall yield of 67% (Scheme 53). Unlike in the cyclisation of (**119b**), some 6-*endo* cyclisation was also observed; tetrahydroisoquinolinone (**134**) was formed in 7% yield. The ratio of 5-*exo* to 6-*endo* products was found to be 9.6:1.



Scheme 53

NMR experiments, including nOe measurements, confirmed that both (**132**) and (**133**) exist as single conformers in CDCl₃ at room temperature with the stereochemistry shown in Figure 8.

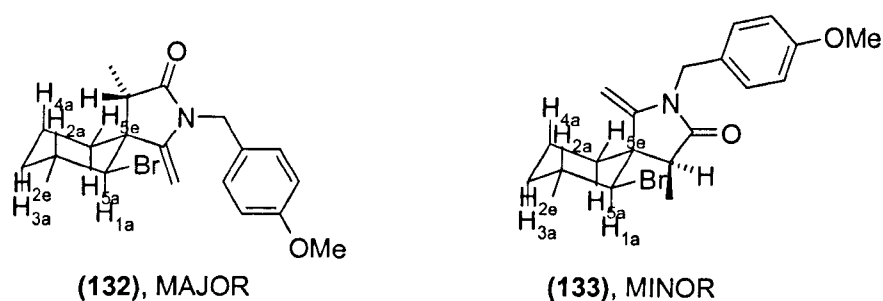
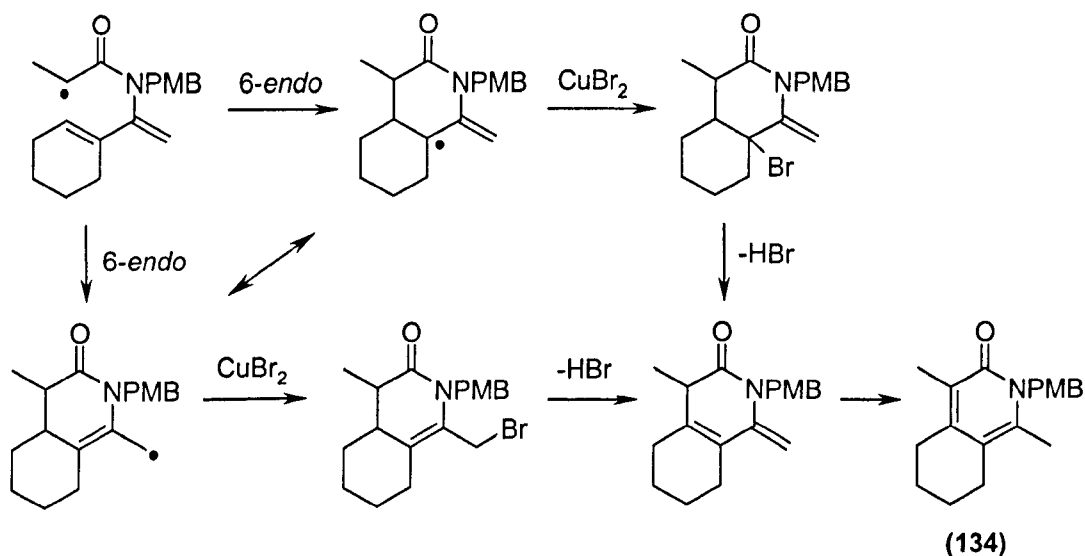


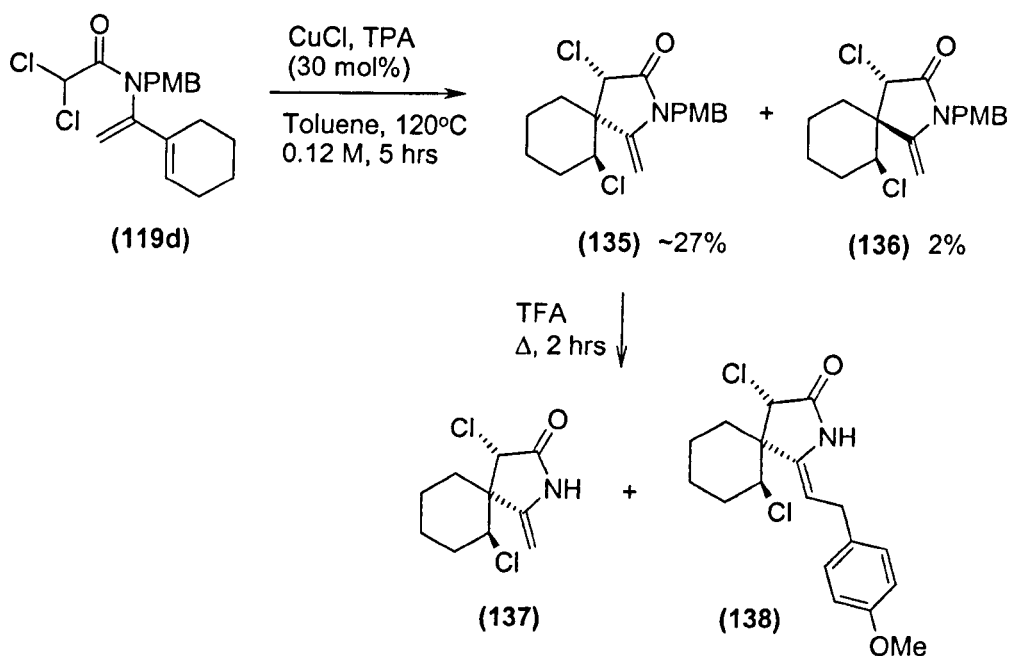
Figure 8

Scheme 54 outlines a possible mechanism for the formation of tetrahydroisoquinolinone (**134**) which has obvious analogy with that proposed for the formation of (**121**) and (**122**) from trichloro dienamide (**119a**) (Scheme 51). Unlike in the cyclisation of (**119a**), there was no evidence for the reduction of intermediate radicals.



Scheme 54

Cyclisation of dichloro dienamide (**119d**) was found to be much slower than the cyclisation of (**119a-c**). After 5 hours in refluxing toluene with 30 mol% CuCl and TPA, considerable starting material was still present (Scheme 55). One major 5-*exo* product (**135**) was formed in low yield together with a few minor products which proved hard to obtain pure by flash column chromatography. One of these, believed to have the structure (**136**) was isolated in 2% yield.



Scheme 55

The stereochemistry of (135), and its existence as a single conformer in CDCl_3 at room temperature, was confirmed by NMR experiments. Similar experiments provided reasonable evidence that minor product (136) possessed the same stereochemistry as the minor product (133) from the cyclisation of (119c) (Scheme 53). The structure of (136) has been tentatively assigned since H_{1a} has a smaller diaxial coupling constant than the brominated product (133) (9.6 Hz c.f. 12.3 Hz). In addition, when (136) was left in a vial for a period of a few weeks, conversion to a compound believed to be hydrate (139) was observed which does not occur with analogous compound (133) (Figure 9). Full characterisation of (139) proved problematic since it converted back to (136) in CDCl_3 within 24 hours.

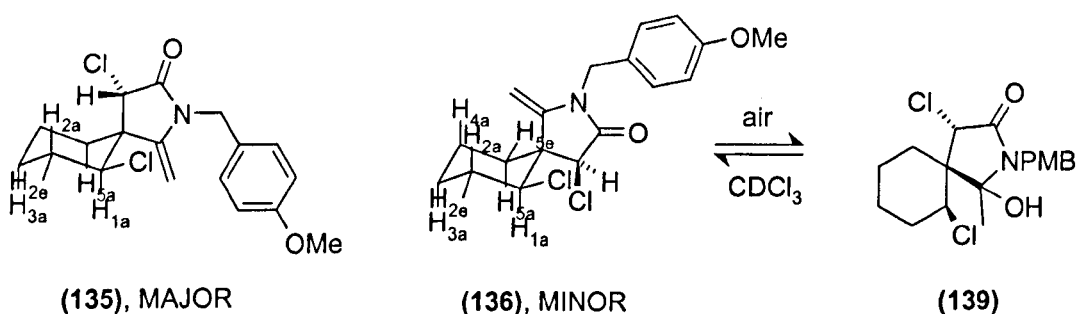
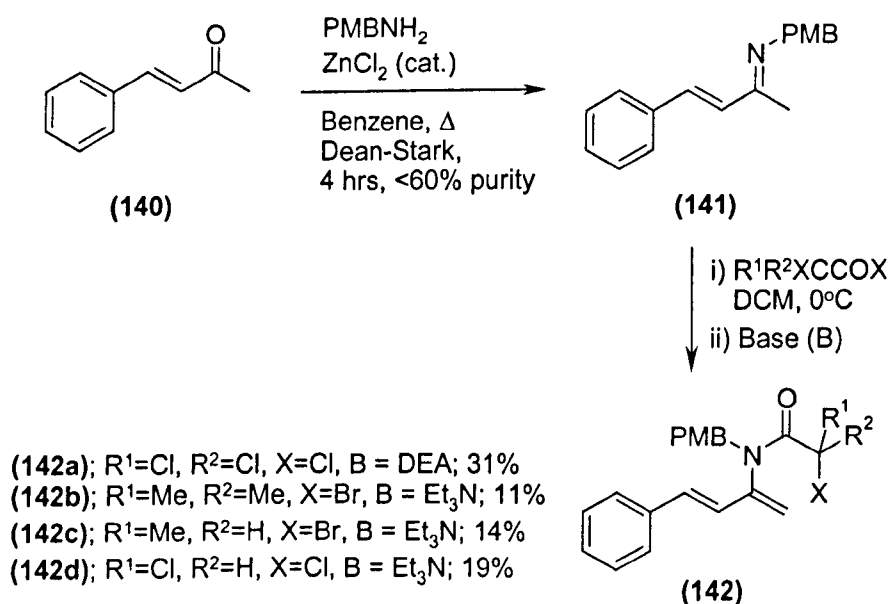


Figure 9

Interestingly, an attempt to deprotect the 4-methoxybenzyl amide of major product (**135**) using TFA at reflux gave an inseparable 1:1 mixture of desired γ -lactam (**137**) and product (**138**) in which the benzyl group has migrated onto the olefin (Scheme 55).

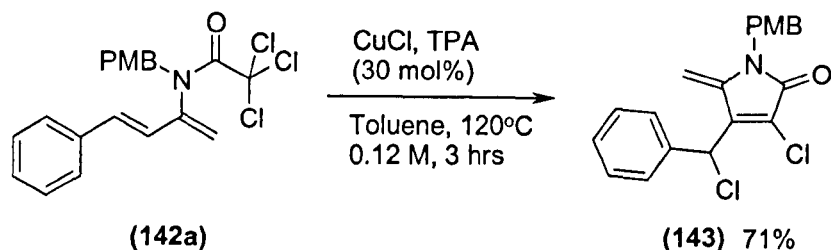
2.5 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM *TRANS*-4-PHENYL-3-BUT-2-ONE

The next α -halo dienamide systems to be investigated were those derived from *trans*-4-phenyl-3-but-2-one (**140**) (Scheme 56). Optimum conditions for imine formation were found to be heating a 1:1 mixture of the ketone and amine in benzene with catalytic zinc chloride for 4 hours.⁸⁶ Use of the higher boiling solvent toluene gave a complex mixture of products which lacked olefinic protons, as did heating in benzene for a period longer than 4 hours. The crude imine (**141**) used in the next acylation steps was found to be less than 60% pure by ¹H NMR which partly accounts for the low yields of the four dienamides (**142a-d**) which were obtained. As previously encountered in the synthesis of (**119a-d**), considerable brown baseline material of no interest was generated in the reaction.



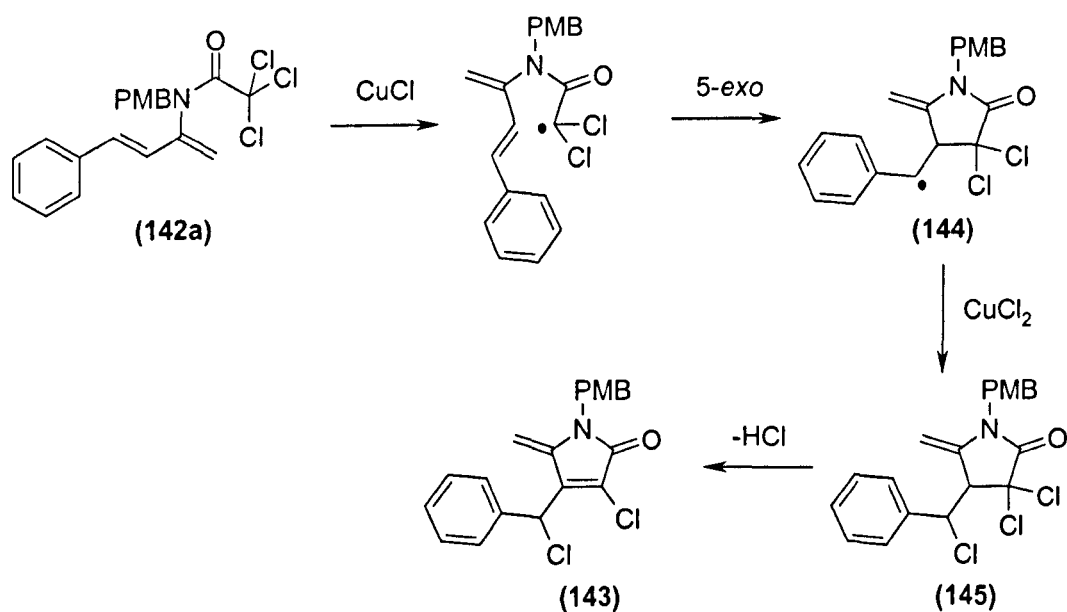
Scheme 56

Satisfyingly, the trichloro dienamide radical precursor (**142a**) was found to convert to a single cyclisation product (**143**) in good yield when treated with catalytic copper (I) chloride and TPA in refluxing toluene (Scheme 57).



Scheme 57

This γ -lactam is formed by 5-*exo* cyclisation followed by elimination of HCl. The stability of the intermediate benzyl radical (**144**) and formation of a thermodynamically stable heterocycle must promote this mode of cyclisation (Scheme 58). Compared with the dienamide system discussed in Section 2.4, 6-*endo* cyclisation is not as favoured because a secondary allyl radical would be formed which is less stable than a tertiary allyl radical. The cyclisation of (**142a**) using novel solid supported catalysts is discussed in Chapter 5, Section 5.4.11.



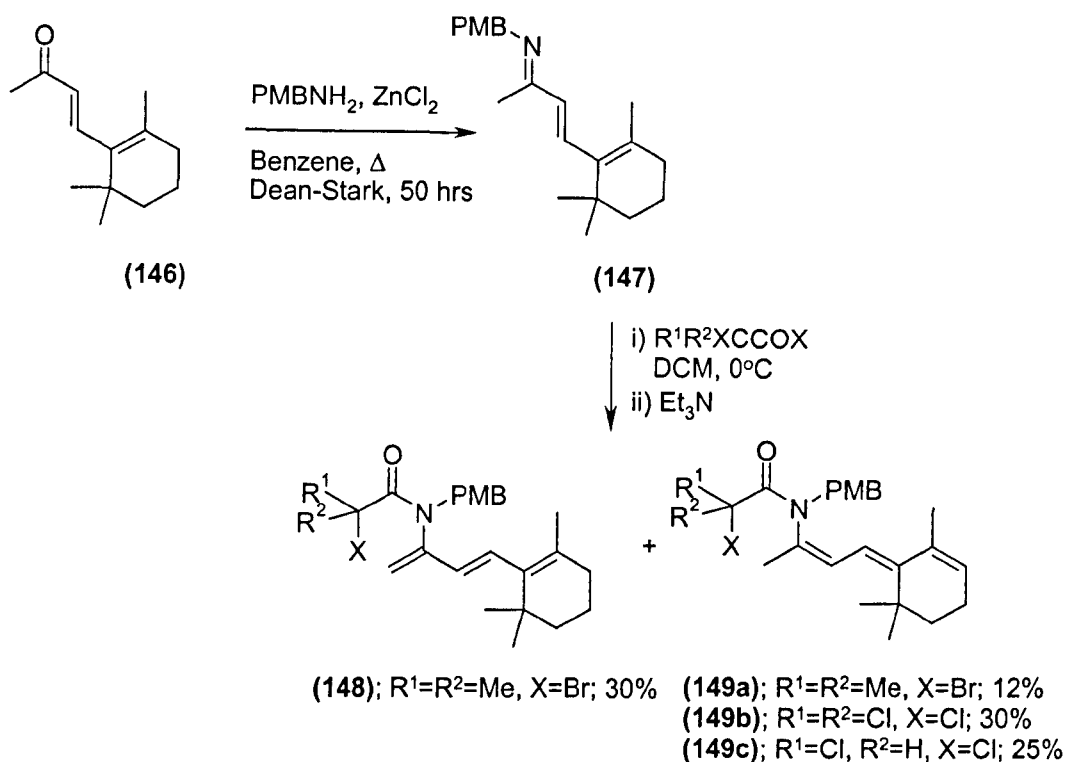
Scheme 58

Treatment of α -bromo dienamide (**142b**) with 30 mol% copper (I) bromide/TPA in refluxing toluene gave an inseparable complex mixture of products with no starting material after 3 hours. The majority of this product mixture was baseline on tlc suggesting that oligomerisation had occurred. Surprisingly, the two remaining dienamide radical precursors (**142c**) and (**142d**) failed to cyclise at all when subjected to the same ATRC conditions over 4 days.

2.6 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM β -IONONE

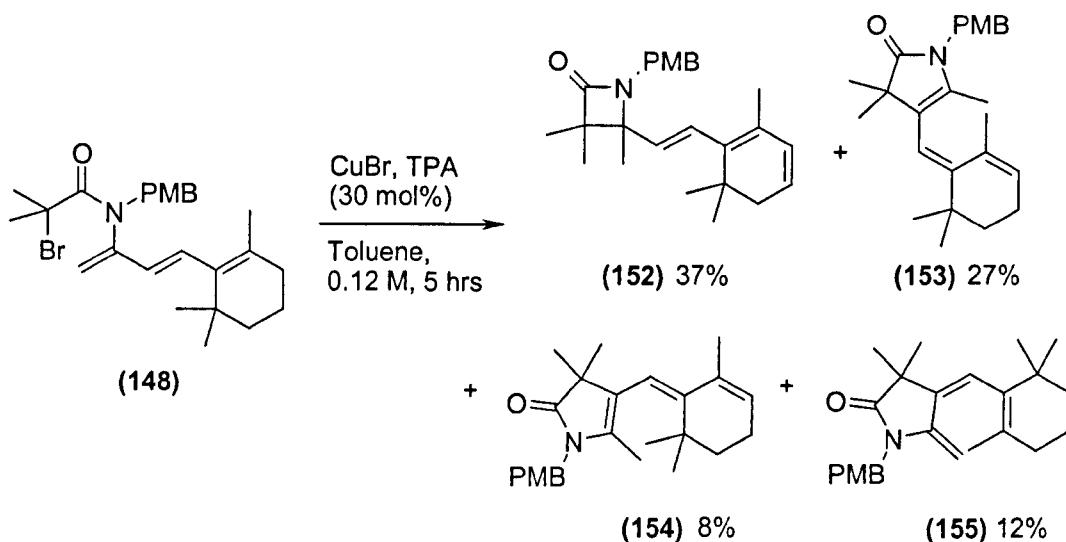
The final class of radical precursor to be prepared from an α,β -unsaturated ketone were the α -halo trienamides (**148**) and (**149a-c**) shown in Scheme 59. The presence of an extra double bond in these substrates provides additional cyclisation possibilities when subjected to copper (I) catalysis. Imine formation of highly conjugated β -ionone (**146**) with 4-methoxybenzylamine required refluxing in benzene with catalytic zinc chloride with a Dean-Stark trap for a total period of 2 days to achieve reaction completion. Carrying out the reaction at a higher temperature (refluxing toluene) in order to reduce the reaction time was unsuccessful.

Acylation of imine (**147**) with trichloroacetyl chloride was found to give tautomer (**149b**) exclusively as a single stereoisomer in 30% overall yield (Scheme 59). Reaction with 2-bromoisobutyryl bromide, in comparison, gave both tautomers (**148**) and (**149a**) in which the amide group is located at the 2- and 1-positions of the triene respectively. Finally, acylation with dichloroacetyl chloride gave three isomers of tautomer (**149c**); one major and two minor isomers. In all three cases, it was found to be essential to ensure that no β -ionone was present in the crude imine prior to acylation since this co-ran with many of the α -halo trienamide products upon silica tlc.



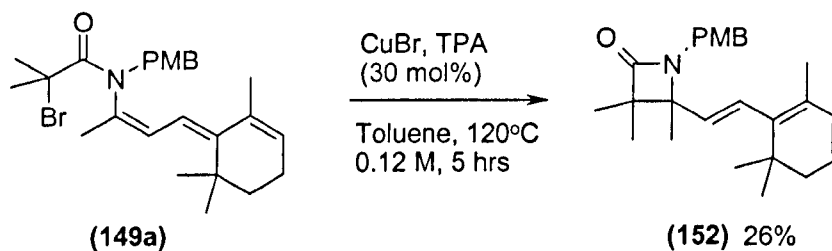
Scheme 59

Surprisingly, the major product of copper (I) catalysed cyclisation of bromo trienamides (148) was found to be β -lactam (152) which was isolated in 37% yield (Scheme 60). Presumably tautomer (149a), which must form under the basic reaction conditions, cyclises faster than (148). The remaining three products (153)-(155), all result from 5-*exo* cyclisation. NOe experiments confirmed the stereochemistry of these γ -lactams. Overall the ratio of 5-*exo* to 4-*exo* cyclisation was found to be 1.3:1. No evidence of 5-*endo*, 6-*endo*, 7-*exo* or 8-*endo* cyclisation was observed.



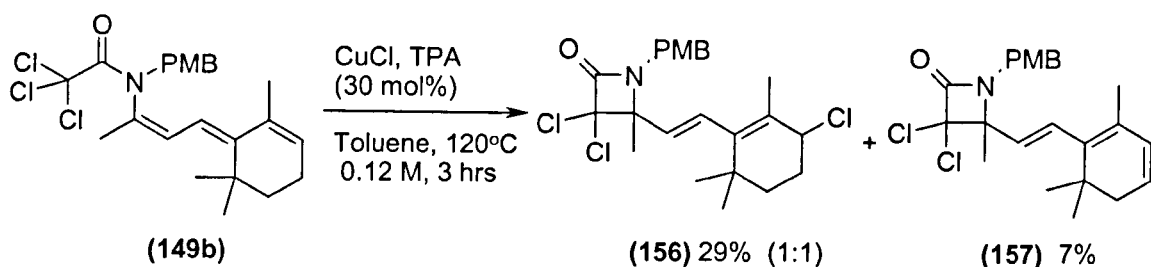
Scheme 60

As anticipated, the tautomeric bromo trienamamide (**149a**) was found to give exclusively β -lactam (**152**) by 4-*exo* cyclisation after 5 hours at reflux in toluene (Scheme 61). Considerable brown baseline material of no interest (presumably oligomeric products) was flushed from the column accounting for the particularly low yield of (**152**).



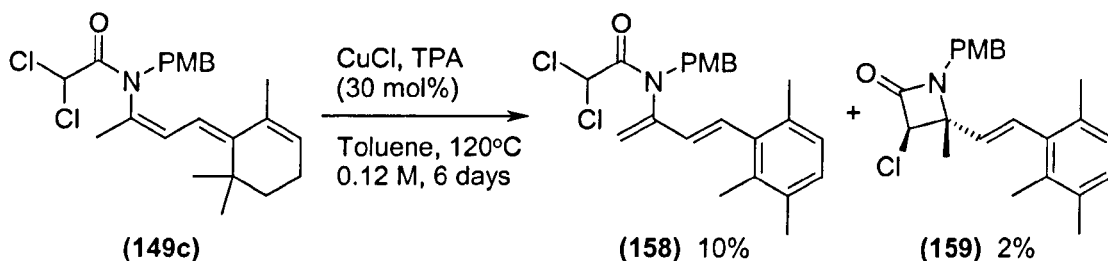
Scheme 61

Analogous trichloro trienamamide (**149b**) was also found to undergo 4-*exo* cyclisation when treated with catalytic copper (I) to give both allyl chloride (**156**) as a 1:1 mixture of diastereoisomers and elimination product (**157**) (Scheme 62).



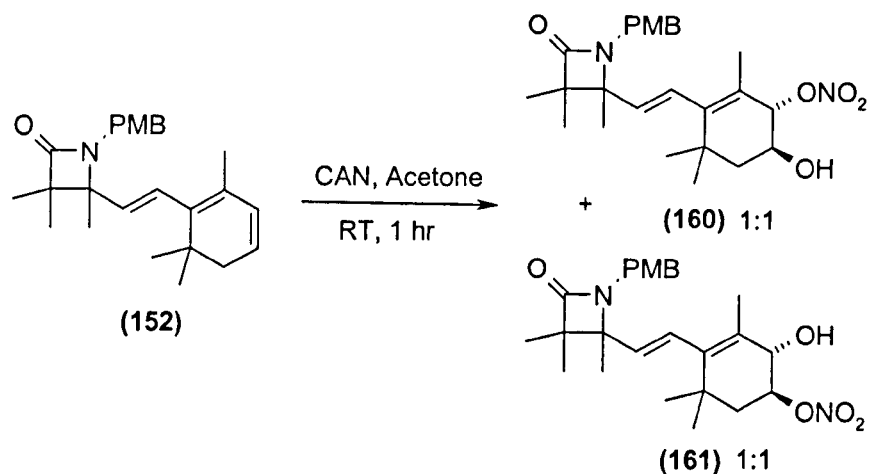
Scheme 62

Cyclisation of dichloro trienamamide **(149c)** was found to be exceedingly slow as encountered for **(119d)** (Schemes 63 and 55). After 8 hours at reflux only starting material was present by tlc. The reaction was left for 6 days, and after this period a complex mixture of products was obtained. Two aromatic products **(158)** and **(159)** were purified from the mixture. In these, oxidation of the cyclohexene ring and methyl migration has taken place. NOe experiments confirmed the stereochemistry of β -lactam **(159)**.



Scheme 63

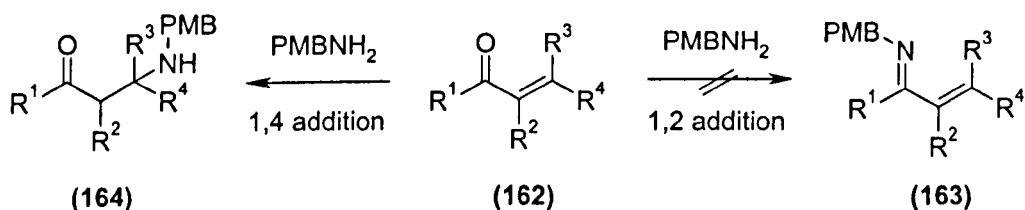
We were interested to see if we could remove the 4-methoxybenzyl group of β -lactam **(152)** to test the product for antibiotic activity (Scheme 64). Unfortunately both oxidative and acidic conditions proved unsuccessful. Treatment of **(152)** with ceric ammonium nitrate in acetone⁸⁷ at room temperature for 1 hour gave four compounds which are believed to be the hydroxy nitrates **(160)** and **(161)** in which the PMB group is still present.⁸⁸ The regiochemistry of each mixture could not be assigned conclusively. These are presumably formed by the diaxial ring opening of epoxides. Use of potassium persulfate⁸⁹ gave a mixture of uncharacterised material in which the PMB group was still attached but the double bonds had been oxidized, and trifluoroacetic acid⁹⁰ gave a complex mixture of products.



Scheme 64

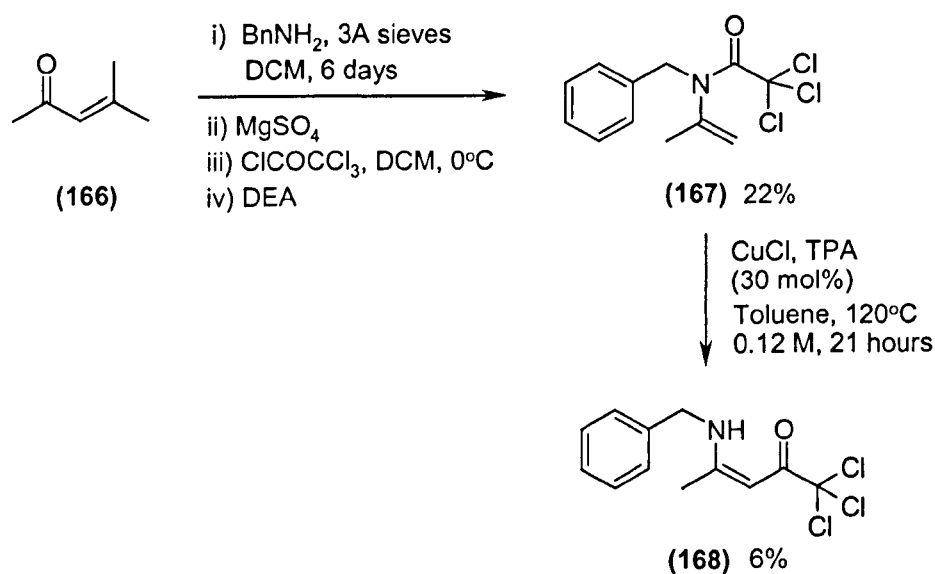
2.7 PROBLEMATIC α,β -UNSATURATED IMINE FORMATION

We were unable to prepare a broad range of α -halo dienamides from unsaturated ketones due to problems encountered in the formation of a number of unsaturated imines (**163**) (Scheme 65). There is extremely limited literature in this area, and it soon became clear why this was the case. When several α,β -unsaturated ketones were reacted with 4-methoxybenzylamine, complex mixtures of products were routinely obtained in which no olefinic signals were present in the crude ^1H NMR spectra. Heating a mixture of ketone and amine to reflux in either benzene or toluene with a Dean-Stark trap, with or without a Lewis acid, or combining the reagents at room temperature in the presence of molecular sieves or a drying agent were largely unsuccessful. In fact, the only unsaturated ketones which could be successfully transformed to the unsaturated imines were 1-acetyl-1-cyclohexene (**117**), *trans*-4-phenyl-3-but-2-one (**140**) and β -ionone (**146**), as discussed in Sections 2.4-2.6.



Scheme 65

Presumably imine formation (1,2 addition) is far slower in most cases than conjugate 1,4 addition to the unsaturated ketone (**162**) to form a β -amino ketone (**164**), which can react further to give a complex mixture of products.⁹¹ Evidence for conjugate addition of the amine to the ketone was provided by the reaction of mesityl oxide (**166**) with benzylamine in the presence of molecular sieves,⁹² followed by acylation with trichloroacetylchloride (Scheme 66). Trichloro enamide (**167**) can only be conceivably formed by conjugate addition of the amine to the ketone,⁹³ followed by base catalysed elimination of acetone, and finally *N*-acylation of the imine formed with the acid halide. When treated with catalytic copper (I) chloride and TPA in refluxing toluene for 21 hours, enamide (**167**) was found to undergo rearrangement to give (**168**) rather than 5-*endo* cyclisation.



Scheme 66

2.8 CONCLUSIONS AND FUTURE WORK

Twelve α -halo dienamides (nine of substructure **104**) and three of substructure **105**) have been prepared in two steps from α,β -unsaturated ketones *via* imine intermediates (Figure 10).

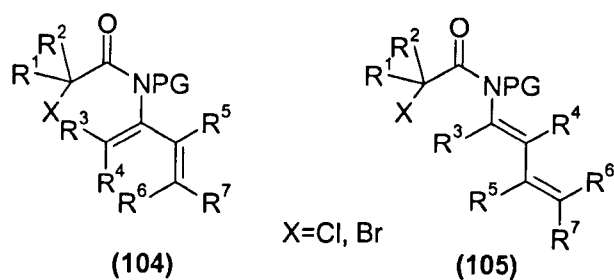
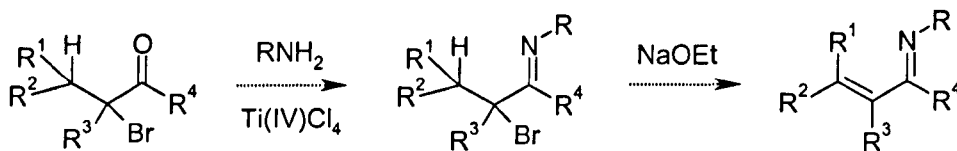


Figure 10

When treated with catalytic copper (I) halide and TPA in refluxing toluene, α -halo dienamides **(104)** (substituted at the 2-position of the diene) were generally found to undergo 5-*exo* cyclisation to give functionalised γ -lactam derivatives. In two examples, however, 6-*endo* cyclisation was also observed where there was the possibility of forming thermodynamically stable aromatic products by this mode of cyclisation. In another example, where tautomerisation to a 1-substituted dienamide competes with 5-*exo* cyclisation, a β -lactam (4-*exo* product) was also formed. α -Halo dienamides **(105)** (substituted at the 1-position of the diene) were found to give β -lactam products by 4-*exo* cyclisation.

The synthesis of a broad range of α -halo dienamides, and a systematic study of their copper (I) mediated ATRC reactions, was prevented by problems encountered in the formation of unsaturated imines from α,β -unsaturated ketones. One potential solution to this problem might be the synthesis of the required unsaturated imines from α -halo ketones using a two-step approach outlined in Scheme 67.⁹⁴



Scheme 67

In summary, copper (I) mediated atom transfer radical cyclisation of α -halo dienamides provides a key step in the efficient synthesis (three steps) of multifunctional β -lactams, γ -lactams and tetrahydroisoquinolinones from unsaturated ketones. These heterocyclic

products contain halogenoalkane and alkene functional groups which render them potential building blocks for drug discovery research.

3. COPPER (I) MEDIATED CYCLISATION OF α -HALO DIENAMIDES

DERIVED FROM α,β -UNSATURATED ALDEHYDES

3.1 METHODOLOGY FOR BETA-LACTAM SYNTHESIS

β -Lactam chemistry is of great importance because of the continued interest in β -lactam derivatives as antibacterial agents, and as serine protease inhibitors for nonantibiotic applications.⁹⁵⁻⁹⁹ Since the discovery in 1945 that the structure of penicillin contains a β -lactam function, a vast amount of effort has been devoted to producing other β -lactam antibiotics with a wider spectrum of activity and a greater resistance to enzymatic cleavage by β -lactamases. The production of β -lactamases is a mechanism by which bacteria become resistant to such antibiotics. The need to achieve more satisfactory activity against Gram-negative bacteria and the evolution of genetically transferable drug resistance has spurred important developments in the synthesis of unusual β -lactams.¹⁰⁰

A large number of chemical methods for the production of β -lactams have been developed.¹⁰¹⁻¹⁰² The direct cyclisation of β -amino acid derivatives,¹⁰³ hydroxamate cyclisation ($R^5=OR^6$) (a),¹⁰⁴ the metalloester enolate-imine condensation (Gilman-Speeter reaction) (b),¹⁰⁵ the chromium carbene-imine reaction (c),¹⁰⁶⁻¹⁰⁷ the isocyanate-alkene [2 + 2] cycloaddition (d),¹⁰⁸⁻¹⁰⁹ and the ketene-imine [2 + 2] cycloaddition (Staudinger reaction) (e),¹¹⁰ are the approaches most often employed for the construction of the β -lactam ring (Figure 11).

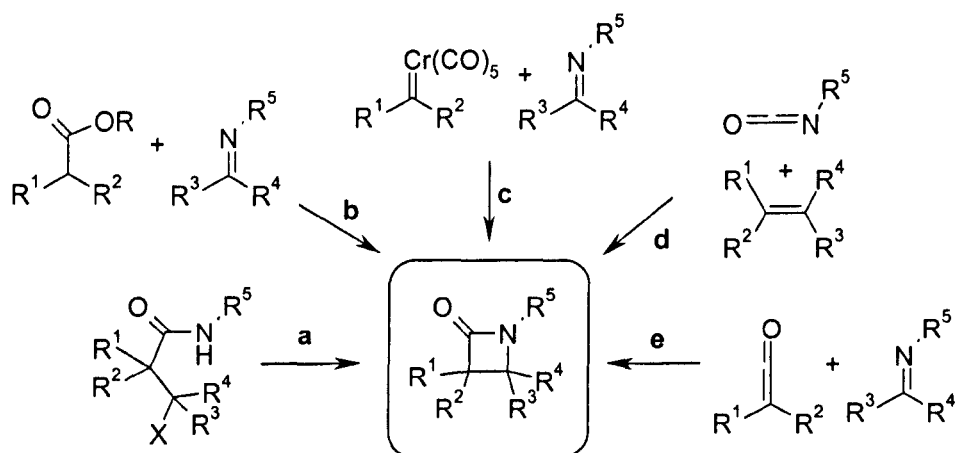
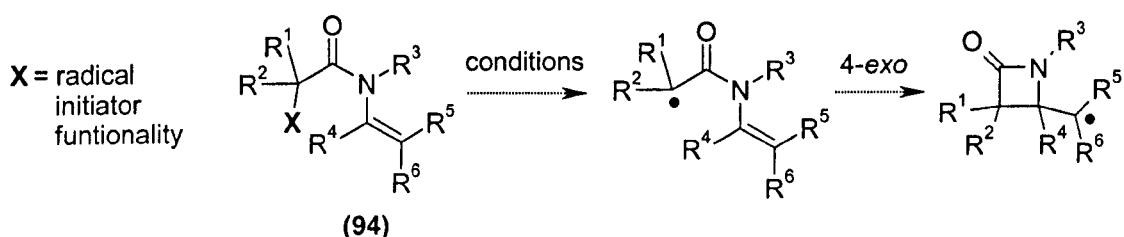


Figure 11

More recently, free radical cyclisation reactions have been developed to broaden the range of methodologies available to synthesise more unusual β -lactam derivatives. Enamides (**94**), usually derived from saturated aldehydes, are key radical precursors for β -lactam synthesis by 4-*exo* cyclisation (Scheme 68). The majority of this work has utilised Bu_3SnH as a mediator,^{47,111-114} but reactions involving nickel,¹¹⁵ cerium (IV),⁷¹ manganese (III),⁶⁶⁻⁶⁹ ruthenium (II)³⁷ or copper (I)^{4,36} complexes have also been reported. The absence of a radical stabilising group on the enamide carbon adjacent to the nitrogen (R^4), and the existence of radical stabilising groups at R^5 and/or R^6 have been found to promote 4-*exo* cyclisation in preference to 5-*endo* cyclisation.



Scheme 68

3.2 COPPER (I) MEDIATED RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM UNSATURATED ALDEHYDES

Selected α -halo enamides (**169**) have been found to undergo 4-*exo* atom transfer radical cyclisation in the presence of catalytic copper (I) salts and activating amine ligands (Figure 12).^{4,36} In all of these methods, radical stabilising alkyl groups were required at both R^3 and R^4 to achieve cyclisation, which limits the range of β -lactam derivatives that may be prepared.

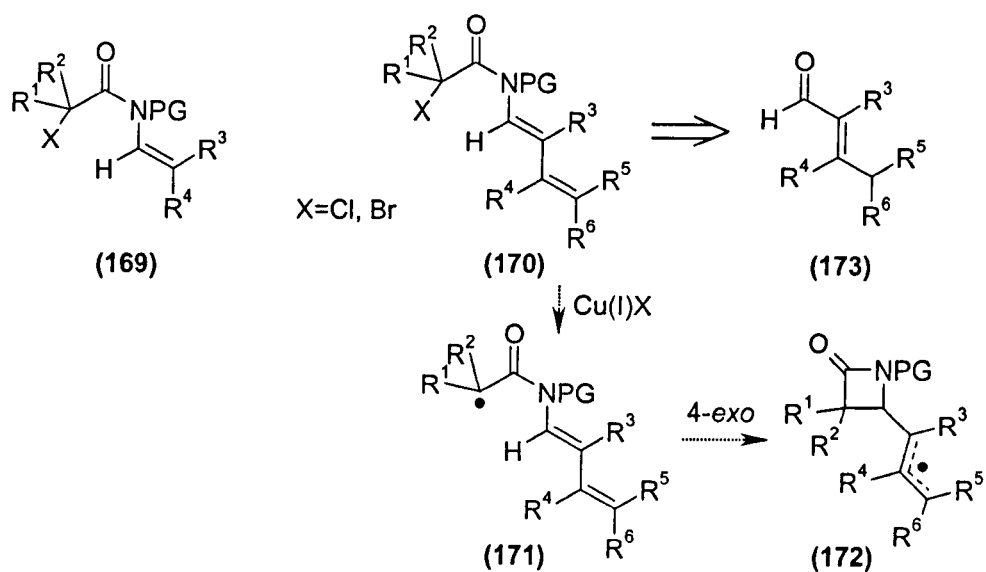


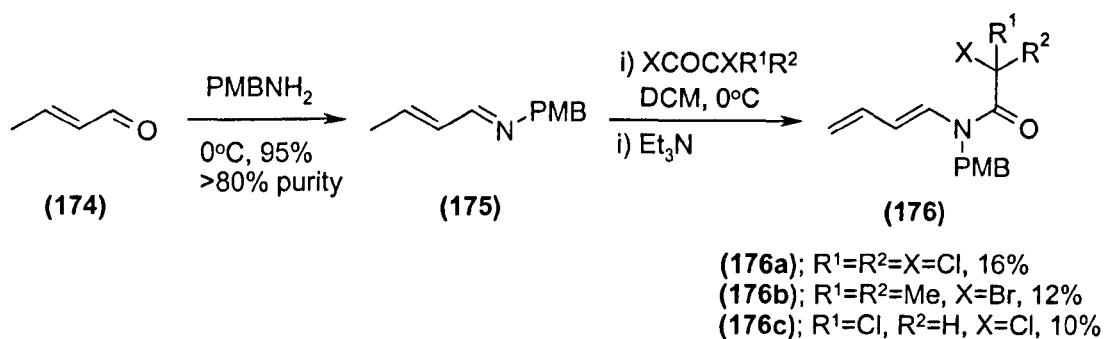
Figure 12

Our findings for the copper (I) mediated cyclisation of 1-substituted α -halo dienamides (**105**) (Figure 4, Chapter 2) encouraged us to explore the radical cyclisation of related dienamides (**170**) derived from α,β -unsaturated aldehydes. We anticipated that radical precursors (**170**) would also cyclise in the 4-*exo* mode to form a unique range of functionalised β -lactam derivatives, and that the generation of a stable allyl radical (**172**) on cyclisation of initial radical (**171**) might remove the necessity for alkyl substituents at R^3 , R^5 and R^6 . In addition, since the condensation of α,β -unsaturated aldehydes (**173**) with primary amines to form unsaturated imines is well documented,¹¹⁶⁻¹¹⁷ we believed that the synthesis of a range of substrates of type (**170**) would be straightforward, and that a systematic evaluation of cyclisation outcome versus substitution pattern would be possible.

3.3 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM *TRANS*-CROTONALDEHYDE

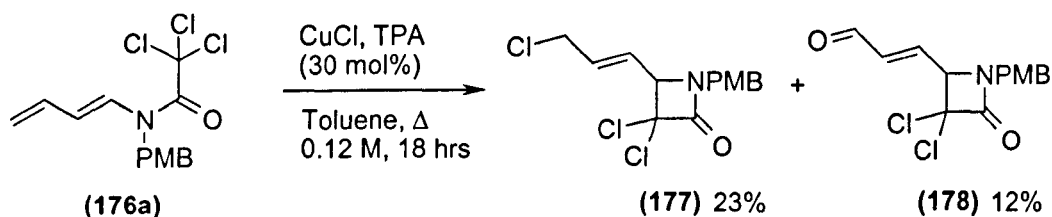
Condensation of *trans*-crotonaldehyde (**174**) with 4-methoxybenzylamine gave unsaturated imine (**175**)¹¹⁸ which was acylated with three different acid halides in the presence of triethylamine to furnish α -halo dienamides (**176a-c**) (R^3 - R^6 =H) (Scheme 69).

The acylation steps were found to give a complex mixture of products which included the desired dienamide in low yield and also the secondary 4-methoxybenzylamides. All three dienamides were found to be sensitive to hydrolysis in air (particularly **(176a)**) to give the secondary amides, so were subjected to radical cyclisation conditions within two hours of purification.



Scheme 69

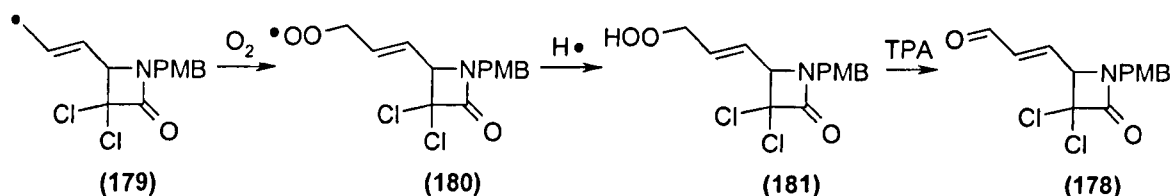
Trichloro dienamide **(176a)** was treated with 30 mol% copper (I) chloride and TPA in refluxing toluene under a stream of nitrogen (Scheme 70). No reaction was observed to take place at room temperature. After a total of 18 hours, all dienamide was consumed to give uncharacterised baseline material, 2,2,2-trichloro-*N*-(4-methoxybenzyl)acetamide and two β -lactam cyclisation products **(177)** and **(178)** in 35% overall yield. Allyl chloride **(177)**, which forms by atom transfer of chlorine from copper (II) chloride to the intermediate allyl radical, was found to predominate over aldehyde **(178)**.



Scheme 70

Aldehyde **(178)** presumably forms by the advantageous intervention of oxygen in the reaction. A likely mechanism for the formation of **(178)** is illustrated in Scheme 71. Trapping of allyl radical **(179)** with an oxygen molecule gives peroxy radical **(180)**

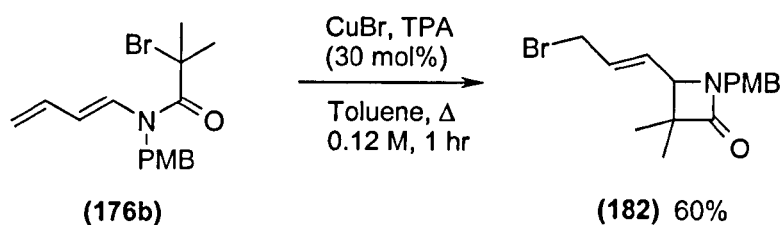
which may be converted to the hydroperoxide (**181**) by hydrogen atom transfer. Base catalysed elimination of (**181**) provides unsaturated aldehyde (**178**).



Scheme 71

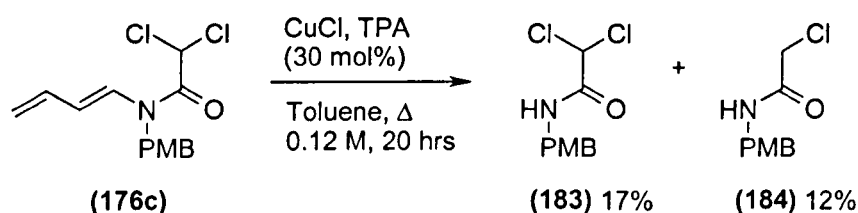
The reaction was repeated with more rigorous deoxygenation of the reaction system by several vessel evacuations prior to addition of the nitrogen atmosphere. After the same time period, allyl chloride (**177**) was formed in an increased yield of 46% and the aldehyde (**178**) was isolated in a reduced yield of 7%, confirming the formation of (**178**) from molecular oxygen. The overall yield was increased to 53%. As anticipated, when the reaction was repeated for a third time in the open air, the yields obtained for (**177**) and (**178**) were 9% and 17% respectively. The reduction in overall yield to 26% is presumably caused by partial oxidation of the Cu(I)Cl.TPA complex to the corresponding Cu(II)Cl.TPA complex. This result provides the first example of a copper (I) mediated radical cyclisation where the radical intermediate is trapped with oxygen, although oxygenation of stabilised radicals is known.¹¹⁹

Bromo dienamide (**176b**), which was more stable in air than (**176a**), was found to cyclise under the same atom transfer conditions (stream of nitrogen over the reaction) to give β -lactam allyl bromide (**182**) exclusively in an improved yield of 60% (Scheme 72). 4-*Exo* cyclisation of (**176b**) was found to be much faster than that of (**176a**) (reaction time of 1 hour cf. 18 hours for (**176a**)) which contrasts with the relative rates for the 5-*exo* cyclisation of *N*-allyl halo amides where trichloro amides were found to cyclise with the highest rates.²⁰ The higher cyclisation rate for (**176b**) is no doubt responsible for the improvement in yield of β -lactam products from 35% to 60%; a shorter reaction time reduces the extent of substrate decomposition prior to cyclisation.



Scheme 72

Dichloro dienamide (176c) gave no cyclisation products on treatment with catalytic copper (I) chloride and TPA in refluxing toluene after 20 hours, despite disappearance of starting material (Scheme 73). Only amides (183) and (184) were isolated from the reaction mixture indicating that decomposition is faster than radical cyclisation in this case. Based on this result, dichloro dienamides were not evaluated further, and subsequent studies were restricted to activated halo dienamides where $R^1=R^2=X=Cl$ and $R^1=R^2=Me$, $X=Br$.



Scheme 73

At this point in our investigation we decided to set up competition experiments to probe the cyclisation of bromo dienamides (185) and (186) in which the initial radical can cyclise in either a 4-*exo* or 5-*exo* fashion for (185), or can cyclise in either a 4-*exo* or 6-*exo* fashion for (186) (Figure 13).

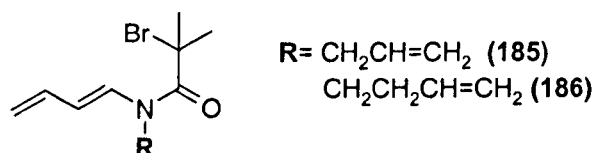
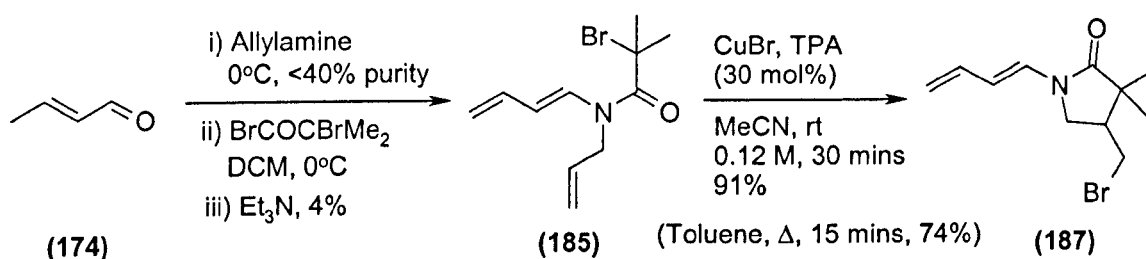


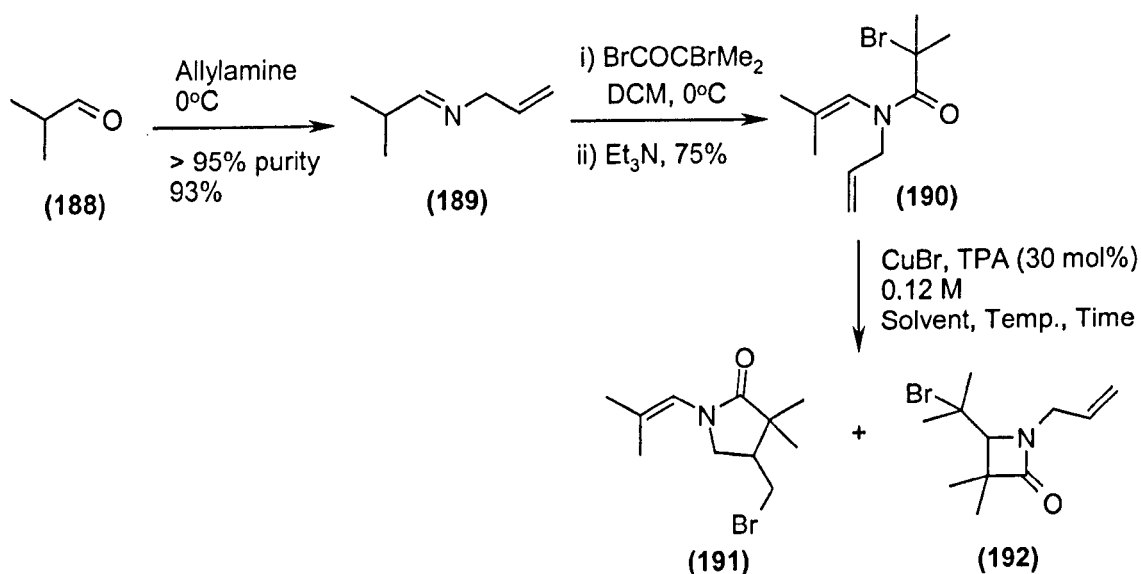
Figure 13

Bromo dienamide (**185**), synthesised in two steps from allylamine, was found to cyclise within 15 minutes in refluxing toluene (30 mol% Cu(I)Br.TPA) to furnish 5-*exo* product (**187**) in 74% yield and no 4-*exo* product (Scheme 74). The yield of γ -lactam (**187**) was found to be increased to 91% when the reaction was conducted at room temperature in acetonitrile. As routinely found, (**185**) failed to cyclise in toluene at room temperature, and this is believed to be due to poor solubility of the Cu(I)Br.TPA complex in toluene at this temperature. The use of acetonitrile as solvent did not allow 4-*exo* cyclisation of radical precursors (**176a-b**) at room temperature illustrating the relative rates of 5-*exo* versus 4-*exo* cyclisation.



Scheme 74

5-*Exo* cyclisation was also found to be favoured over 4-*exo* cyclisation for bromo enamide (**190**) which forms a tertiary alkyl radical intermediate on 4-*exo* cyclisation (Scheme 75, Table 5).

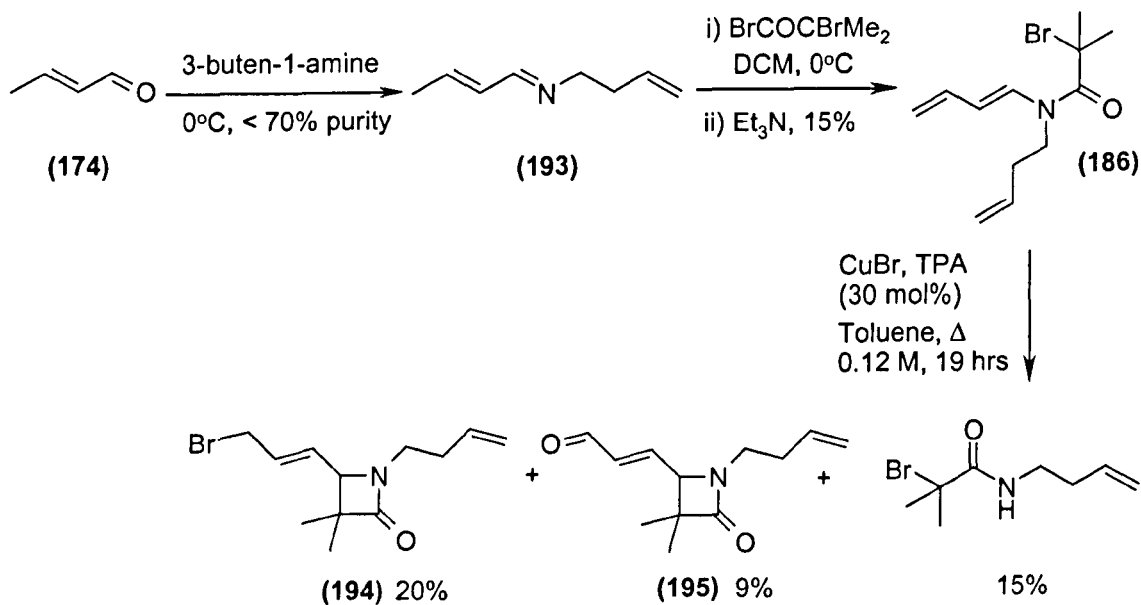


Scheme 75

Solvent	Temp. (°C)	Time	Yield (191) (%)	Yield (192) (%)
Toluene	110	15 mins	95	0
Toluene	22	16 hours	0	0
Toluene	60	5 hours	<10	0
DCM	22	5 mins	79	15

Table 5

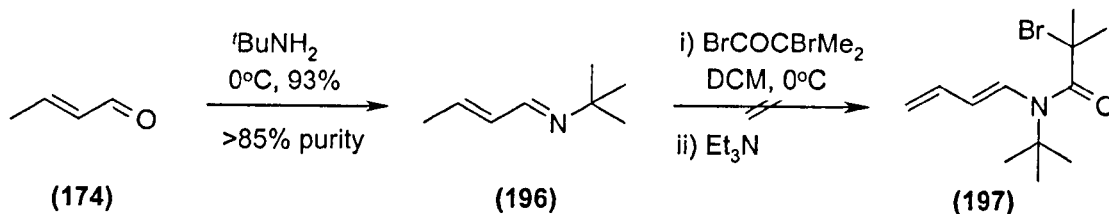
The homoallyl dienamide (**186**), in comparison, was found to cyclise to give only β -lactam products (**194**) and (**195**) by 4-*exo* cyclisation (Scheme 76). Evidently 4-*exo* cyclisation to give an allyl radical intermediate is faster than 6-*exo* cyclisation to give a primary alkyl radical intermediate. The cyclisation was found to be slower and lower yielding than that for the related dienamide (**176b**) which has the larger 4-methoxybenzyl group attached to the nitrogen. Presumably a bulkier nitrogen protecting group increases the population of the conformer which can cyclise onto the diene in the 4-*exo* mode.



Scheme 76

We were also interested in the 4-*exo* cyclisation of *tert*-butyl dienamide (**197**), since we envisaged that deprotection of the cyclisation product would be more facile, and less

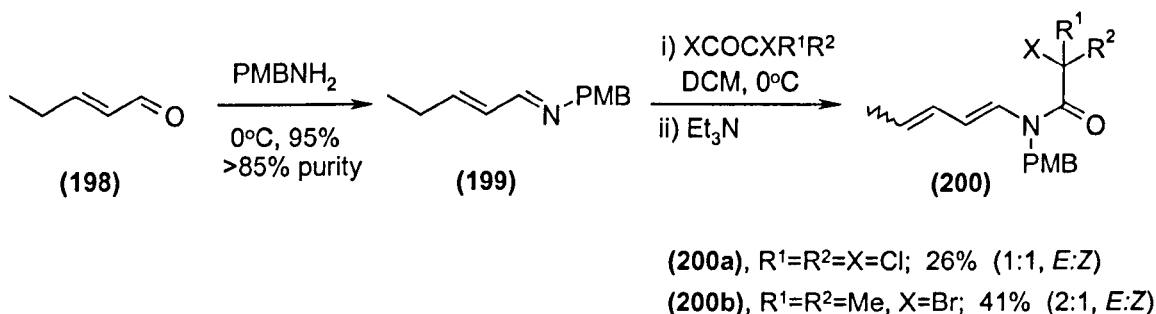
likely to affect other functionality in the β -lactam product, than deprotection of the 4-methoxybenzylamide group of **(182)** (Schemes 72 and 77). Unfortunately, the desired radical precursor **(197)** could not be prepared due to problems encountered in the acylation of imine **(196)** using a number of methods.



Scheme 77

3.4 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM *TRANS*-2-PENTENAL

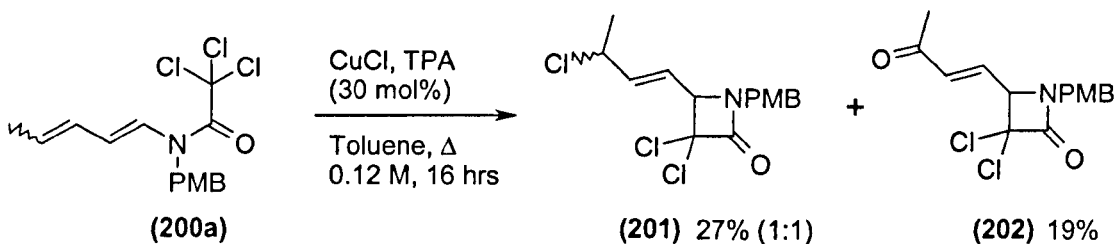
Having explored dienamides **(176a-c)**, where $\text{R}^3\text{-R}^7=\text{H}$, we next turned our attention to related systems **(200a-b)** which have a methyl substituent at the end of the diene (Scheme 78). These were prepared as inseparable mixtures of *E*- and *Z*- isomers in two steps from *trans*-2-pentenal **(198)**.



Scheme 78

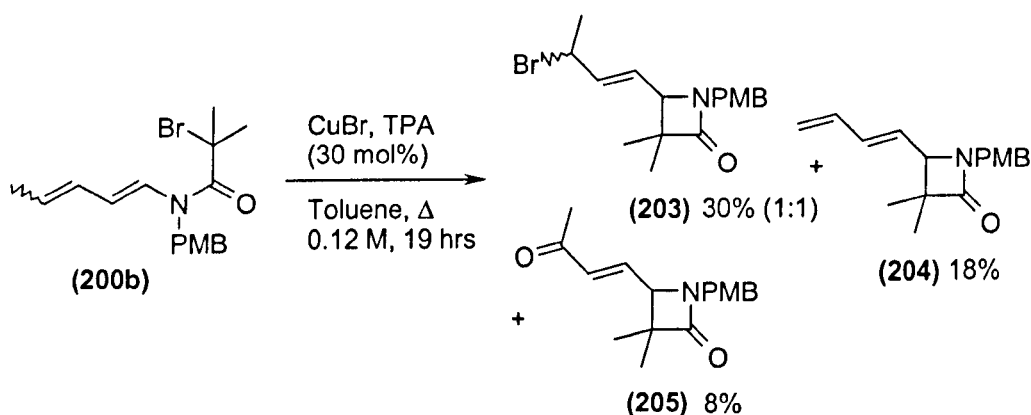
When treated with catalytic copper (I) chloride, trichloro dienamide **(200a)** was found to cyclise to give two β -lactam products **(201)** and **(202)** in 27% and 19% yields respectively (Scheme 79). As previously encountered for dienamide **(176a)**, we see a product **(202)** which results from trapping of the intermediate allyl radical with molecular

oxygen. The introduction of a radical stabilising methyl group at the end of the diene system did not increase the rate of 4-*exo* cyclisation nor improve the overall yield of β -lactam products.



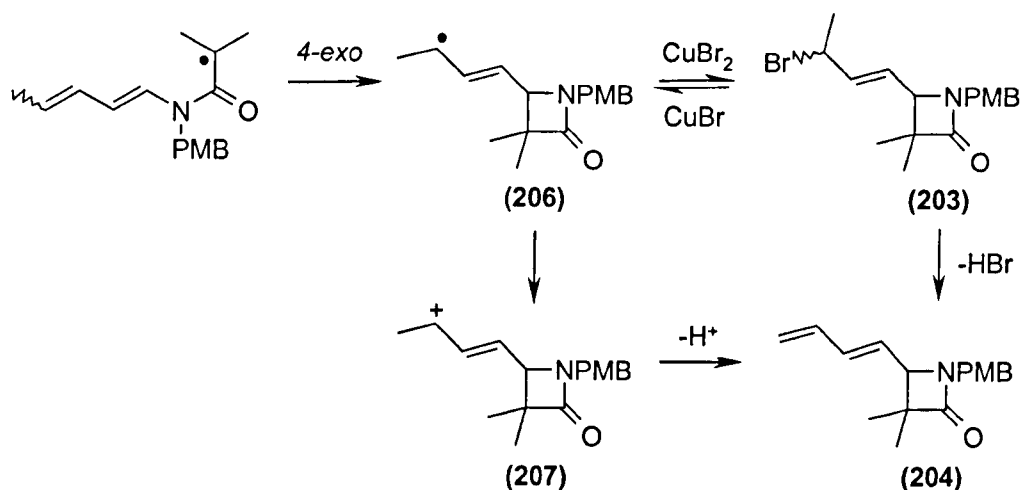
Scheme 79

Similarly, cyclisation of bromo dienamide (**200b**) was found to give both allyl bromide (**203**) and ketone (**205**) on treatment with copper (I) bromide, although oxidation to (**205**) was observed to a lesser extent (Scheme 80). In addition, β -lactam diene (**204**) was isolated in 18% yield, bringing the overall yield of 4-*exo* products to 56%.



Scheme 80

Possible mechanisms for the formation of diene (**204**) are illustrated in Scheme 81. Either E1 or E2 elimination of allyl bromide (**203**) is the most likely route to diene (**204**). Alternatively, the allyl radical (**206**) generated on cyclisation may be oxidised to an allyl cation (**207**) which undergoes proton loss to give (**204**). It is possible that allyl radical (**206**) could also be reformed by the reaction of bromide (**203**) with copper (I) bromide.¹²⁰

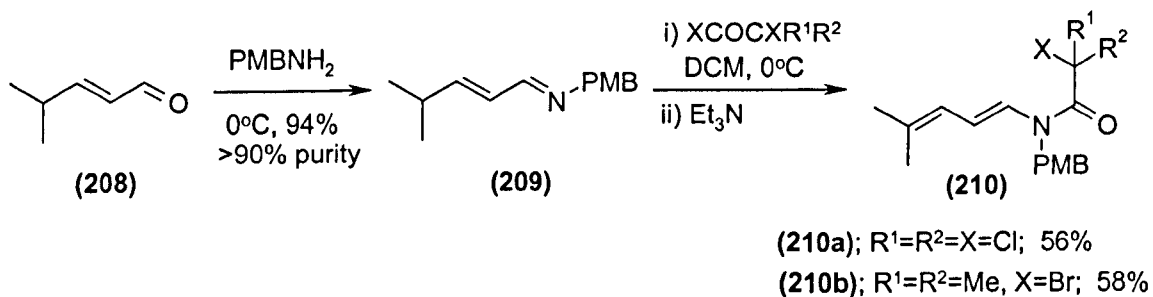


Scheme 81

Thus, heating bromide **(203)** to reflux in toluene (0.12 M) for 6 hours resulted in ~22% conversion to the diene **(204)**. This conversion was not increased by treating the bromide with 30 mol% TPA under the same conditions, or with 30 mol% TPA and Cu(I)Br. These observations suggest that diene **(204)** forms by thermal E1 elimination of bromide **(203)**.

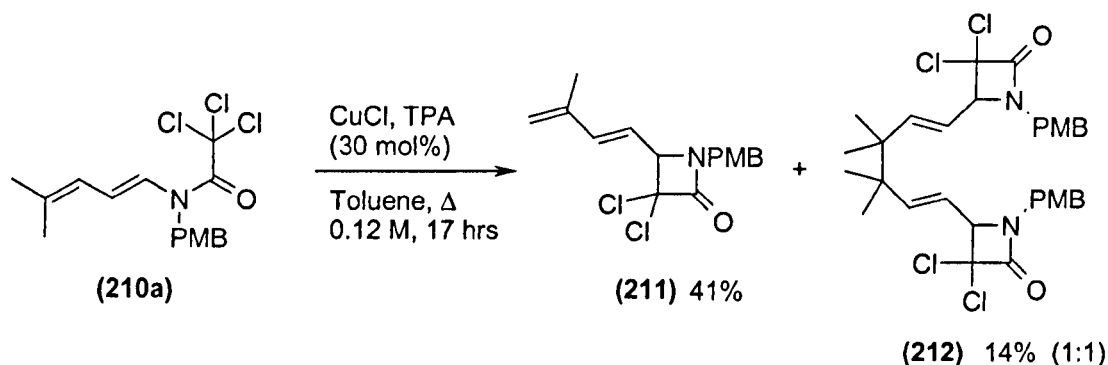
3.5 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM 4-METHYL-2-PENTENAL

The introduction of two methyl substituents at the end of the diene ($R^3=R^4=H$, $R^5=R^6=Me$) of dienamides **(210a-b)** produced some interesting radical cyclisation results (Scheme 82).



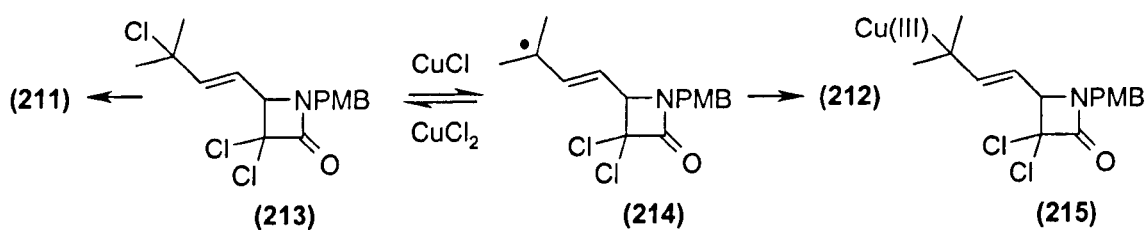
Scheme 82

Treatment of trichloro dienamide (**210a**) with 30 mol% Cu(I)Cl.TPA in refluxing toluene gave β -lactam diene (**211**) in 41% yield and also a 1:1 diastereomeric mixture of dimeric product (**212**) (14%) (Scheme 83).



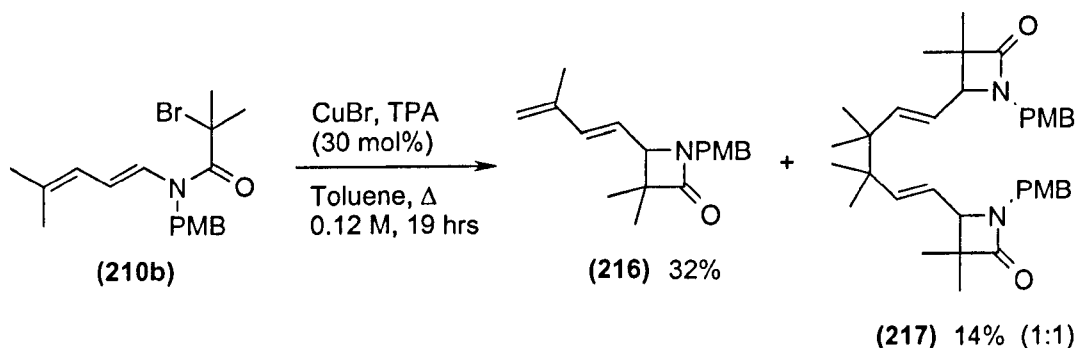
Scheme 83

Product (**211**) is likely to arise from HCl elimination of the potential undetected tertiary chloride (**213**) and not through disproportionation of the intermediate tertiary allyl radical (**214**), as is evident by the inability to detect the reduced form of (**214**) expected from this disproportionation (Scheme 84). It has been suggested recently that related copper mediated atom transfer radical polymerisation reactions may proceed not by free-radicals but by the intermediacy of caged carbon-copper radical pairs/alkyl copper complexes.¹²¹ Thus, an alternative explanation is that free radical (**214**) is not involved and elimination of CuH from an intermediate copper alkyl complex (**215**) leads to diene (**211**). The longevity of the tertiary allyl radical intermediate (**214**) or tertiary alkyl copper complex (**215**) must account for the production of dimeric product (**212**) which was not encountered for trichloro dienamides (**176a**) and (**200a**).



Scheme 84

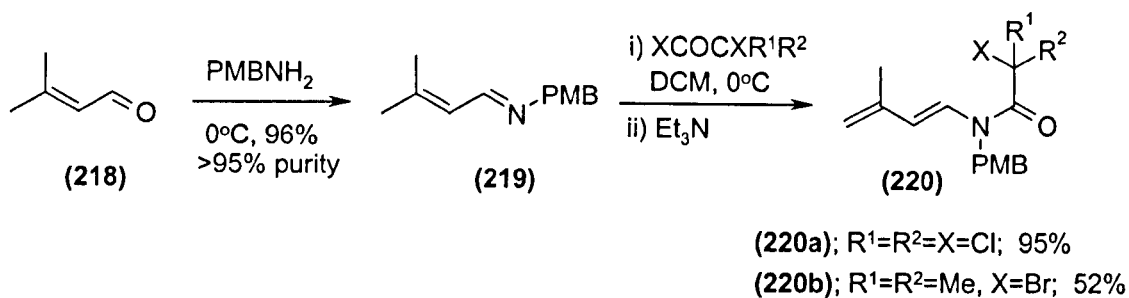
Similarly, bromo dienamide (**210b**) was found to cyclise to give analogous β -lactam products (**216**) and (**217**) in 32% and 14% yields respectively (Scheme 85). The reaction time was surprisingly longer than that for bromo dienamide (**176b**) (19 hours cf. 1 hour) which has no obvious explanation. In addition, the reaction was found to be significantly slower than that of analogous enamide (**169**) ($R^1=R^2=Me$, $X=Br$, $R^3=R^4=Me$), which cyclises using the same catalyst to form a β -lactam product in 97% yield after 20 minutes at room temperature (Figure 12).³⁶ We anticipated that use of acetonitrile as solvent for this reaction might decrease the yield of dimeric product (**217**) by increasing the rate of capture of a bromine atom from copper (II) bromide by the cyclisation intermediate. Instead, after the same period of time at reflux temperature, the isolated yields of (**216**) and (**217**) were 21% and 17% respectively; the overall yield was found to be reduced and the amount of dimer increased.



Scheme 85

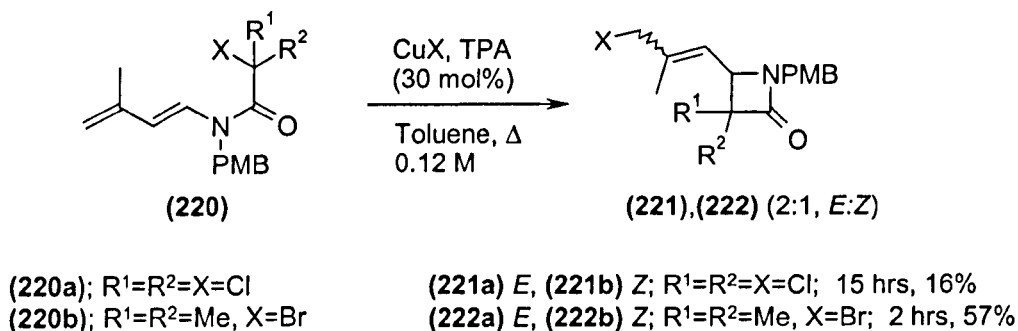
3.6 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM 3-METHYL-2-BUTENAL

α -Halo dienamides (**220a-b**), in which $R^3=R^5=R^6=H$ and $R^4=Me$, were prepared in good yield from 3-methyl-2-butenal (**218**) (Scheme 86). Both radical precursors were found to be more stable in air than those discussed in Sections 3.3-3.5.



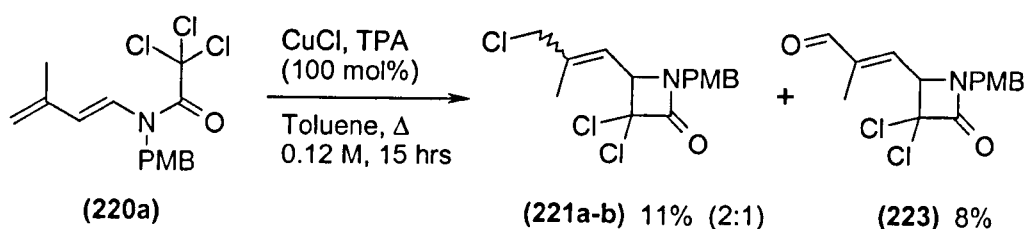
Scheme 86

Both dienamides were found to undergo 4-*exo* cyclisation to give 2:1 mixtures of *E*- and *Z*-allyl halides on treatment with 30 mol% Cu(I)X.TPA in refluxing toluene (Scheme 87). As encountered for (176b), bromo dienamide (220b) was found to cyclise more rapidly than the analogous trichloro dienamide (220a) (2 hours vs. 15 hours), and the yield of the allyl bromides (222a-b) was found to be significantly higher than that of the allyl chlorides (221a-b).



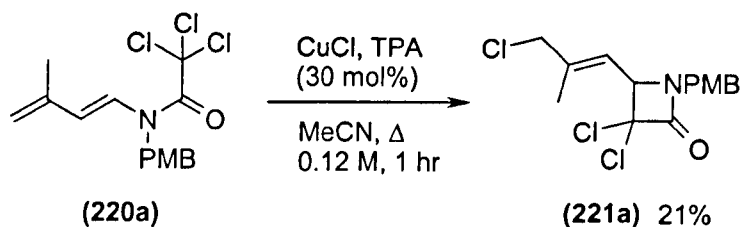
Scheme 87

The poor yield of 16% for the β -lactam allyl chlorides (221a-b) encouraged us to explore the effect of using stoichiometric Cu(I)Cl.TPA on the cyclisation of (220a) (Scheme 88). After the same time period of 15 hours, the allyl chlorides (221a-b) were actually isolated in a reduced yield of 11% and the unsaturated aldehyde (223) was also isolated as a single stereoisomer in 8% yield.



Scheme 88

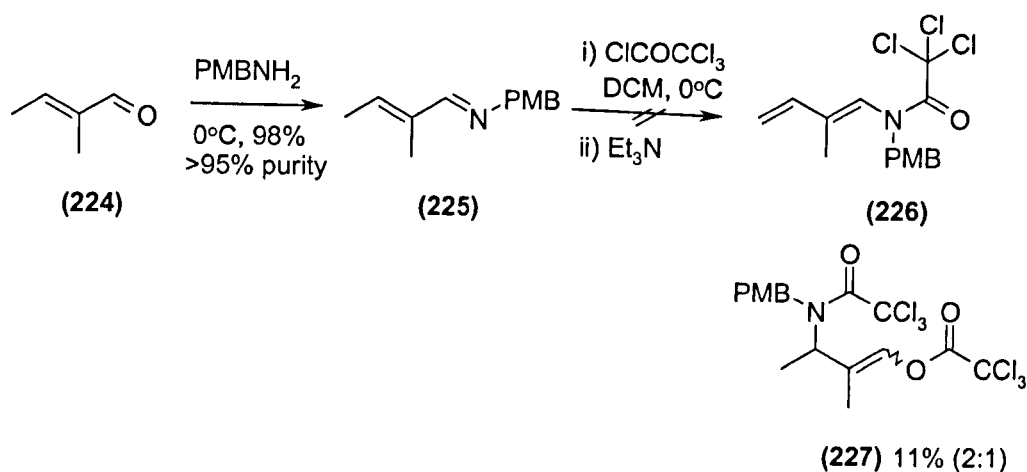
When the cyclisation of **(220a)** was performed in refluxing acetonitrile using 30 mol% Cu(I)Cl.TPA , the *E*-allyl chloride **(221a)** was formed selectively in a low yield of 21% after a much shorter reaction time of 1 hour (Scheme 89).



Scheme 89

3.7 RADICAL CYCLISATION OF α -HALO DIENAMIDES DERIVED FROM β -CYCLOCITRAL

The synthesis of halo dienamides with a methyl substituent at R^3 ($\text{R}^4=\text{R}^5=\text{R}^6=\text{H}$) was found to be problematic (Scheme 90). Whilst the imine **(225)** of *trans*-2-methyl-2-butenal **(224)** could be prepared, treatment with trichloroacetyl chloride in the presence of triethylamine gave product **(227)** and none of the desired dienamide **(226)**. Presumably introduction of an alkyl substituent at this position slows down the acylation step and allows time for the imine **(225)** to be hydrolysed back to the aldehyde and amine which subsequently react together in a conjugate fashion before undergoing both *N*- and *O*-acylation.



Scheme 90

The preparation of dienamides (228) and (229) which have alkyl groups at both R³ and R⁵ (R⁴=R⁶=H) was also unsuccessful due to problems encountered in the acylation steps (Figure 14).

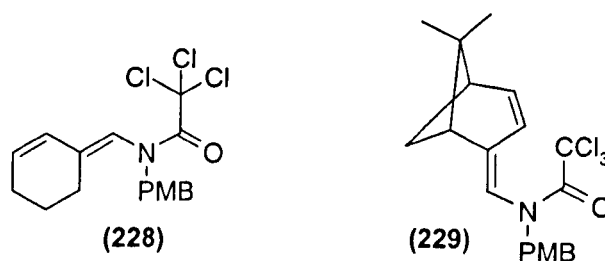
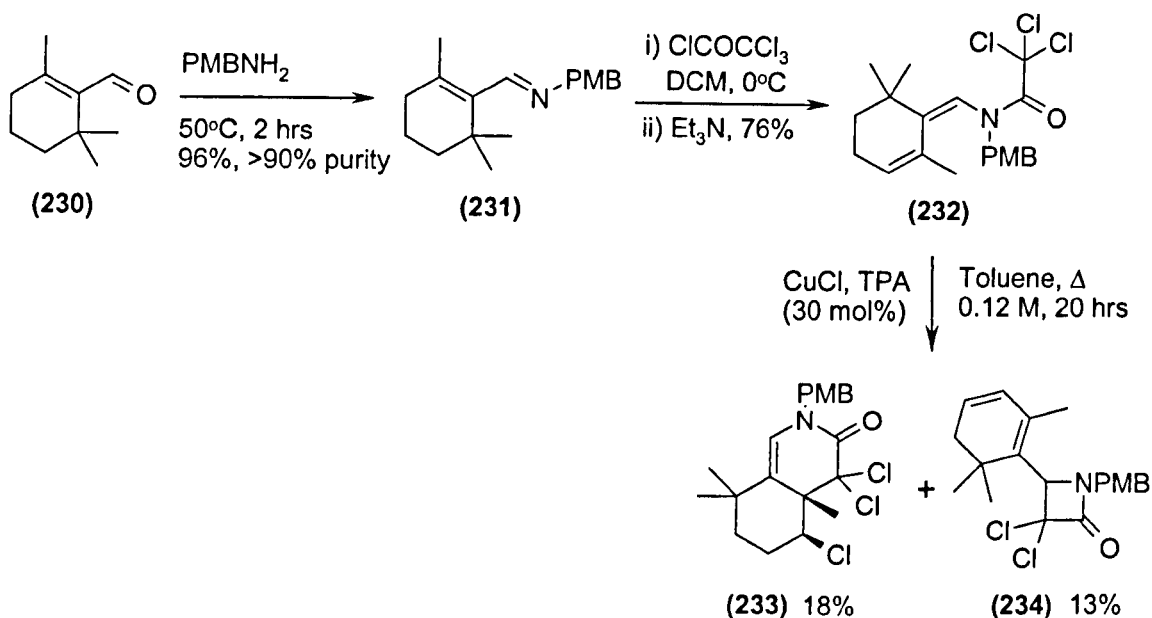


Figure 14

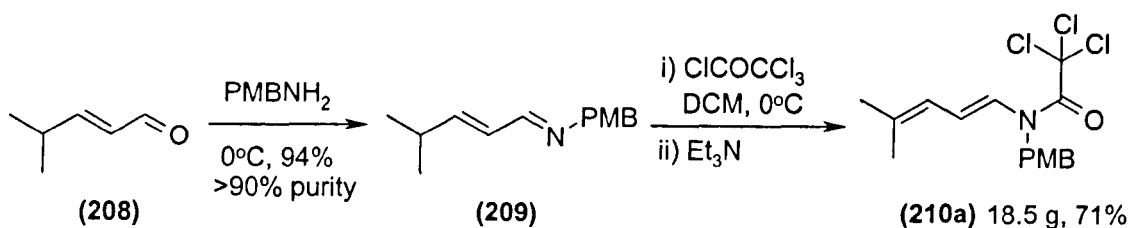
Finally, the synthesis of trichloro dienamide (232), which has alkyl groups at R³, R⁴ and R⁵ (R⁶=H), could be achieved in 76% yield from β -cyclocitral (Scheme 91). Imine formation was found to be slower than previous examples and required heating to 50°C to achieve reaction completion within a reasonable time frame. Interestingly, when (232) was treated with catalytic Cu(I)Cl.TPA in refluxing toluene for 20 hours both a 6-*exo* and a 4-*exo* cyclisation product was isolated from the reaction mixture. Large steric interactions in the 4-*exo* transition state no doubt play an important part in favouring the 6-*exo* product in this case. NOe experiments confirmed the *cis* stereochemistry of the methyl and chloro groups of 6-*exo* product (233).



Scheme 91

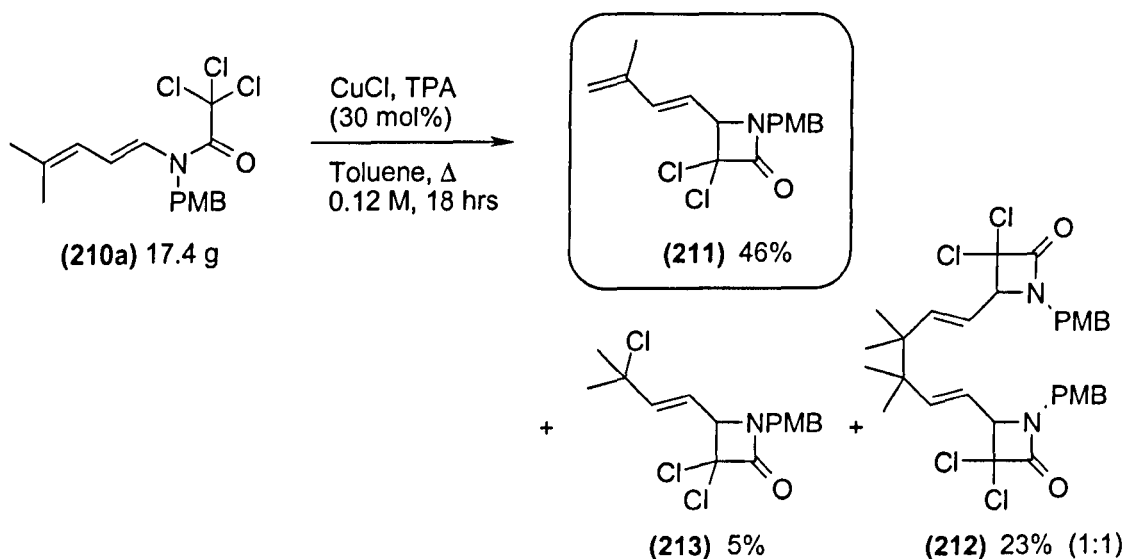
3.8 LARGE SCALE BETA-LACTAM SYNTHESIS BY RADICAL CYCLISATION OF A α -HALO DIENAMIDE

Having explored a number of copper (I) mediated α -halo dienamide cyclisations, we decided to investigate the scalability of one reaction and to take a brief look at functionalisation of the product. The large scale synthesis of β -lactam diene (**211**) was chosen since it had been formed in reasonable yield (41%) on a small scale, and it offered opportunity for functionalisation of both the diene and the β -lactam (on removal of the *gem* dichloro group) (Scheme 83). In addition, (**211**) could be separated easily from dimer (**212**) by chromatography. Dienamide (**210a**) was successfully prepared in 71% yield from 4-methyl-2-pentenal (**208**) on a multigram scale within 8 hours (Scheme 92). This yield is an improvement on the small scale yield of 56% for this two step sequence.



Scheme 92

Over 17 g of dienamide (210a) was then treated with 30 mol% Cu(I)Cl.TPA in refluxing toluene for 18 hours in the largest scale copper mediated ATRC reaction that has ever been reported (Scheme 93). This multigram scale reaction was found to proceed smoothly to give an improved yield of both diene (211) and dimer (212). Over 7 g (46%) of the desired diene (211) was isolated after repeated chromatography. The chromatography was not as straightforward as for the small scale cyclisation reaction since a close running product (believed to be the tertiary chloride (213)) was also formed in low yield which proved difficult to separate from diene (211).

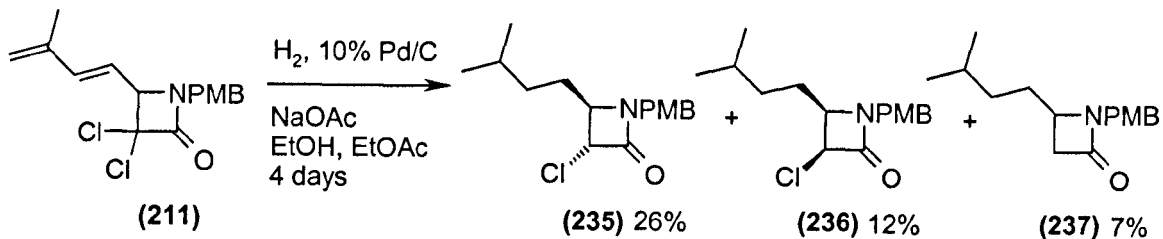


Scheme 93

Having prepared several grams of diene (211), we turned our attention to functionalisation of this derivative. A number of reductive methods have been reported in the literature for the removal of the *gem* dichloro group from γ - and δ -lactams. These include hydrogenation in the presence of sodium acetate,¹²² zinc in acetic acid,¹²³ zinc in

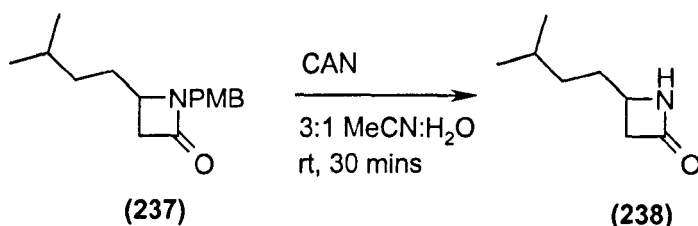
methanol with ammonium chloride,¹²⁴ Raney nickel in ethanol, or tributyltin hydride in toluene.¹²² There are no reports for the reduction of the *gem* dichloro group from a β -lactam. Some of these methods are likely to cause transformation of the diene moiety of **(211)** in addition to dichloro reduction, but this did not concern us since novel β -lactam derivatives could still be prepared and tested for biological activity.

We first decided to investigate the reduction of diene **(211)** using catalytic hydrogenation (Scheme 94).¹²² We anticipated that fully reduced product **(237)** would be formed in high yield, but soon became aware that solubility issues were going to have a dramatic impact on the opportunities to functionalise **(211)**. Diene **(211)**, which exists as a pale yellow oil, was found to be highly insoluble in ethanol, ethyl acetate and in fact all organic solvents compatible with hydrogenation. This was extremely enigmatic since **(211)** had been purified by flash column chromatography using a petrol/ethyl acetate mixture and solution of the oil forming around the neck of the tube fractions had been achieved using ethyl acetate. For some inexplicable reason, once all traces of petrol/ethyl acetate are removed on the rotary evaporator, **(211)** only dissolves in halogenated solvents such as DCM or DCE. The pure oil has peculiar physical properties where it can be stretched to huge lengths using the tip of a glass pipette suggesting high intermolecular forces of attraction. These forces of attractions are likely to involve strong associations between the chlorine atoms since they are only broken, and solution achieved, by the addition of a chlorinated solvent. Attempts to crystallise **(211)** (to obtain its x-ray crystal structure) by addition of a range of solvents to the oil produced only white gums. After a total of 4 days, 0.4 mmol of **(211)** was found to have achieved only partial solubility in 70 ml of a 2:5 mixture of ethanol and ethyl acetate in the presence of hydrogen, sodium acetate and catalytic Pd/C. The material in solution was found to consist of mono chloro β -lactams **(235)** and **(236)**, and the fully reduced product **(237)** in low yield. The major product **(235)** has the 2- and 3-substituents on the β -lactam ring arranged *trans* to one another.



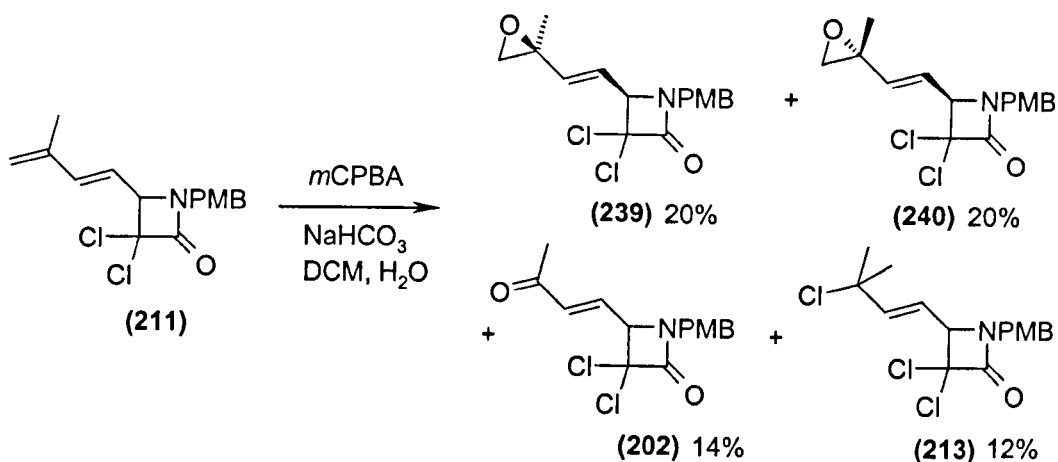
Scheme 94

Attempted reductions, 4-methoxybenzylamide deprotections, Diels-Alder reactions and hydroborations of **(211)** were all found to be unsuccessful. In most cases this was due to problems of solubility of the starting material. For those few reactions where solution was eventually achieved a complex mixture of products was obtained. The deprotection of **(237)** using ceric ammonium nitrate was achieved on a small scale but the highly polar β-lactam product **(238)** could not be obtained in pure form.¹²⁵



Scheme 95

Compelled to study reactions of **(211)** in chlorinated solvents, the *m*CPBA oxidation of the diene moiety was investigated. Treatment of **(211)** with one equivalent of *m*CPBA in DCM at room temperature was found to give a mixture of four products after a period of two hours (Scheme 96).¹²⁶ This mixture included a 1:1 mixture of the two diastereoisomers of the desired epoxides **(239)** and **(240)** in a total yield of 40%. A pure sample of each epoxide was obtained by repeated preparative tlc. Two unexpected products were also isolated from the crude mixture. These include the previously prepared unsaturated ketone **(202)** in 14% yield and tertiary chloride **(213)** in 12% yield. The mechanism by which these additional unexpected products are formed is not obvious.



Scheme 96

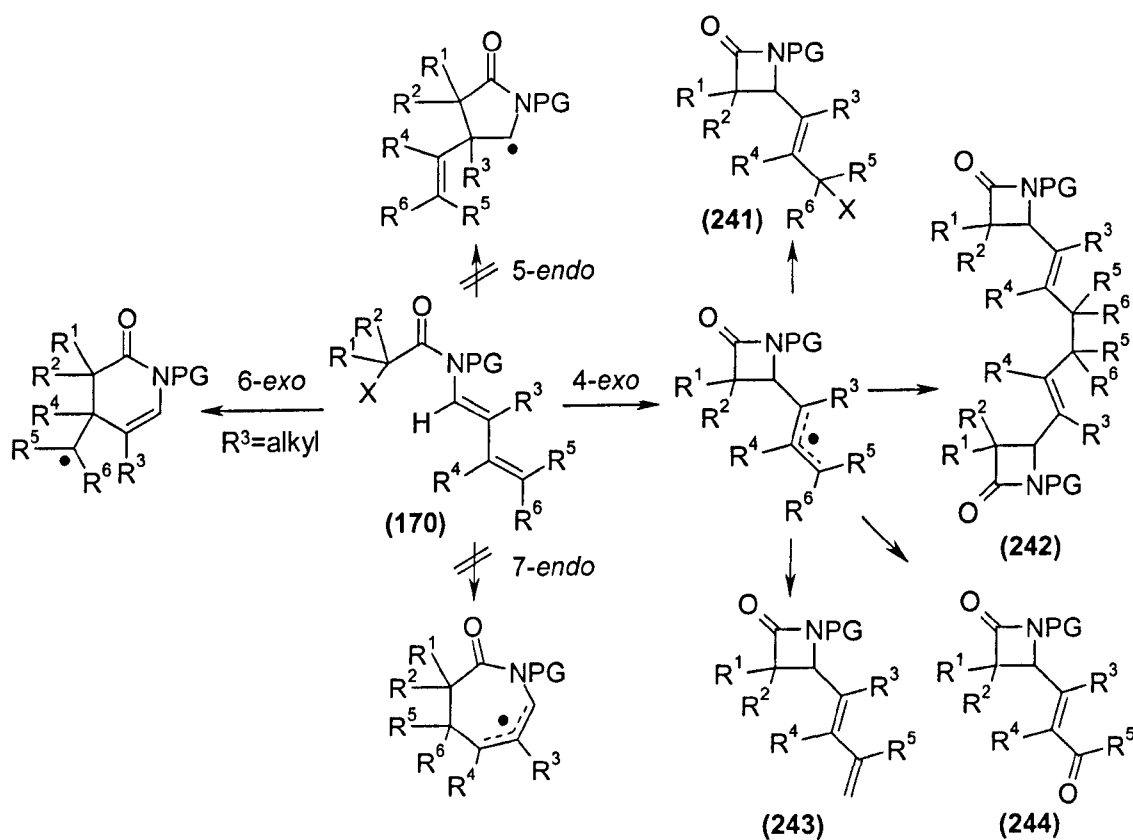
3.9 CONCLUSIONS

Reaction of α -halo dienamides (**170**) (derived from unsaturated aldehydes) with catalytic amounts of Cu(I)X.TPA complexes furnishes β -lactams *via* 4-*exo* radical cyclisation with no competitive cyclisation *via* 5-*endo*, 6-*exo* or 7-*endo* modes (Scheme 97). (α -Halo dienamide (**232**) substituted with an alkyl group at R³ with *cis* stereochemistry undergoes 6-*exo* cyclisation). Termination of the reactions occurs *via* halogen atom transfer, trapping with oxygen, elimination or radical-radical coupling depending upon the reaction conditions and the diene substitution pattern.

The results for eight dienamide cyclisation reactions conducted with 30 mol% Cu(I)X.TPA in refluxing toluene (PG=PMB) are summarised in Table 6. These results indicate that the outcome of the cyclisation reactions is highly substrate dependent, with both the initiator functionality and the diene substitution pattern playing a crucial role in determining the rate of reaction and products formed. Termination of the cyclisation by a primary allyl radical (R⁵=R⁶=H, (**176a-b**) and (**220a-b**)) generally leads to halogen atom transfer, while termination by a secondary radical (R⁵=H, R⁶=Me, (**200a-b**)) leads to atom transfer, elimination and oxygen trapping. Cyclisation leading to a tertiary radical (R⁵=R⁶=Me, (**210a-b**)) leads to elimination and dimerisation products.

	X	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Time (hrs)	Yield Halide (241) (%)	Yield Dimer (242) (%)	Yield Diene (243) (%)	Yield Ox. Prod. (244) (%)	Total Yield (%)
(176a)	Cl	Cl	Cl	H	H	H	H	18	23	0	0	12	35
(176b)	Br	Me	Me	H	H	H	H	1	60	0	0	0	60
(200a)	Cl	Cl	Cl	H	H	H	Me	16	27	0	0	19	46
(200b)	Br	Me	Me	H	H	H	Me	19	30	0	18	8	56
(210a)	Cl	Cl	Cl	H	H	Me	Me	17	0	14	41	0	55
(210b)	Br	Me	Me	H	H	Me	Me	19	0	14	32	0	46
(220a)	Cl	Cl	Cl	H	Me	H	H	15	16	0	0	0	16
(220b)	Br	Me	Me	H	Me	H	H	2	57	0	0	0	57

Table 6



Scheme 97

The overall yield of β -lactam products, which varies from 16-60%, is related to both the stability of the radical precursors and also the rate of 4-*exo* cyclisation. Surprisingly, the rate of 4-*exo* cyclisation is reduced by radical stabilising alkyl substituents at R^3 , R^5 and R^6 , and is higher when $R^1=R^2=Me$, $X=Br$ ((**176b**) and (**220b**)) than when $R^1=R^2=R^3=Cl$ ((**176a**) and (**220a**)). The fastest (reaction time < 2 hours) and also highest yielding (57-60%) cyclisation reactions occur when $R^1=R^2=Me$, $X=Br$, and $R^5=R^6=H$ ((**176b**) and (**220b**)).

A range of highly functionalised and novel β -lactam derivatives may be prepared in 3 steps (1-2 days) from unsaturated aldehydes using cheap starting materials and mild reaction conditions by the application of copper (I) mediated ATRC methodology. All three steps were found to be scalable to produce multigram quantities of β -lactam products. The functionalisation and biological screening of these β -lactam products will be investigated in due course.

Competition experiments indicate that an α -halo dienamide (**185**) ($R^3-R^6=H$) where 4-*exo* and 5-*exo* cyclisation can compete produces a γ -lactam by 5-*exo* cyclisation, and an α -halo dienamide (**186**) where 4-*exo* and 6-*exo* cyclisation can compete produce β -lactams by 4-*exo* cyclisation. These results indicate the rate order 5-*exo* > 4-*exo* > 6-*exo*. The rate of 4-*exo* cyclisation onto the dienamide system was found to be dependent on the nitrogen substituent (PG), with the rate of cyclisation being higher for the larger 4-methoxybenzyl group.

**4. SYNTHETIC STUDIES TOWARDS ZG-1494 α , AN INHIBITOR OF PAF
ACETYLTRANSFERASE**

4.1 INTRODUCTION

ZG-1494 α (**245**) is a novel inhibitor of platelet-activating factor (PAF) acetyltransferase, an essential enzyme in the remodeling pathway of platelet-activating factor synthesis (Figure 15).¹²⁷⁻¹³¹ It was identified by a high throughput screen of natural product extracts of microbial origin, and was isolated from an extract of a culture broth of *Penicillium rubrum* through bioassay fractionation. The structure of ZG-1494 α was determined by NMR experiments. A ¹³C-¹³C INADEQUATE was used to unambiguously determine the regiochemistry of this molecule.¹³²

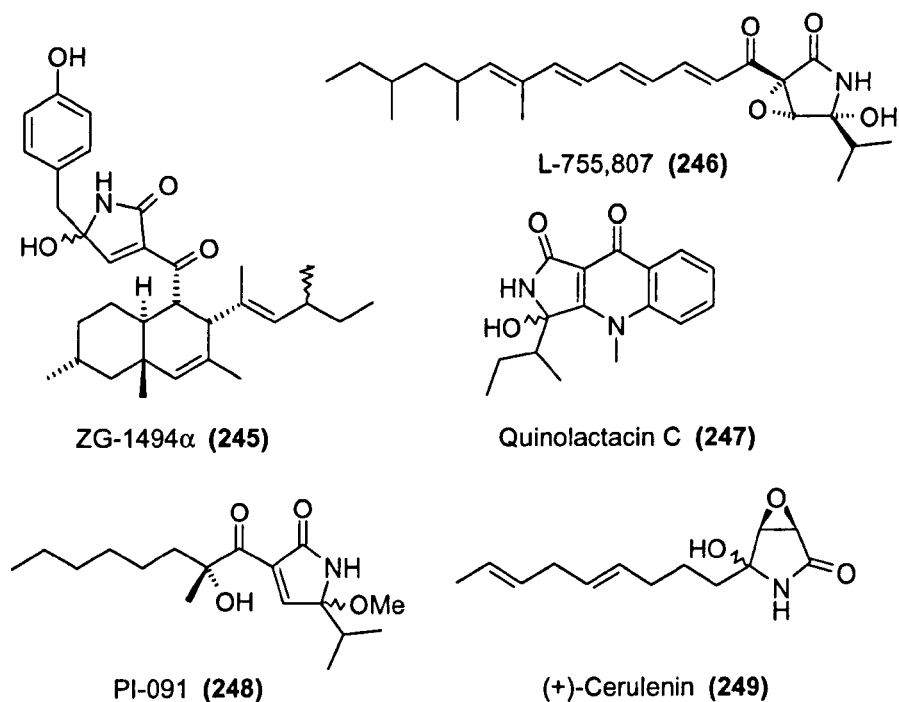
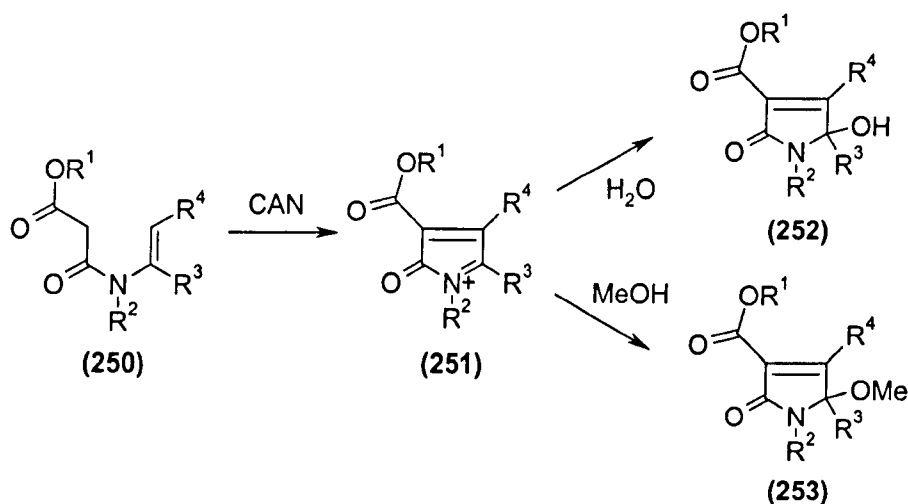


Figure 15

A key feature of the structure of ZG1494- α is the 5-hydroxy-1,5-dihydropyrrolin-2-one moiety, which is relatively rare amongst natural products. Closely related heterocyclic systems are found in the natural products L-755,807 (**246**),¹³³ Quinolactacin C (**247**),¹³⁴ PI-091 (**248**)¹³⁵⁻¹³⁶ and (+)-Cerulenin (**249**)¹³⁷⁻¹³⁹ (Figure 15). An opportunity exists to assemble the 5-benzyl-5-hydroxy-1,5-dihydropyrrolin-2-one ring of ZG-1494 α using a novel 5-*endo* radical cyclisation step.

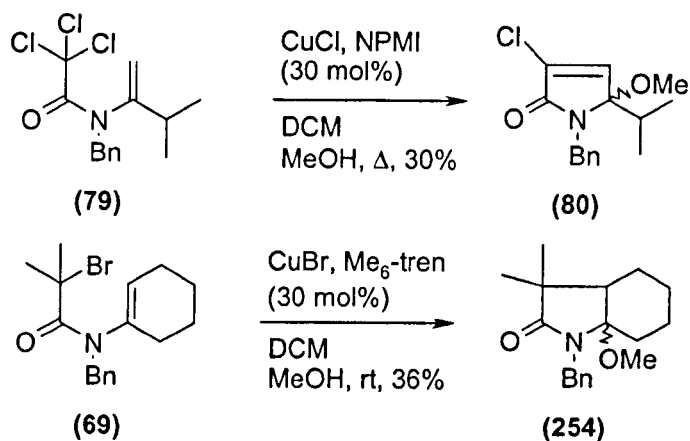
4.2 5-HYDROXY-1,5-DIHYDROPYRROLIN-2-ONE ASSEMBLY USING 5-*ENDO* RADICAL CYCLISATION

Ceric (IV) ammonium nitrate has been found to mediate the oxidative 5-*endo* radical-polar crossover reactions of β -enamide esters (**250**) to give 5-hydroxy- (**252**) or 5-methoxy-1,5-dihydropyrrolin-2-ones (**253**) (Scheme 98).⁷² Trapping of the cation intermediate (**251**) leads to 5-hydroxy- or 5-methoxy derivatives depending on whether water or methanol is present in the cyclisation reaction.



Scheme 98

Copper (I) mediated 5-*endo* cyclisation of α -halo enamides (**79**) and (**69**) in the presence of methanol have also been reported to produce 5-methoxy-1,5-dihydropyrrolin-2-ones (**80**) and (**254**) (Scheme 99).^{4,42} Both cerium (IV) and copper (I) radical cyclisation methodologies provide the opportunity to assemble heterocyclic ring fragments suitable for the synthesis of the natural products shown in Figure 15.



Scheme 99

4.3 SYNTHETIC APPROACHES TO ZG-1494 α

Disconnection of the C21-C22 bond of ZG-1494 α (**245**) (disconnection **a**) suggests either the Weinreb¹⁴⁰⁻¹⁴¹ or Stille¹⁴²⁻¹⁴³ coupling of a suitably protected intermediate (**255**) with (**256**) (Figure 16). Similarly, disconnection of the C4-C21 bond of ZG-1494 α (**245**) (disconnection **b**) suggests either the Weinreb or Stille coupling of a suitably protected intermediate (**257**) with (**258**).

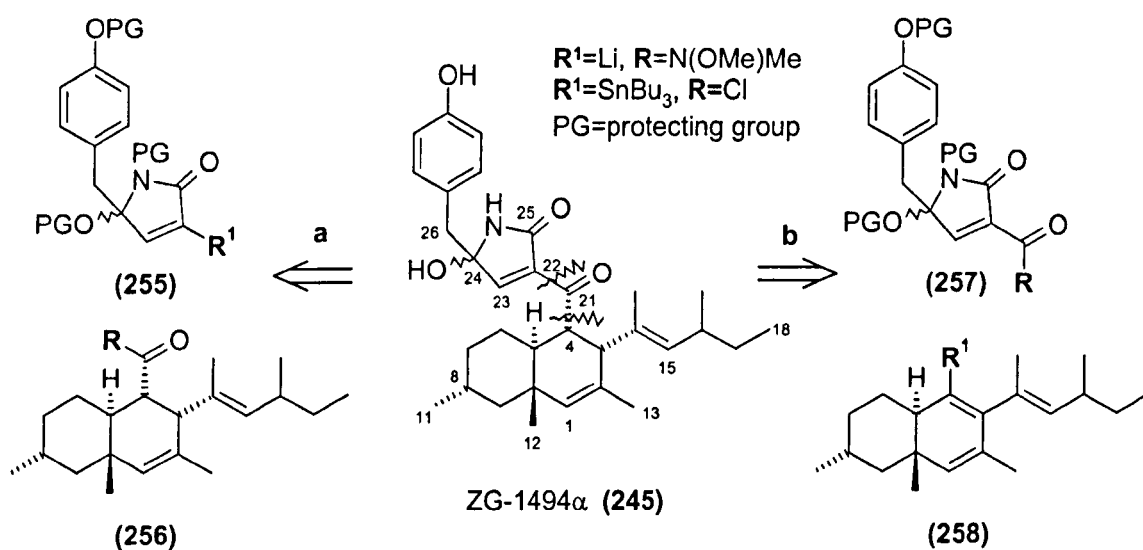


Figure 16

Intermediates **(255)** (disconnection **a**) could conceivably be formed from vinyl halide **(259)**, which may be accessible by the copper (I) mediated radical cyclisation of α -trihalo enamides **(260)** (Figure 17).

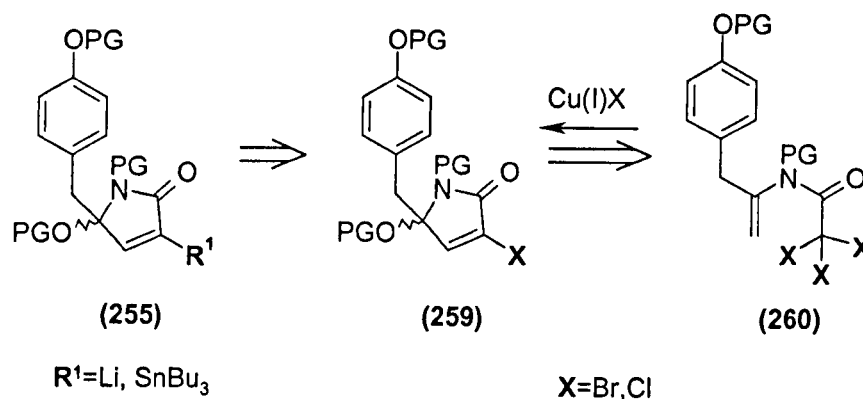


Figure 17

Intermediates **(257)** (disconnection **b**) could be prepared from ester **(261)**, which may be accessible by a cerium (IV) mediated radical cyclisation of β -enamide ester **(262)** (Figure 18).

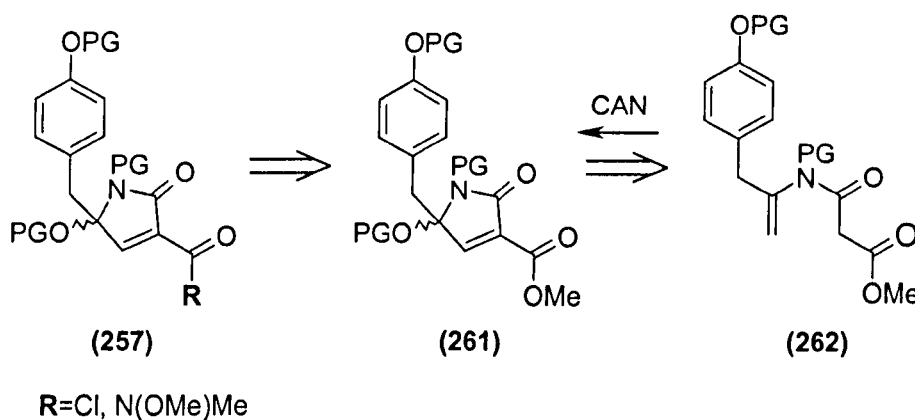
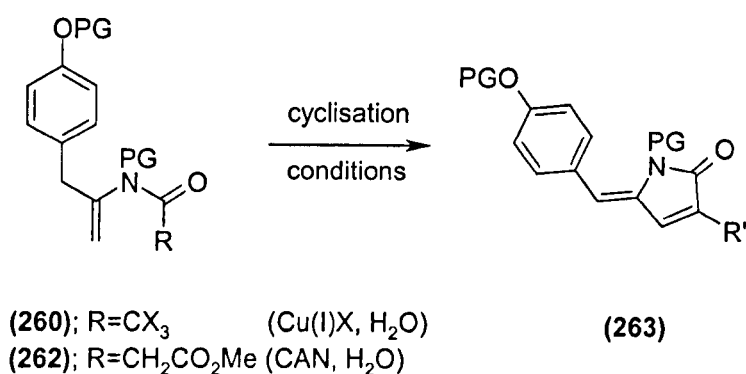


Figure 18

In both cyclisation reactions there is the possibility that elimination will occur under the reaction conditions to give a styryl derivative **(263)** (Scheme 100).¹⁴⁴ Formation of a styryl group could also take place by elimination of (PG)OH or water on removal of any of the oxygen or nitrogen protecting groups at a later stage in the synthesis. Such elimination could be prevented by the introduction of a blocking group, such as a carbonyl group, at the benzylic carbon, which could be removed at the end of the

synthesis. Alternatively, rehydration of the styryl olefin to give the desired 5-hydroxy functional group may be possible.¹⁴⁵⁻¹⁴⁶



Scheme 100

It was anticipated that both *5-endo* cyclisations would be promoted by the use of a bulky protecting group on the nitrogen, since such a group increases the population of the conformer which can cyclise. This protecting group must be easily removed at the end of the synthesis. The 4-methoxybenzyl group (PMB) is an obvious choice of protecting group since it is both sterically demanding and may also be removed under both oxidative and acidic conditions. Thus compounds (264)-(269) were selected as our initial targets (Figure 19).

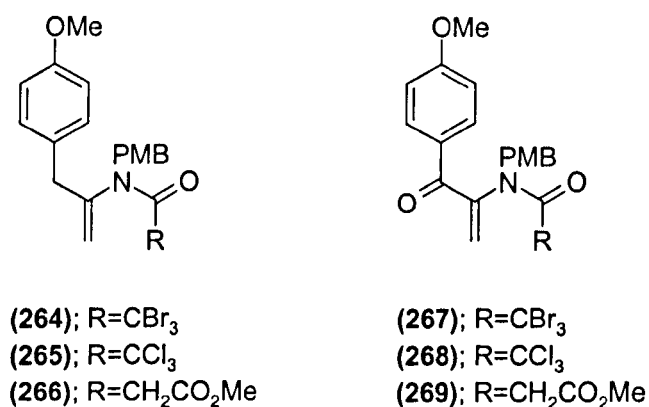
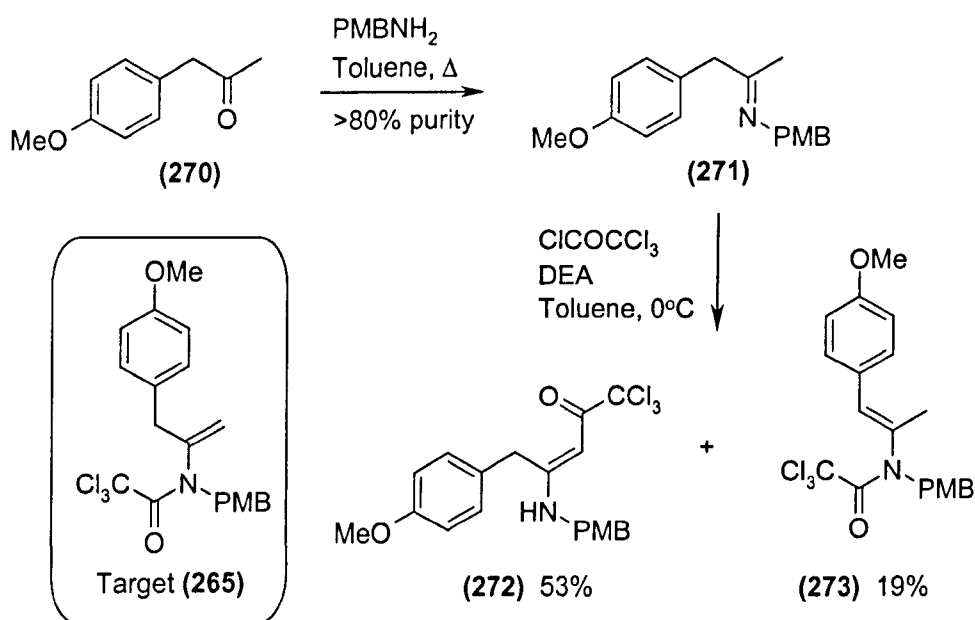


Figure 19

4.4 SYNTHESIS AND COPPER (I) MEDIATED 5-ENDO RADICAL CYCLISATION OF α -HALO ENAMIDES

The most direct approach to α -trihalo enamides (**264**) and (**265**) would involve a two step procedure from 4-methoxyphenylacetone in which the imine is formed and then acylated with the appropriate trihaloacetyl halide (Figure 19). There is the possibility, however, that two enamide regioisomers could form in the acylation step, the most probable outcome being the formation of the undesired isomer in which the enamide double bond is in conjugation with the phenyl ring. Despite the unlikely success of this sequence, these reactions were nevertheless attempted (Scheme 101).



Scheme 101

A 1:1 mixture of 4-methoxyphenylacetone (**270**) and 4-methoxybenzylamine was refluxed in toluene with a Dean-Stark trap to give the desired imine (**271**) in quantitative yield and reasonable purity. This was then treated with trichloroacetyl chloride (tribromoacetyl chloride was unavailable at the time) in the presence of *N,N*-diethylaniline (Scheme 101). The two products isolated by chromatography were the C-acylated product (**272**), and the undesired enamide (**273**) in which the enamide double bond is in conjugation with the phenyl ring. The predominance of a C-acylated product

came as a surprise since previous work within the group has suggested that use of *N,N*-diethylaniline (as opposed to a stronger base such as triethylamine) in enamide formation minimises the formation of the C-acylated byproduct.⁴² Both products (**272**) and (**273**) were found to be unstable in air, decomposing within days of their preparation. The regiochemistry of the products formed from the acylation of imine (**271**) with tribromoacetyl chloride was expected to be similar to that obtained with trichloroacetyl chloride. In addition, these products were anticipated to be extremely unstable. For these reasons, the reaction of (**271**) with tribromoacetyl chloride was not attempted.

To overcome the problem of regiochemistry in enamide formation, we proposed that a suitable fragment (**274**) could be synthesised by the 5-*endo* cyclisation of related α -trihalo enamide (**275**) (Figure 20). In precursor (**275**) the benzyl methylene group is replaced with a carbonyl group which blocks the preferred site of enolisation. This carbonyl group could be removed before the formation of the C21-C22 bond of ZG-1494 α (**245**) using a number of methods (Figure 16). This approach was attractive since the synthesis of radical precursors (**275**) was envisaged from D,L-serine (**276**), and the 5-*endo* cyclisation of related enamide esters (**277**) and enamide ketones (**278**), using tributyltin hydride as mediator, has already been reported.^{48,76-77,147-151} The presence of the keto group on the enamide carbon adjacent to the nitrogen captively stabilises the radical intermediate formed on 5-*endo* cyclisation.

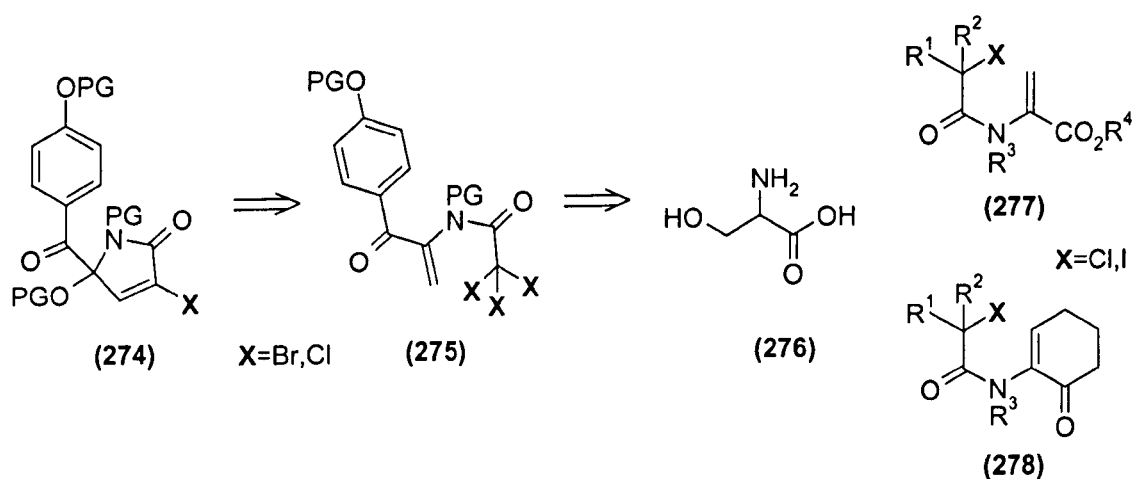
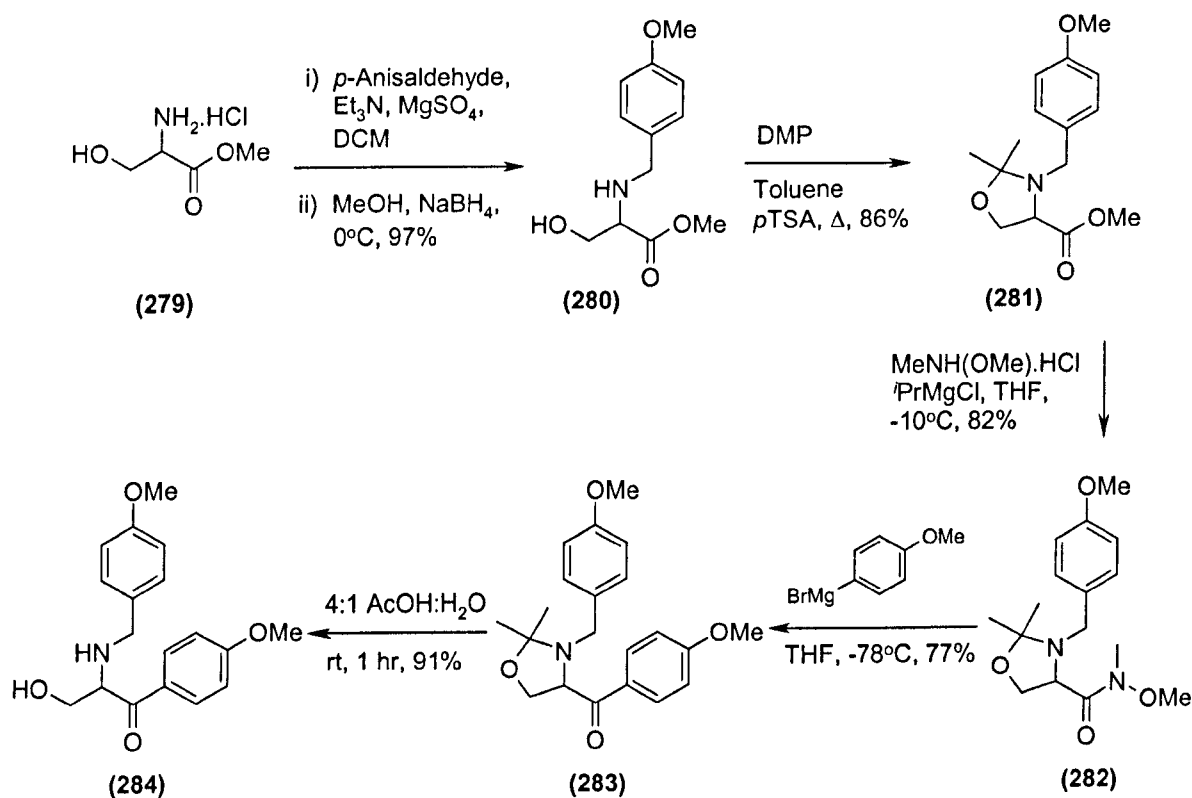


Figure 20

The synthesis of ketone intermediate (**284**) was achieved on a multigram scale in 48% yield by the five step route outlined in Scheme 102. The selected PMB nitrogen protecting group was introduced in the first step by the reductive alkylation of D,L-serine methyl ester (**279**) with *p*-anisaldehyde to give *p*-methoxybenzylamine (**280**) in excellent yield.^{149,152} The amino alcohol (**280**) was then protected as its oxazolidine derivative (**281**) by treatment with an excess of 2,2-dimethoxypropane in refluxing toluene with catalytic *p*-toluenesulfonic acid.¹⁵² Direct conversion of the fully protected ester (**281**) to the Weinreb amide (**282**) was achieved in 82% yield by the addition of the magnesium salt of *N,O*-dimethylhydroxylamine, thereby avoiding the problematic isolation of the carboxylic acid.¹⁵³ Grignard addition of excess 4-methoxyphenylmagnesium bromide to the Weinreb amide (**282**) proceeded smoothly to give ketone (**283**) in 77% yield.¹⁵⁴ Finally, the isopropylidene group was removed in 91% yield using 80% acetic acid in water at room temperature to give amino alcohol (**284**) which was purified by recrystallisation.



Scheme 102

Achieving yields of 86%, 82% and 77% for the ester (**281**), amide (**282**) and ketone (**283**) was not a straightforward process. Isolated yields of these three products after chromatography was initially found to be very low (45%, 37% and 35% respectively), despite clean conversions by tlc and good crude ^1H NMR spectra. After columning the ester (**281**) and amide (**282**) using silica gel with petrol/ethyl acetate mixtures as eluents, large quantities of deprotected products (**280**) and (**285**) were isolated from the column (44% and 48% respectively) which were not evident in the crude ^1H NMR spectra (Figure 21). It seemed highly probable that the acid labile oxazolidine group was unstable on silica. To test this theory, 0.015 mmol of each of the three compounds was stirred with 200 mg of silica gel in 1 ml of ethyl acetate for 16 hours. All three compounds (**281**), (**282**) and (**283**) were found to have decomposed to amino alcohols with 68%, 95% and 21% conversions respectively, showing the amide (**282**) to be the most unstable, followed by the ester (**281**), then ketone (**283**). Repeating the same reaction in 19:1 ethyl acetate:triethylamine gave 0%, 67% and 0% conversions to the amino alcohols respectively. By minimising the amount of silica gel used for chromatography and chromatography time, as well as using triethylamine in the eluent, isolated yields of (**281**), (**282**) and (**283**) were improved dramatically to 86%, 82% and 77%.

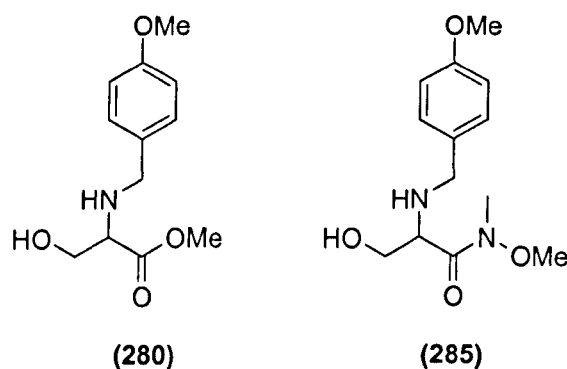
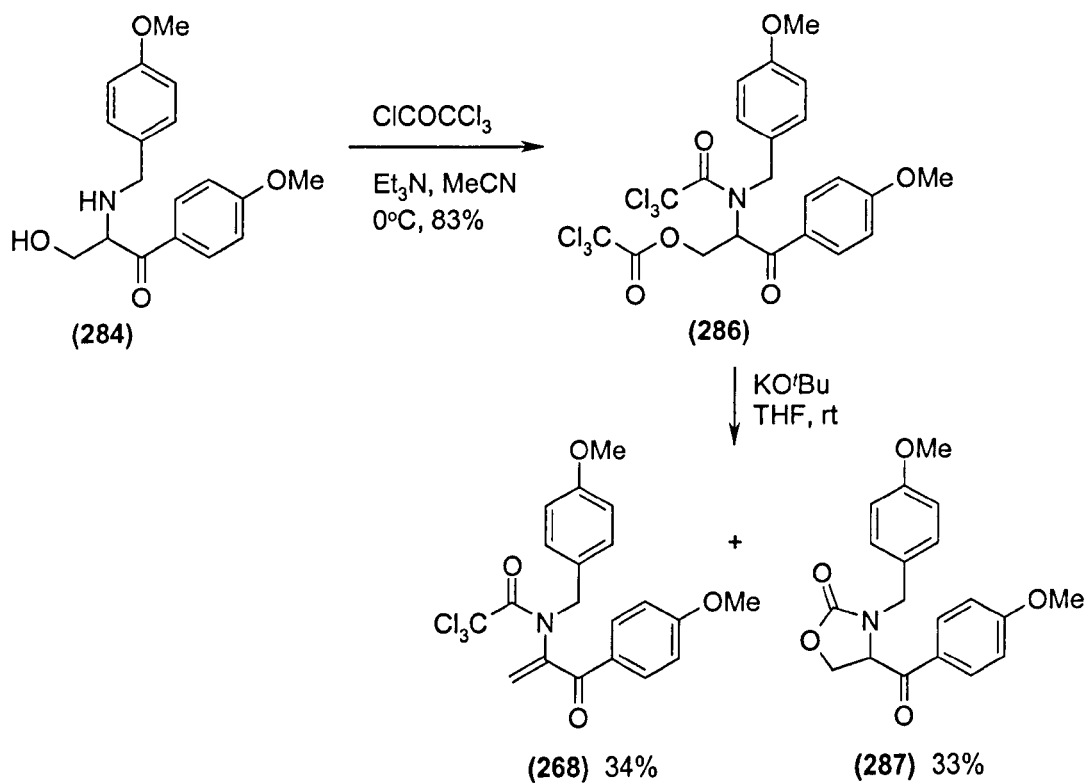


Figure 21

Treatment of amino alcohol (**284**) with both one and two equivalents of tribromoacetyl chloride in the presence of triethylamine gave only complex mixtures of products containing a small quantity of eliminated material with olefinic protons. Reaction of (**284**) with two equivalents of trichloroacetyl chloride, however, proved successful in preparing the desired amido ester (**286**) in excellent yield (Scheme 103). Elimination of

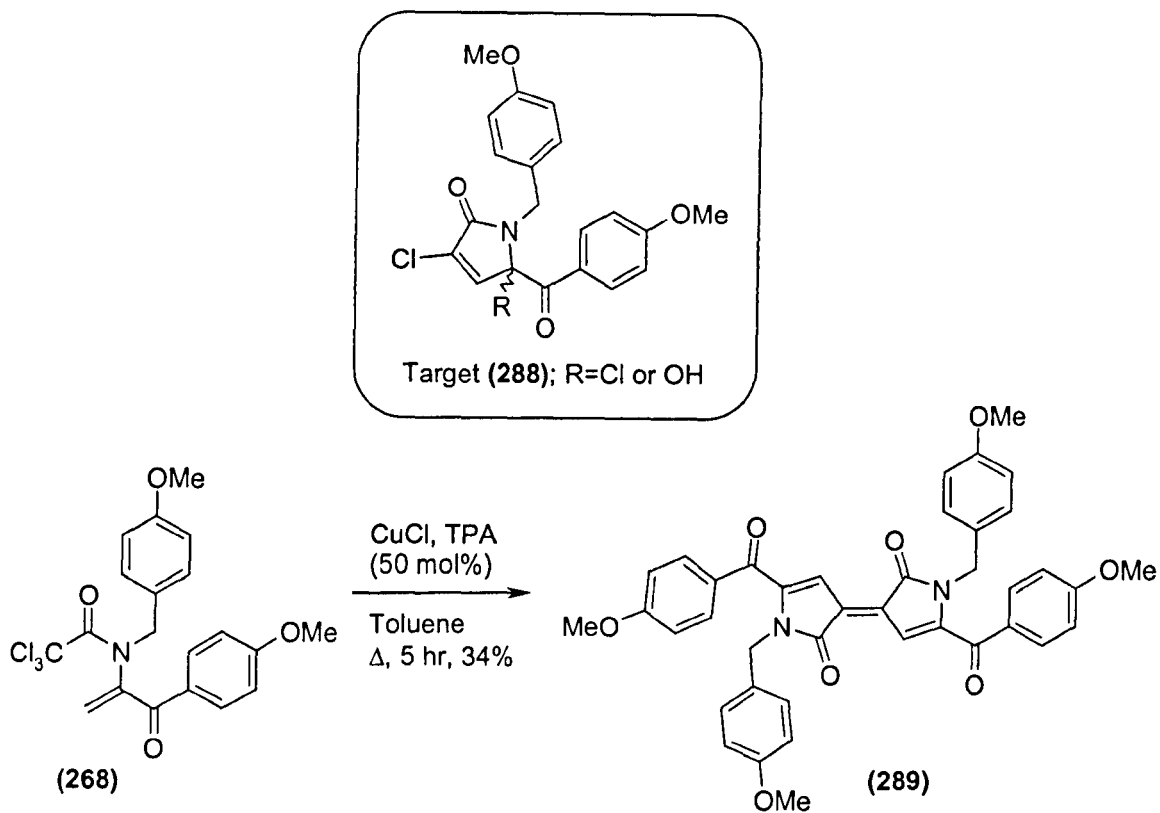
trichloroacetic acid to give the desired α -trichloro enamide (**268**) was then achieved using potassium *tert*-butoxide in THF. The enamide (**268**) was isolated in a low yield of 34% since this elimination reaction was accompanied by the competitive formation of oxazolidinone (**287**) in a similar yield. The formation of oxazolidinones has been reported from trichloroacetamides when a β -hydroxy group, protected as its TBDMS ether, is unmasked using TBAF.¹⁵⁵⁻¹⁵⁶



Scheme 103

With α -trichloro enamide (**268**) in hand, we were ready to explore the novel copper (I) mediated 5-*endo* cyclisation of this radical precursor. Enamide (**268**) was treated with 50 mol% Cu(I)Cl and TPA in refluxing toluene; no reaction was found to take place at room temperature under these conditions (Scheme 104). Disappointingly, the desired heterocyclic fragment (**288**) was not formed. Nevertheless, the result obtained for this reaction proved very interesting. Over the course of 5 hours at reflux temperature, all enamide (**268**) was seen to be consumed by tlc to give a more polar deep purple product together with baseline material. The purple product was purified, characterised and

finally shown to be a single isomer of the highly conjugated dimeric compound (**289**). The stereochemistry of the central double bond has been assumed since crystals of (**289**) suitable for x-ray crystallography could not be obtained.



Scheme 104

Trichotomine (**290**) and its derivatives,¹⁵⁷⁻¹⁶⁴ Trikendiol (**291**),¹⁶⁵ and compounds in the indigo group such as (**292**),¹⁶⁶ which have the same [3,3']bipyrrolidene-2,2'-dione core as (**289**), have been reported in the literature as dyes (Figure 22). These compounds, like (**289**), are highly coloured. The crystallography data for a trichotomine derivative suggests that the heterocyclic core of (**289**) is likely to be planar with C₂ symmetry about the axis perpendicular to this plane.¹⁶² Compound (**289**) is the first example of a compound of this class with a carbonyl group at the 5-position of the heterocycle.

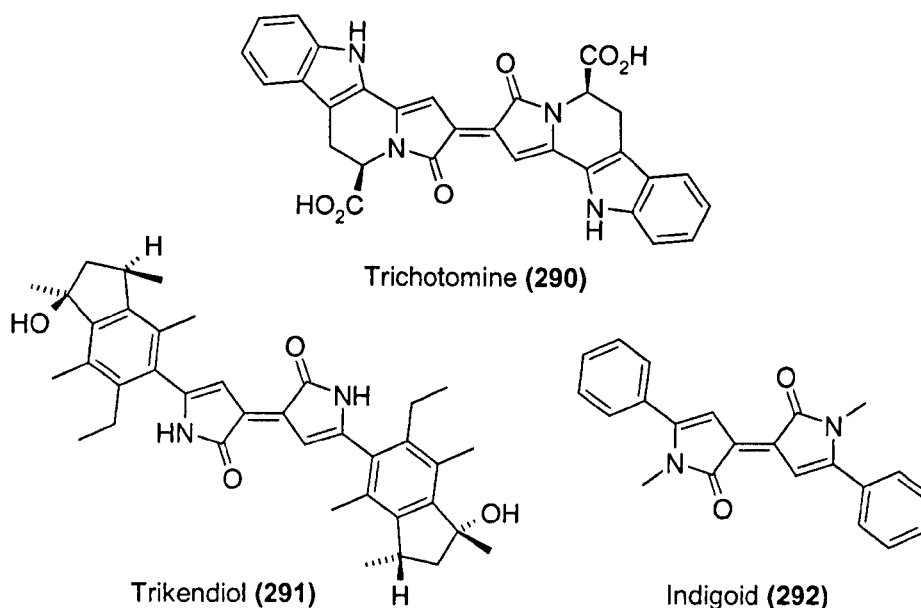
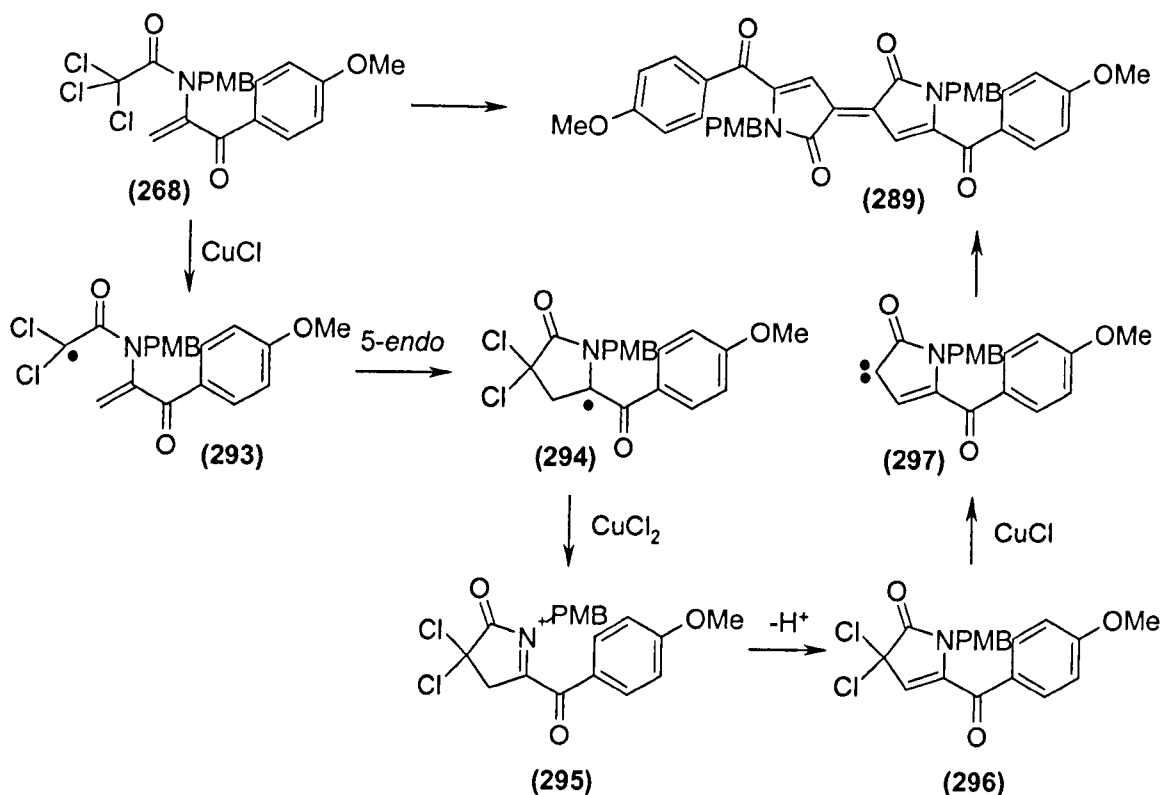


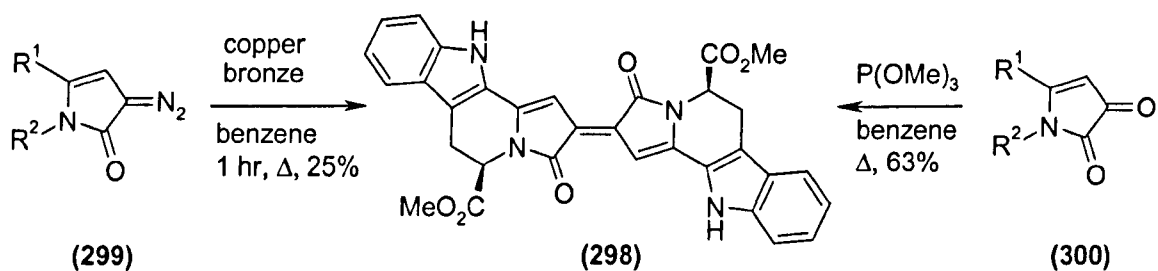
Figure 22

A possible mechanism for the formation of dimer (**289**) is outlined in Scheme 105. Reaction of α -trichloro enamide (**268**) with copper (I) chloride generates an initial tertiary radical (**293**) which undergoes *5-endo* cyclisation onto the enamide double bond to form captodatively stabilised radical (**294**). Subsequent oxidation of radical (**294**) with copper (II) gives iminium ion (**295**) which may form heterocycle (**296**) on proton loss. Further atom transfer of the chlorine atoms of (**296**) to copper (I) may give a carbene intermediate (**297**) which can dimerise to give isolated product (**289**) as a single isomer.

Interestingly, structurally related [3,3']bipyrrolidene-2,2'-diones have been accessed by the dimerisation of appropriate α -keto carbene-carbenoid precursors. Two alternative routes have been developed for the synthesis of the blue trichotomine diester (**298**) (Scheme 106).¹⁶⁷ Assembly of the desired core was achieved in low yield through copper assisted thermolysis of azo lactam (**299**). A more efficient route was achieved *via* carbene-mediated olefination of keto lactam (**300**) using trimethylphosphite. It is also worth noting that copper metal can react with *gem*-dichlorides such as α,α -dichloroacid ester in DMSO to produce copper carbenoid intermediates which dimerise to form substituted olefins.¹⁶⁸



Scheme 105



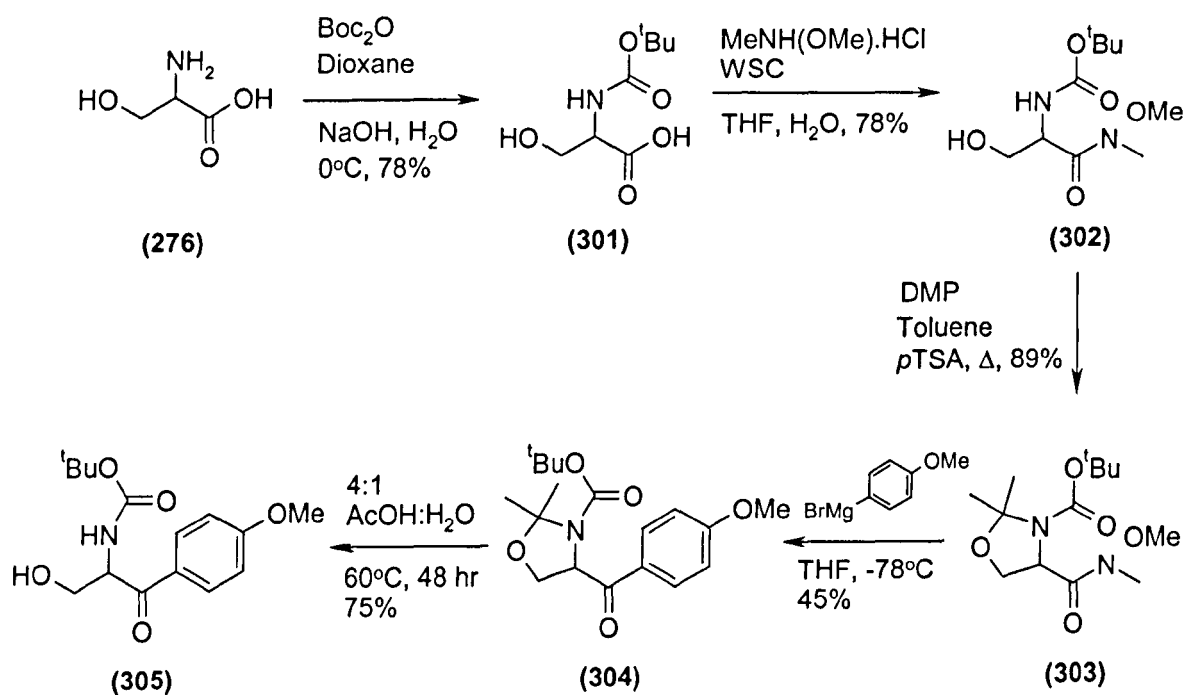
Scheme 106

Although the α -tribromo enamide radical precursor (267) could not be prepared, one anticipates that a similar dimerisation reaction would take place if it was treated with copper (I) bromide (Figure 19).

At this stage in our investigation, we wondered if an alternative nitrogen protecting group might provide the desired outcome in the key 5-endo radical cyclisation step by suppressing carbene formation. Having already investigated an electron donating alkyl

nitrogen protecting group (PMB), we decided to explore the electron withdrawing *tert*-butyl carbamate (Boc) nitrogen protecting group.

The five step synthesis of the Boc protected derivative (**305**) was achieved by the route outlined in Scheme 107. D,L-Serine (**276**) was protected as its *tert*-butyl carbamate (**301**), which was then converted to the Weinreb amide (**302**) by the coupling of the acid function of (**301**) with *N,O*-dimethylhydroxylamine in the presence of water soluble carbodiimide.¹⁶⁹ Treatment of amide (**302**) with 2,2-dimethoxypropane in the presence of catalytic *p*-toluenesulfonic acid gave clean conversion to the protected derivative (**303**) in 89% yield.¹⁶⁹ Oxazolidine (**303**) was found to exist as a mixture of rotational isomers in CDCl₃ and d₈-toluene at room temperature, as observed by two sets of signals in the NMR spectra. On warming the sample in d₈-toluene to 363K, exclusive formation of the thermodynamically more stable isomer was observed.



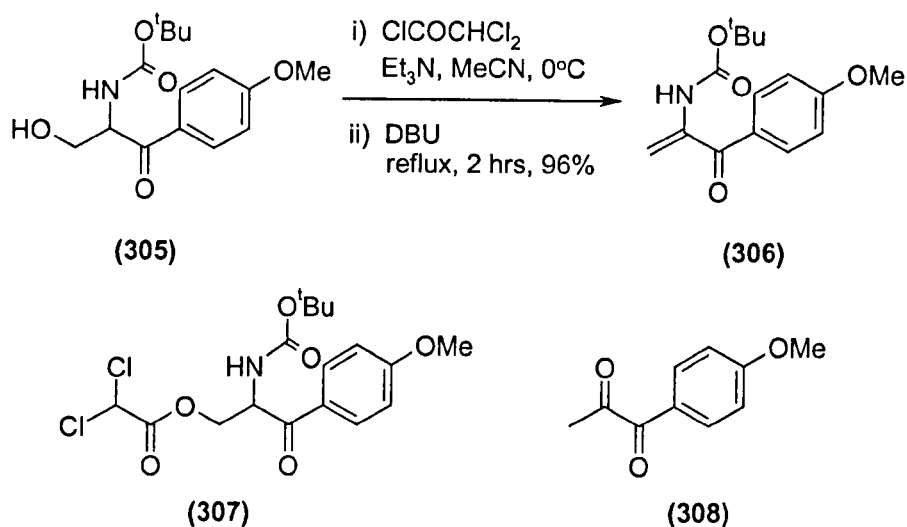
Scheme 107

Grignard addition of 4-methoxyphenylmagnesium bromide to (**303**) was found to give an optimum yield of 45% for ketone (**304**) using two equivalents of the Grignard reagent on

an 18 mmol scale (Scheme 107). As for amide (**303**), ketone (**304**) was found to exist as a mixture of rotational isomers in CDCl₃ and d₈-toluene at room temperature, and as a single isomer in d₈-toluene at 363K. When the Grignard addition was performed on a much smaller scale, the yield of (**304**) was reduced to 31%. The requirement to use an excess of Grignard reagent in this reaction led to considerable production of *bis*-aryl impurities which were not completely separated from the desired ketone (**304**) by chromatography. Trituration of the impure product with petroleum ether proved effective in removing these impurities. Guanti has also reported poor yields (<34%) for the addition of ethylmagnesium bromide and other organometallic reagents to Weinreb amide (**303**).¹⁶⁹

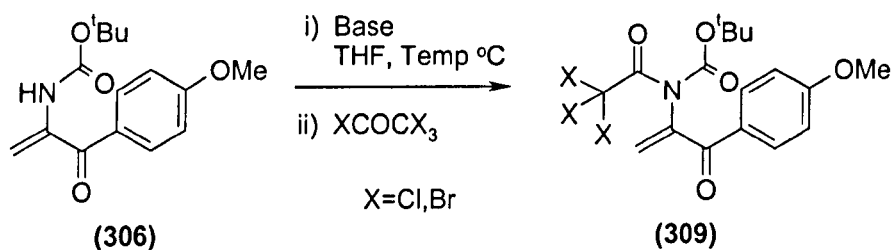
Considerable work was required to obtain an optimum yield of 75% for deprotection of the isopropylidene group of (**304**) to give alcohol (**305**) (Scheme 107). No reaction was observed at room temperature in 80% acetic acid after 16 hours, and a complex mixture of undesired products was obtained when (**304**) was heated to 100°C for 5 hours under the same conditions.¹⁷⁰⁻¹⁷¹ Finally, at an intermediate temperature of 60°C for a time period of 48 hours, a 75% yield of (**305**) was obtained with 10% recovery of starting material. Deprotection of (**304**) with catalytic *p*TSA in methanol was also tried, but this reaction was found to be exceedingly slow at room temperature and on heating.¹⁶⁹

Conversion of β-hydroxy ketone (**305**) to enone (**306**) was achieved in excellent yield by a two step, one-pot sequence involving formation of the dichloroacetate (**307**) followed by elimination of dichloroacetic acid with DBU, similar to that utilised by Parsons (Scheme 108).¹⁷² The elimination step was performed in refluxing acetonitrile since no reaction was observed in refluxing DCM, and the inseparable byproduct dichloro-acetic acid 2-chloro-ethyl ester was formed in refluxing DCE. Initially, desired enone (**306**) was only obtained in 28% yield, with 30% formation of diketone (**308**), when the DBU was removed by a 10% citric acid wash. The yield of enone (**306**) was improved dramatically to 96% when the reaction mixture was simply concentrated under reduced pressure and purified directly by flash column chromatography, which is an improvement on the yields reported by Parsons for related intermediates.



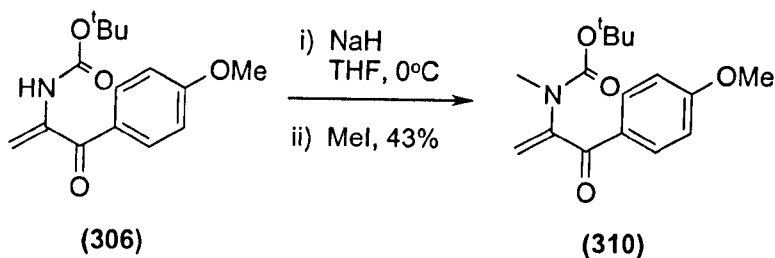
Scheme 108

Unfortunately, the preparation of the desired α -trihalo enamides (**309**) was found to be unachievable due to problems encountered in the final step of the synthesis (Scheme 109). Treatment of **(306)** with a range of strong bases followed by the trihaloacetyl halide invariably gave complex mixtures of products, recovered starting material, or diketone **(308)**. The alternative reaction of the alcohol precursor **(305)** with two equivalents of base followed by two equivalents of acid halide simply gave enone **(306)**.



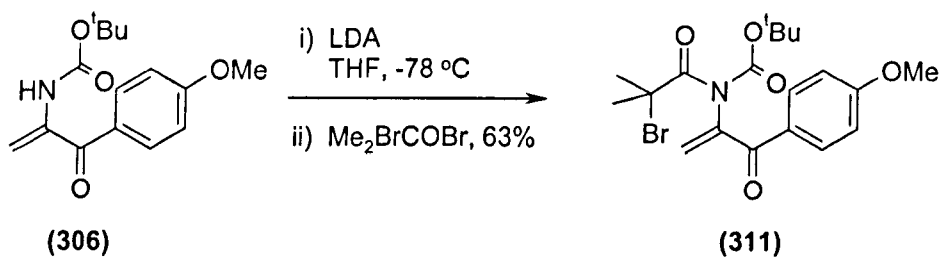
Scheme 109

Deprotonation of **(306)** using sodium hydride, followed by reaction with methyl iodide, did, however, form *N*-methylated product **(310)** in 43% yield, suggesting that problems encountered in the formation of **(309)** occur in the second acylation step (Scheme 110).



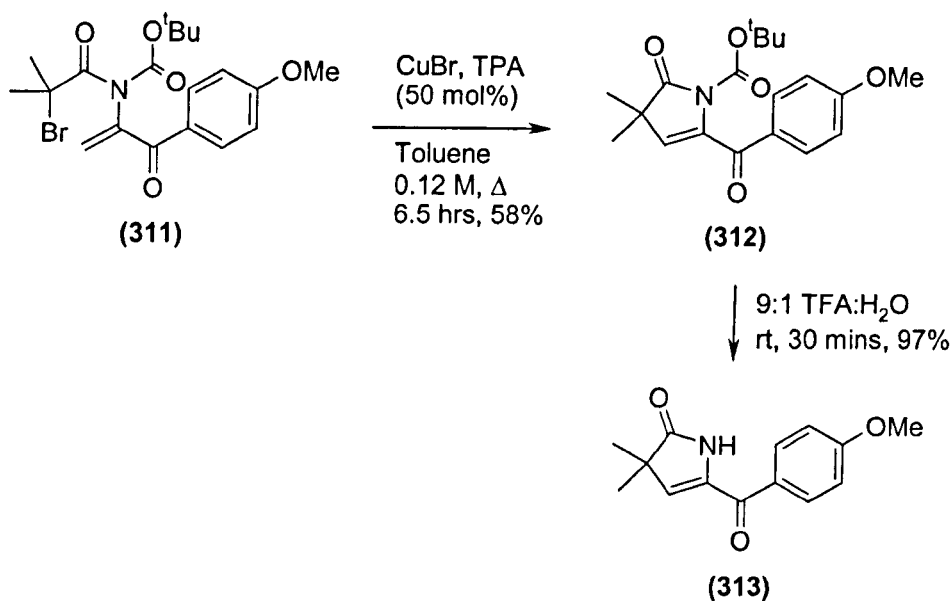
Scheme 110

By changing the base to lithium diisopropylamide, acylation of **(306)** with 2-bromoisobutyryl bromide to give **(311)** was also achieved in 63% yield (Scheme 111). Inexplicably, enamide **(311)** was not formed when sodium hydride was used as the base in this reaction.



Scheme 111

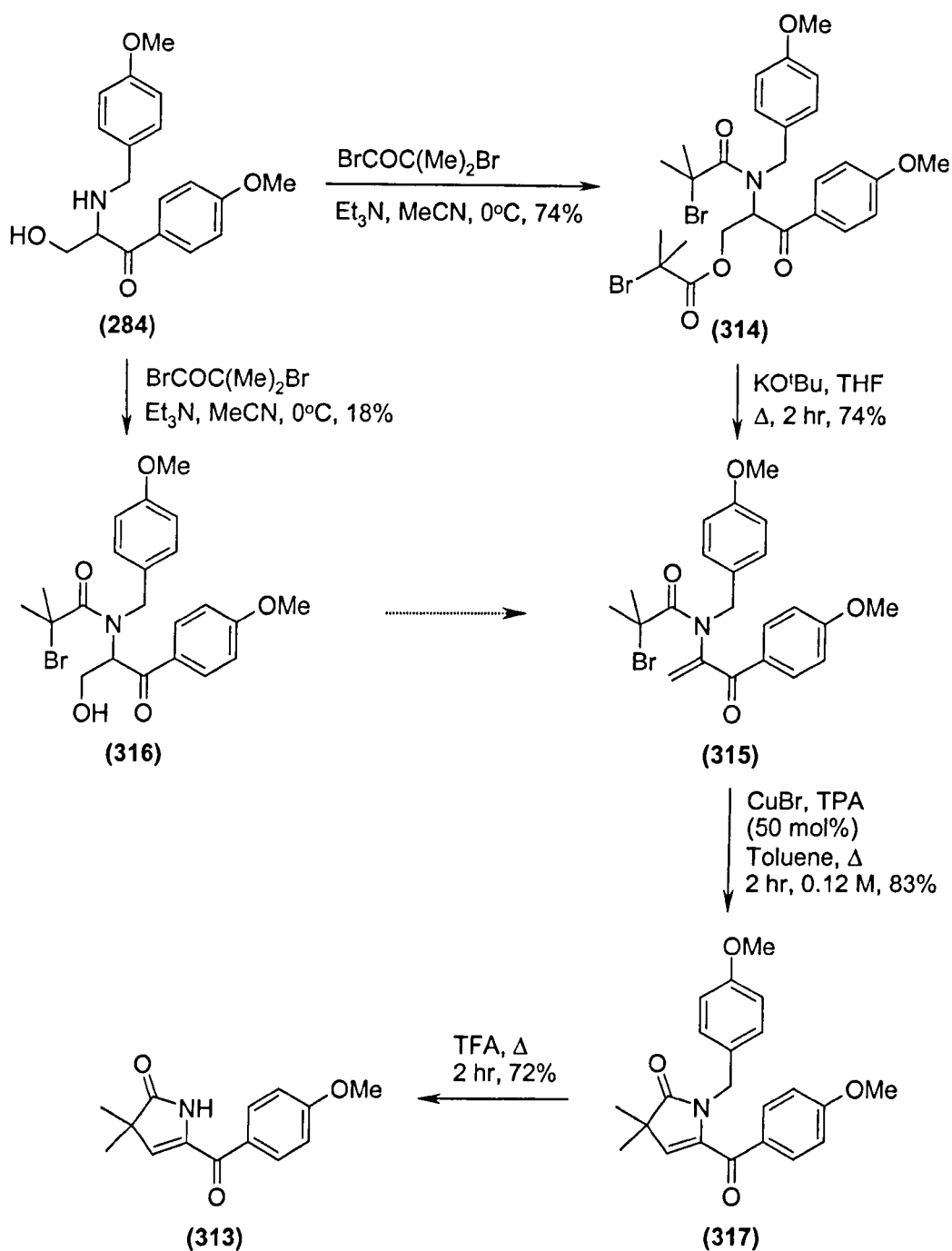
Having prepared α -bromo enamide **(311)**, we decided to investigate the treatment of **(311)** with copper (I) bromide. The 5-*endo* cyclisation of novel radical precursor **(311)** was achieved using 50 mol% Cu(I)Br and TPA in refluxing toluene to give heterocycle **(312)** in 58% yield (with 40% recovered starting material) after 6.5 hours (Scheme 112). The reaction appeared to stop after four hours, and leaving the reaction for longer periods of time did not improve the yield of **(312)**. Satisfyingly, lactam **(313)** was then prepared in excellent yield by the facile removal of the Boc group of **(312)** using trifluoroacetic acid.¹⁷³



Scheme 112

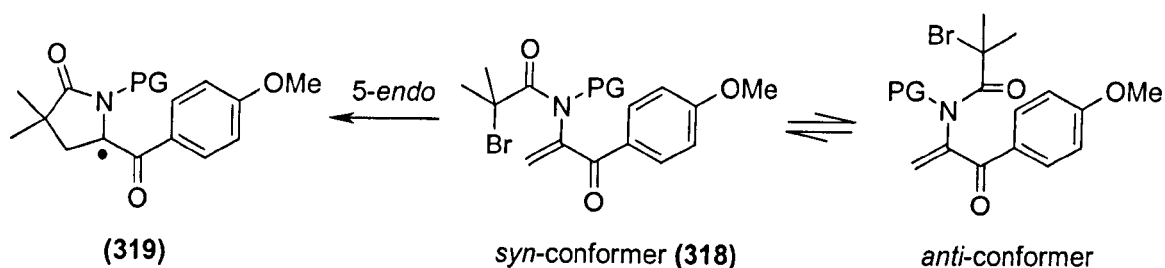
Having successfully achieved the *5-endo* cyclisation of (311), we decided to compare the rate of cyclisation of (311) with the PMB protected analogue (315) (Scheme 113). α -Bromo enamide (315) was prepared in good yield from amino alcohol (284) using the previously employed *bis*-acylation elimination approach. As anticipated, the elimination reaction was not accompanied by the formation of an oxazolidinone byproduct. The amido alcohol (316) could only be formed in 18% yield from (284) preventing a viable route to enamide (315) by elimination of (316).

The *5-endo* cyclisation of enamide (315) was achieved using 50 mol% Cu(I)Br.TPA in refluxing toluene to give (317) in 83% yield after two hours. All starting material was consumed in this reaction, and the cyclisation was found to be faster and higher yielding than the cyclisation of the analogous Boc protected derivative (311) under the same conditions. Deprotection of the PMB group was achieved using TFA at reflux temperature to give (313) in 72% yield.¹⁷⁴ Use of ceric (IV) ammonium nitrate proved unsuccessful in removing the protecting group.¹⁷⁵



Scheme 113

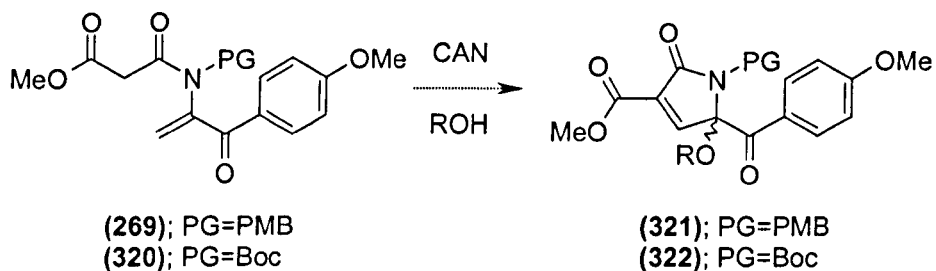
This difference in rate is most probably due to a larger population of the *syn*-conformer (318) which can cyclise, and also due to greater stability of the radical (319) formed on 5-*endo* cyclisation, when PG=PMB than when PG=Boc (Scheme 114). In radical (319) mesomeric stabilisation by the nitrogen lone pair is likely to be greater when PG=PMB.



Scheme 114

4.5 SYNTHESIS OF β -KETO ENAMIDES

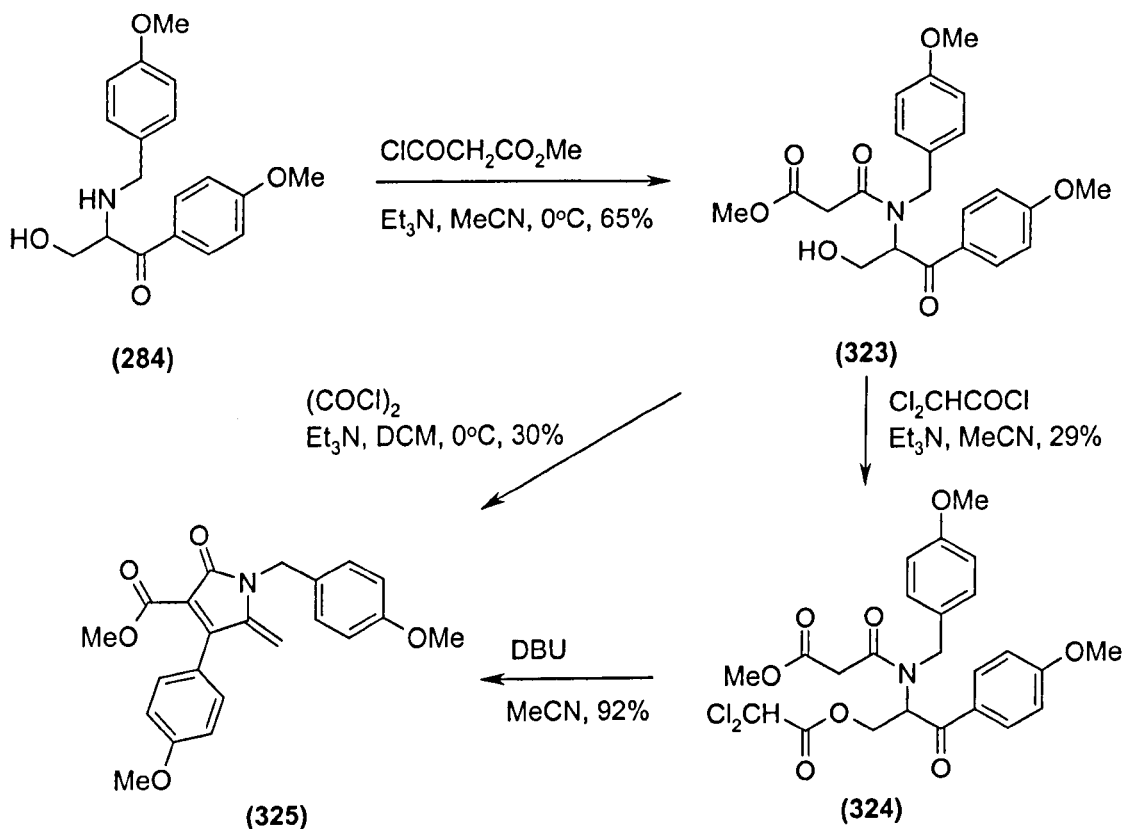
Having evaluated α -trichloro enamide (**268**) as a potential radical precursor to vinyl halide fragment (**288**) (Scheme 104), we next decided to evaluate the feasibility of synthesising β -enamide esters (**269**) and (**320**) which could potentially cyclise in the presence of ceric (IV) ammonium nitrate to give useful fragments (**321**) and (**322**) (Scheme 115).⁷²



Scheme 115

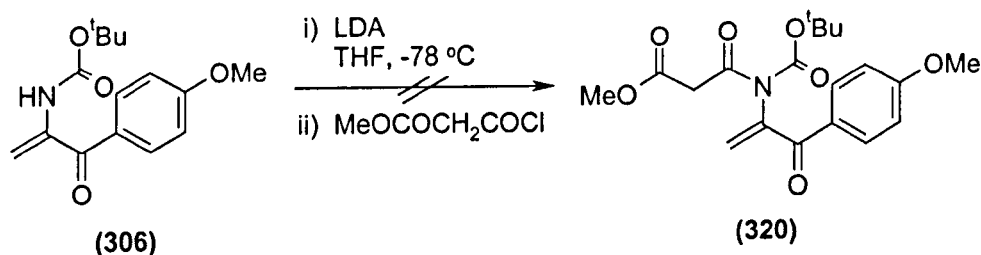
The approach taken towards the synthesis of β -enamide ester (**269**) is outlined in Scheme 116. Selective *N*-acylation of amino alcohol (**284**) with one equivalent of methyl malonyl chloride gave amido alcohol (**323**) in reasonable yield. Unfortunately, however, all attempts to eliminate the alcohol to give the desired enamide (**269**) resulted in the formation of heterocycle (**325**) which is formed by an intramolecular condensation reaction. Product (**325**) was formed in 92% yield from dichloroacetate (**324**) on treatment with DBU,¹⁷² and in 30% yield by reaction of alcohol (**323**) with oxalyl chloride in the

presence of triethylamine.¹⁷⁶ Other conditions investigated for the direct transformation of alcohol **(323)** to **(269)** include CDI/Et₃N,¹⁷⁷ DiPCD/Cu(I)Cl¹⁷⁸ and DAST/pyridine.¹⁷⁹ All of these methods gave complex mixtures of products with small amounts of the undesired product **(325)**.



Scheme 116

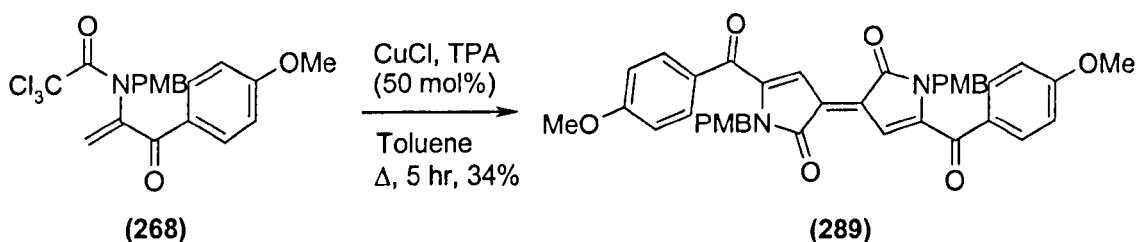
The attempted synthesis of β -enamide ester **(320)** by deprotonation of Boc protected intermediate **(306)** with LDA followed by treatment with methyl malonyl chloride at -78°C gave only recovered starting material (Scheme 117).



Scheme 117

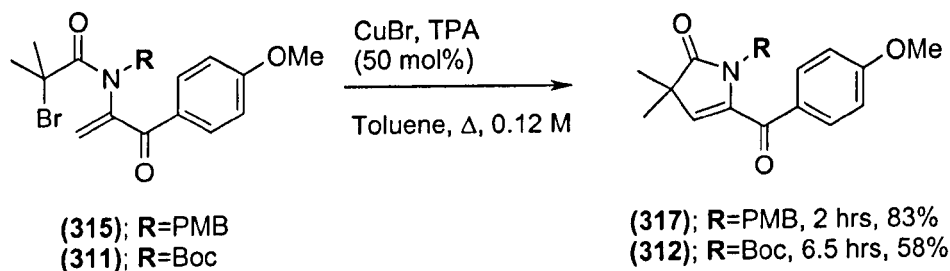
4.6 CONCLUSIONS

Studies towards the heterocyclic ring fragment of ZG-1494 α have resulted in the evaluation of three novel copper (I) mediated 5-*endo* cyclisation reactions involving captodatively stabilised radicals. Cyclisation of α -trichloro enamide (**268**) in the presence of catalytic copper (I) chloride was found to produce the purple dimeric product (**289**), which is likely to be formed from a carbene intermediate (Scheme 118).



Scheme 118

5-*Endo* cyclisation of α -bromo enamides (**315**) and (**311**) with catalytic copper (I) bromide was found to give 1,3-dihydropyrrol-2-ones (**317**) and (**312**) in 83% and 58% yields (Scheme 119). The reaction time required and yield obtained was found to be related to the nitrogen protecting group, with the PMB protected radical precursor (**315**) giving the highest yield and shortest reaction time. The nitrogen protecting group is believed to affect both the conformer population of the radical precursor and the stability of the captodatively stabilised radical formed on 5-*endo* cyclisation. Both PMB and Boc protecting groups were readily removed from (**317**) and (**312**) under acidic conditions.



Scheme 119

The synthesis of **(268)**, **(315)** and **(311)** was achieved in several steps from the naturally occurring amino acid D,L-serine or D,L-serine methyl ester.

5. SOLID SUPPORTED CATALYSTS FOR COPPER (I) MEDIATED RADICAL CYCLISATION

5.1 INTRODUCTION

Homogeneous catalysis with transition metals is an important area of organic synthesis where very few examples have been developed into industrial processes. The underutilisation of this methodology is due to the difficulty in removing the toxic transition metal from the product, and the inability to recycle the catalysts, which are often very expensive. To overcome these problems, there has been a growing interest in the use of solid supported transition metal complexes as catalysts for organic transformations.¹⁸⁰⁻¹⁸² This heterogenisation of the transition metal complex facilitates the separation of the catalyst from reagents and products, simplifies the efficient recovery of the expensive or toxic catalysts, and potentially allows the application of the immobilised catalysts to continuous flow type processes. A large number of solid supported catalysts with different supports, linkers and catalyst structures have been developed and applied in the areas of hydrogenation, dihydroxylation, epoxidation, cycloaddition, 1,4-conjugate addition, aldol, carbonyl alkylation, metathesis, and carbon-carbon cross-coupling chemistry.^{180,183}

Solid supported catalysts have also found application in atom transfer polymerisation (ATRP), which is a living radical polymerisation process using transition metal complexes as catalysts to mediate the propagation of the polymerisation.¹⁸⁴ Solution phase ATRP has proved effective in the synthesis of a wide range of polymers with controlled structures. Various solution phase ATRP catalysts have been developed based on Cu (I), Ni (II), Ru (II), Fe (II), Rh (II) and Te, but those based on Cu (I) has been studied most extensively. The ligands most suitable for copper (I) based ATRP catalysts are usually pyridines or multidentate amines, which are similar to those found to be effective for copper (I) mediated atom transfer radical cyclisation (ATRC). However, a high concentration of catalyst is required in the ATRP process, and these catalysts generally co-precipitate in the products as coloured and toxic contaminants.

Immobilisation of the copper (I) ATRP catalyst on a solid support enables the efficient and economical removal of the catalyst residue from polymeric products in large-scale industrial productions. Figure 23 illustrates some of the silica and polystyrene supported

ligands that have been purchased or prepared, complexed to copper (I) bromide, and used as ATRP catalysts by Kicelbick and Matyjaszewski ((326)-(328)),¹⁸⁵ Haddleton ((329)),¹⁸⁶ Shen ((330)-(332)),¹⁸⁷⁻¹⁸⁸ Nguyen and Jones ((333)),¹⁸⁹⁻¹⁹⁰ and Honigfort and Brittain ((334)-(335))¹⁹¹ over the past six years. In spite of the advantages of easy catalyst separation/recovery and the possibility of scaling up with these solid supported copper (I) ATRP catalysts, control over polymerisation was found to be inferior to that achieved with analogous homogeneous catalysts. Current research effort aims to find a catalyst that is homogeneous for catalysis but heterogeneous for separation/recovery.¹⁸⁴

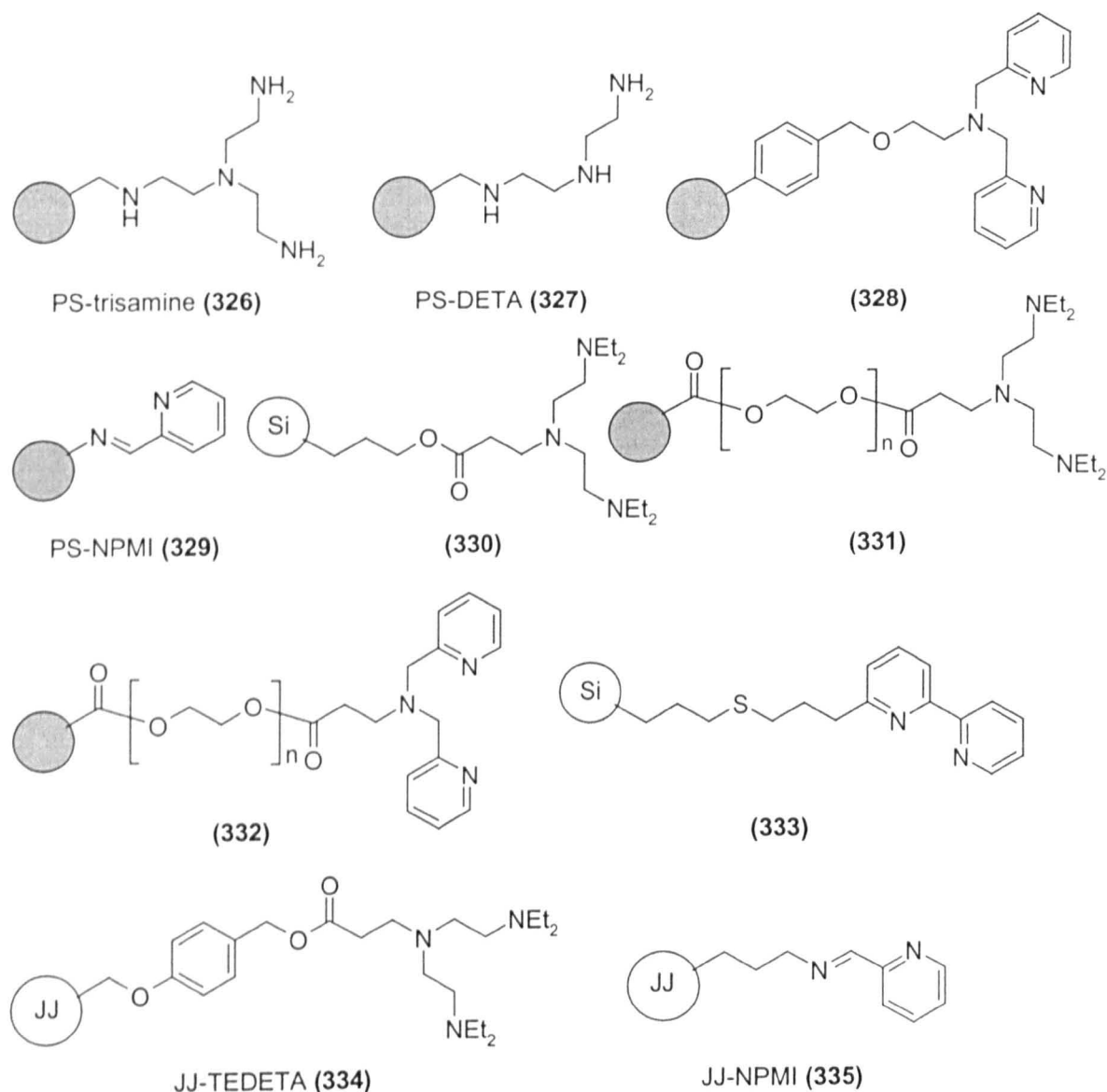
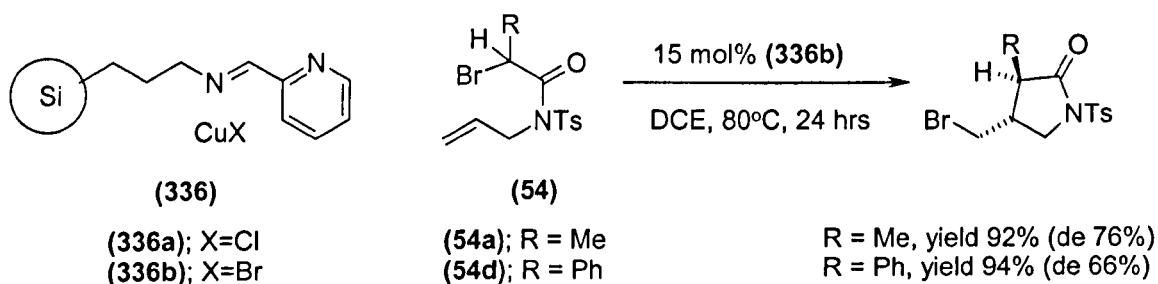


Figure 23

The application of solid supported copper (I) catalysts to ATRC reactions is an area which remains largely unexplored. The Clark group has prepared silica supported catalysts (**336a-b**) whose structures are based on the active solution ligand *N*-alkyl-2-pyridylmethanimine (NPMI) (**40**) (Scheme 120, Figure 2).³⁵ Reaction of pyridine-2-carboxaldehyde with commercially available aminopropylated silica, followed by stirring of the solid supported methanimine ligand with a solution of either CuCl or CuBr gave dark brown catalysts (**336a-b**). These catalysts have been shown to be active in the ATRC of trichloro-, dichloro- and monobromo substrates. Both efficient 5-*exo* and 5-*endo* cyclisations could be mediated with this reagent system. In addition, the catalyst (**336a**) was found to be re-usable in the cyclisation of *N*-tosyl-*N*-allyl-2,2,2-trichloroacetamide at room temperature albeit with a decrease in activity with each reaction.



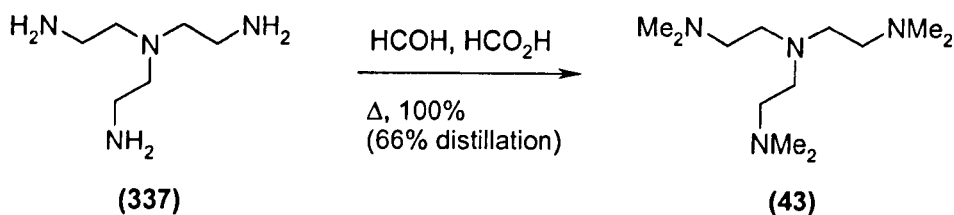
Scheme 120

The solid supported catalysts (**336a-b**) were found to be less active than their solution equivalent (**40**) (Figure 2, Chapter 1). Since the rate enhancement for solution phase ATRCs generally follows the order Me₆-tren (**43**) > PMDETA (**42**) > NPMI (**40**), it was anticipated that immobilisation of Me₆-tren and PMDETA onto solid supports would enable access to re-usable solid supported catalysts which are more active than catalysts (**336a-b**).

5.2 SYNTHESIS OF SOLID SUPPORTED COPPER (I) CATALYSTS FOR ATOM TRANSFER RADICAL CYCLISATION

5.2.1 Synthesis and Characterisation of Solid Supported Me₆-tren Copper (I) Catalysts

N,N,N',N',N'',N''-hexamethyltriethylenetetramine (Me₆-tren) (**43**) may be synthesised by the Eschweiler Clarke reductive methylation of commercial *tris*-(2-aminoethyl)amine (**337**).¹⁹² Treatment of (**337**) with an excess of formaldehyde and formic acid at reflux over 16 hours gives Me₆-tren (**43**) in quantitative crude yield (Scheme 121).

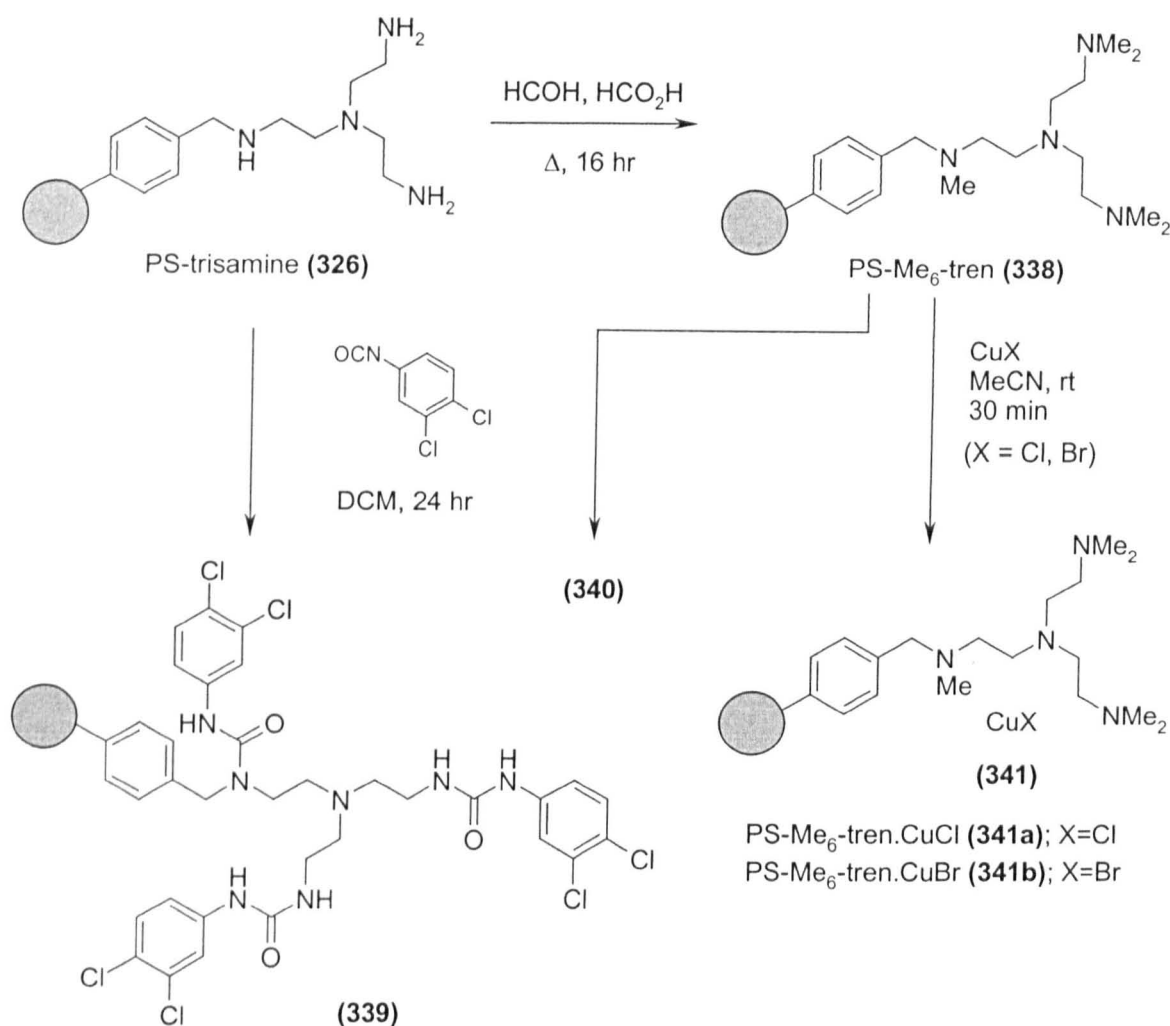


Scheme 121

The same Eschweiler Clarke conditions were applied to PS-trisamine (**326**) (*ex* Argonaut) to synthesise PS-Me₆-tren (**338**) (Scheme 122).¹⁹³ PS-Trisamine, a polystyrene backbone that has been functionalised with *tris*-(2-aminoethyl)amine, is extensively used as a scavenging reagent for the removal of excess acid halides or isocyanates from solution phase combinatorial libraries.¹⁹⁴ It is synthesised on a large scale industrially by the reaction of *tris*-(2-aminoethyl)amine (**337**) with Merrifield resin.¹⁹⁴

Product resin (**338**) was characterised using microanalysis, infra-red spectroscopy¹⁹⁵ and other tests which sensitively determine the presence of primary and secondary amines.¹⁹⁶ The extent of methylation of starting resin (**326**) was partly determined by reaction of both PS-trisamine (**326**) and product (**338**) with an excess of the highly reactive electrophile 3,4-dichlorophenyl isocyanate.¹⁹⁴ Comparison of the chlorine content of products (**339**) and (**340**) indicated that less than 0.7 of 5 possible methylation sites on (**326**) had been unmethylated using the Eschweiler Clarke conditions (Table 7). The

absence of primary amines in the product resin (**338**) was confirmed by a negative Kaiser test,¹⁹⁶ although the *p*-chloranil test indicated that secondary amines were still present. Nitrogen analysis of (**338**) indicated the loading of the tetramine ligand on the polystyrene support to be 1.02 mmol/g.



Scheme 122

Treatment of PS-Me₆-tren (**338**) with 1.2 equivalents of copper (I) halide in acetonitrile furnished PS-Me₆-tren.CuX catalysts (**341a-b**) as bright green resin beads. These were washed with acetonitrile, dried to constant weight and then stored under nitrogen. Nitrogen and ICP copper analysis of (**341a-b**) indicated loading of the Me₆-tren ligand and copper on the solid supported catalysts. As can be seen in Table 7, the loading of copper was found to be higher than the loading of ligand in both cases. The infra-red

spectra of (326), (338), (341a) and (341b) are shown in Figure 32 (Appendix). The infra-red spectra of all ligands and catalysts discussed within this section are also given in the Appendix (Figures 31-41).

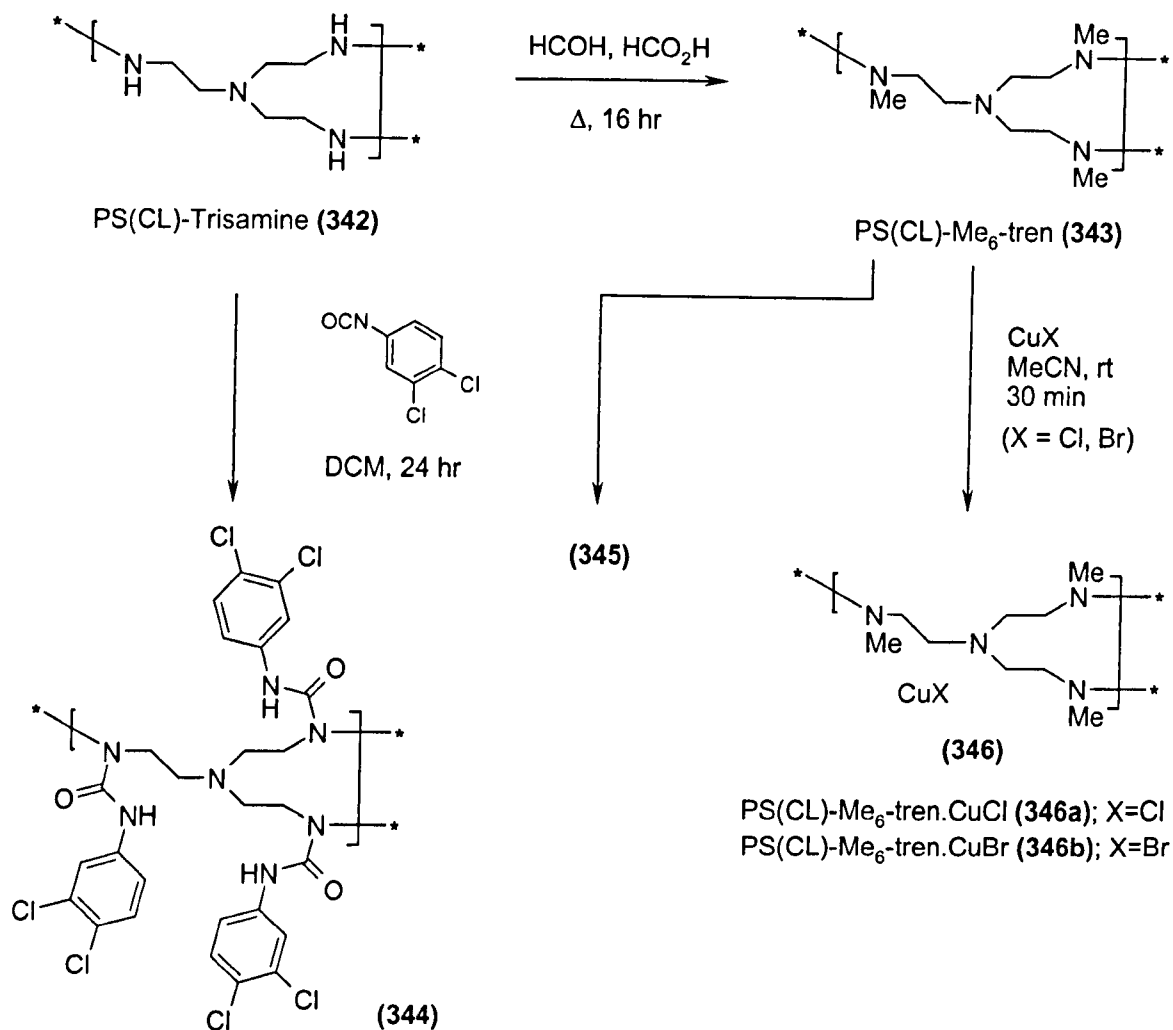
Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cl	%Cu	Loading Copper (mmol/g)
PS-Trisamine (326)	81.82	8.16	6.59	1.18	0.58	NA	NA
PS-Me ₆ -tren (338)	84.34	8.54	5.69	1.02	0.14	NA	NA
(339)	70.31	6.06	6.29	NA	12.78	NA	NA
(340)	81.73	8.32	4.24	NA	1.72	NA	NA
PS-Me ₆ -tren.CuCl (341a)	69.98	7.05	4.81	0.858	NA	8.10	1.27
PS-Me ₆ -tren.CuBr (341b)	68.04	6.87	4.67	0.834	NA	6.78	1.07

^a All numerical values are the mean of duplicate microanalysis results

Table 7

The same Eschweiler Clarke methodology was applied to commercial resin (342) (*ex* Aldrich) to synthesise a further polystyrene supported Me₆-tren ligand, PS(CL)-Me₆-tren (343) (Scheme 123). Unlike (326), the tetramine unit in starting resin (342) is cross-linked to the polymer support.

Chlorine analysis of urea products (344) and (345) indicated that approximately 1.0 of 3 possible methylation sites on PS(CL)-trisamine (342) had remained unmethylated in product resin (343) (Table 8). The *p*-chloranil test showed (as anticipated) that secondary amines were still present on (343). Solid supported catalysts PS(CL)-Me₆-tren.CuCl (346a) and PS(CL)-Me₆-tren.CuBr (346b) were synthesised by the complexation of supported ligand (343) with copper (I) halide. Microanalysis indicated the ligand and copper loadings shown in Table 8.



Scheme 123

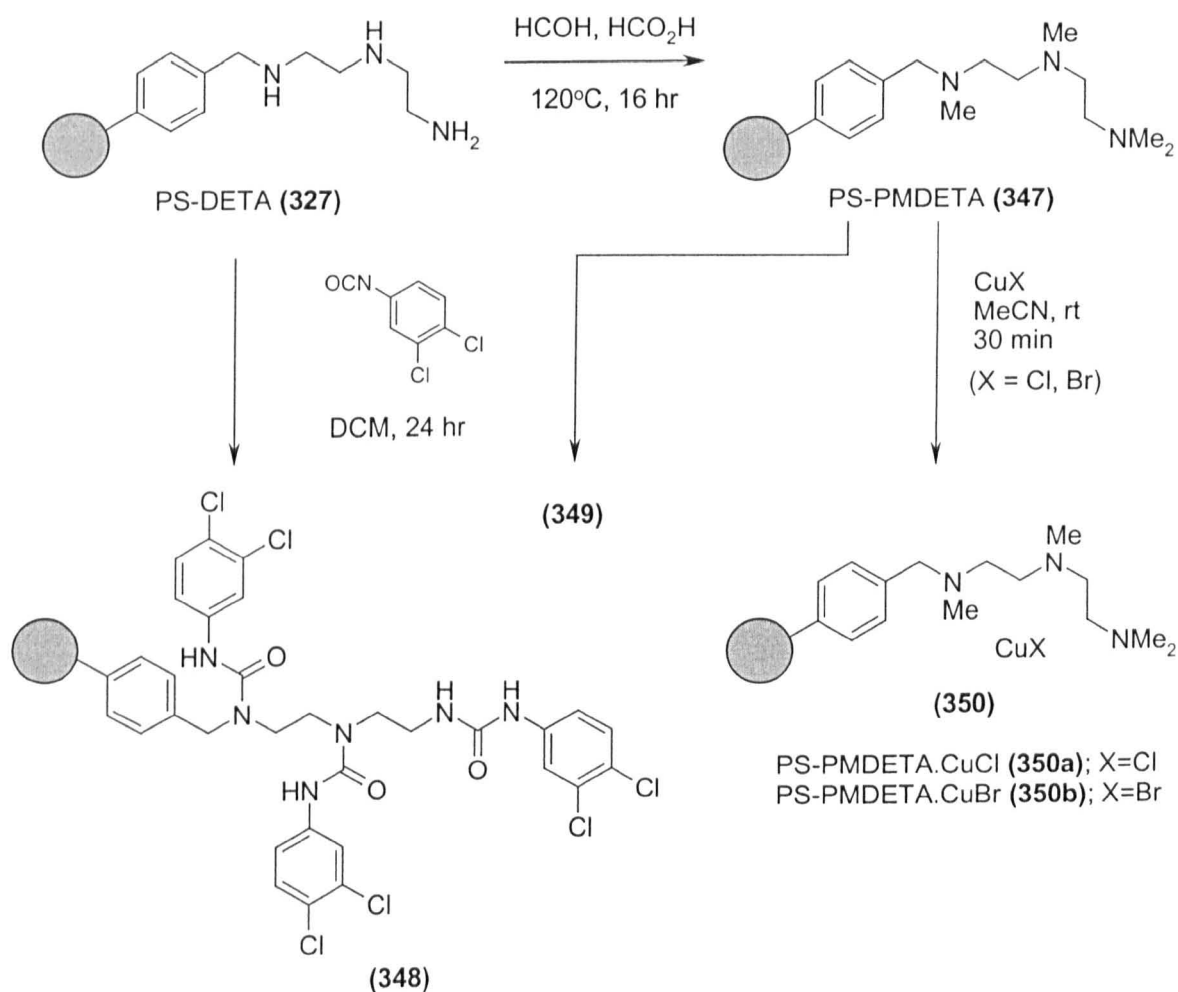
Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cl	%Cu	Loading Copper (mmol/g)
PS(CL)-Trisamine (342)	82.19	8.15	6.34	1.13	0.38	NA	NA
PS(CL)-Me ₆ -tren (343)	84.11	8.55	6.00	1.07	0.15	NA	NA
(344)	71.59	6.25	6.44	NA	10.59	NA	NA
(345)	80.48	8.37	5.42	NA	3.23	NA	NA
PS(CL)-Me ₆ -tren.CuCl (346a)	70.63	7.16	4.97	0.887	NA	6.78	1.07
PS(CL)-Me ₆ -tren.CuBr (346b)	68.43	6.91	4.76	0.850	NA	6.40	1.01

^a All numerical values are the mean of duplicate microanalysis results

Table 8

5.2.2 Synthesis and Characterisation of Solid Supported PMDETA Copper (I) Catalysts

The commercial availability of polystyrene supported DETA (**327**) (Aldrich) enabled access to a solid supported PMDETA ligand (**347**) (Scheme 124). Yet again, the Eschweiler Clarke reaction was successful in introducing most (>3.3) of the four desired methyl groups. As before, a negative Kaiser test and a positive *p*-chloranil test indicated that no primary amines existed on the product resin (**347**) but secondary amines were still present. Dark green solid supported catalysts PS-PMDETA.CuCl (**350a**) and PS-PMDETA.CuBr (**350b**) were synthesised without difficulty, this time showing close agreement between ligand and copper loading (Table 9).



Scheme 124

Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cl	%Cu	Loading Copper (mmol/g)
PS-DETA (327)	77.45	8.77	11.44	2.72	0.07	NA	NA
PS-PMDETA (347)	78.90	9.24	9.88	2.35	0.03	NA	NA
(348)	56.44	4.54	8.59	NA	21.94	NA	NA
(349)	75.23	8.83	9.44	NA	3.48	NA	NA
PS-PMDETA.CuCl (350a)	58.77	7.32	7.60	1.81	NA	12.59	1.98
PS-PMDETA.CuBr (350b)	54.34	6.62	6.61	1.57	NA	11.28	1.78

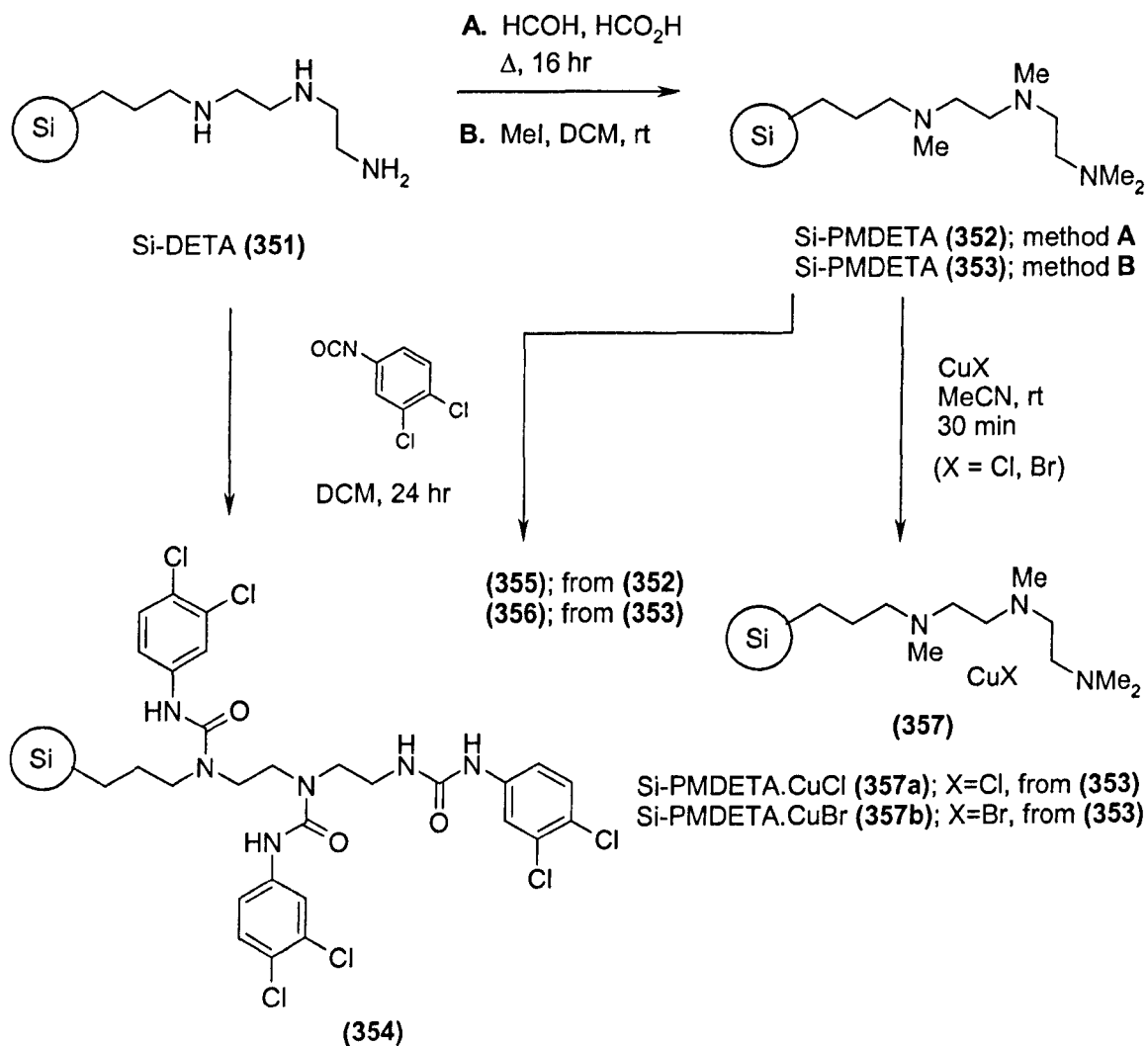
^a All numerical values are the mean of duplicate microanalysis results

Table 9

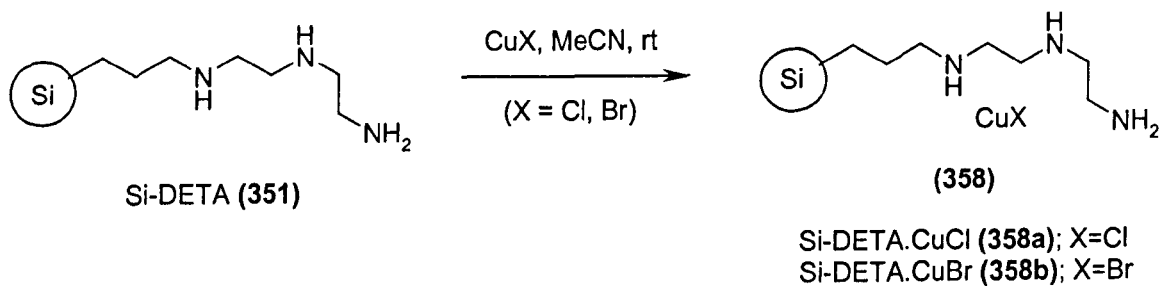
The synthesis of a silica supported PMDETA ligand from commercial Si-DETA (351) (*ex Aldrich*) proved problematic (Scheme 125). Application of the Eschweiler Clarke reaction to (351) (method A) gave a product (352) with low nitrogen content (Table 10). This suggests that significant quantities of triamine are cleaved from the silica support under the reaction conditions.

Alkylation of aliphatic amines with alkylating agents is invariably an unsuccessful approach to the synthesis of tertiary amines from primary and secondary amines.¹⁹⁷⁻¹⁹⁸ This is due to the greater nucleophilicity of tertiary amines towards alkyl halides compared with secondary amines which leads to the formation of quaternary salts. Occasionally this approach has proved successful; hence reaction of Si-DETA (351) with 4 equivalents of methyl iodide in DCM at room temperature was attempted (method B). Unfortunately, product resin (353) was found to contain iodine indicating the presence of quaternary salts (Table 10). Comparison of the chlorine content of (354) and (356) did not provide encouragement that methylation of (351) using methyl iodide had been particularly successful (Table 10). However, the chlorine content of (354) did not reflect the loading of the amine ligand on (351) indicating that the accessibility of DETA on a silica support to electrophilic attack by 3,4-dichlorophenyl isocyanate is considerably diminished compared with the accessibility of DETA on a polystyrene support. Nevertheless, copper (I) complex (357a) was formed from (353), and its ability to cyclise

radical precursor (**7b**) was compared to that of Si-DETA.CuCl (**358a**) (Scheme 126, Section 5.4.1).



Scheme 125



Scheme 126

Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cl	%I	%Cu	Loading Copper (mmol/g)
Si-DETA (351)	12.28	3.00	5.36	1.28	0.31	NA	NA	NA
Si-PMDETA (352) (Method A)	7.45	1.90	1.79	0.426	0.00	NA	NA	NA
Si-PMDETA (353) (Method B)	12.26	2.72	4.80	1.14	NA	6.59	NA	NA
(354)	17.16	2.63	5.81	NA	5.87	NA	NA	NA
(355)	8.23	1.67	1.91	NA	0.85	NA	NA	NA
(356)	15.33	2.65	5.01	NA	3.81	NA	NA	NA
Si-PMDETA.CuCl (357a)	11.46	2.54	4.51	1.07	NA	NA	4.86	0.765
Si-PMDETA.CuBr (357b)	11.26	2.48	4.42	1.05	NA	NA	4.25	0.669
Si-DETA.CuCl (358a)	10.36	2.36	4.62	1.10	NA	NA	6.92	1.09
Si-DETA.CuBr (358b)	10.14	2.26	4.50	1.07	NA	NA	6.12	0.963

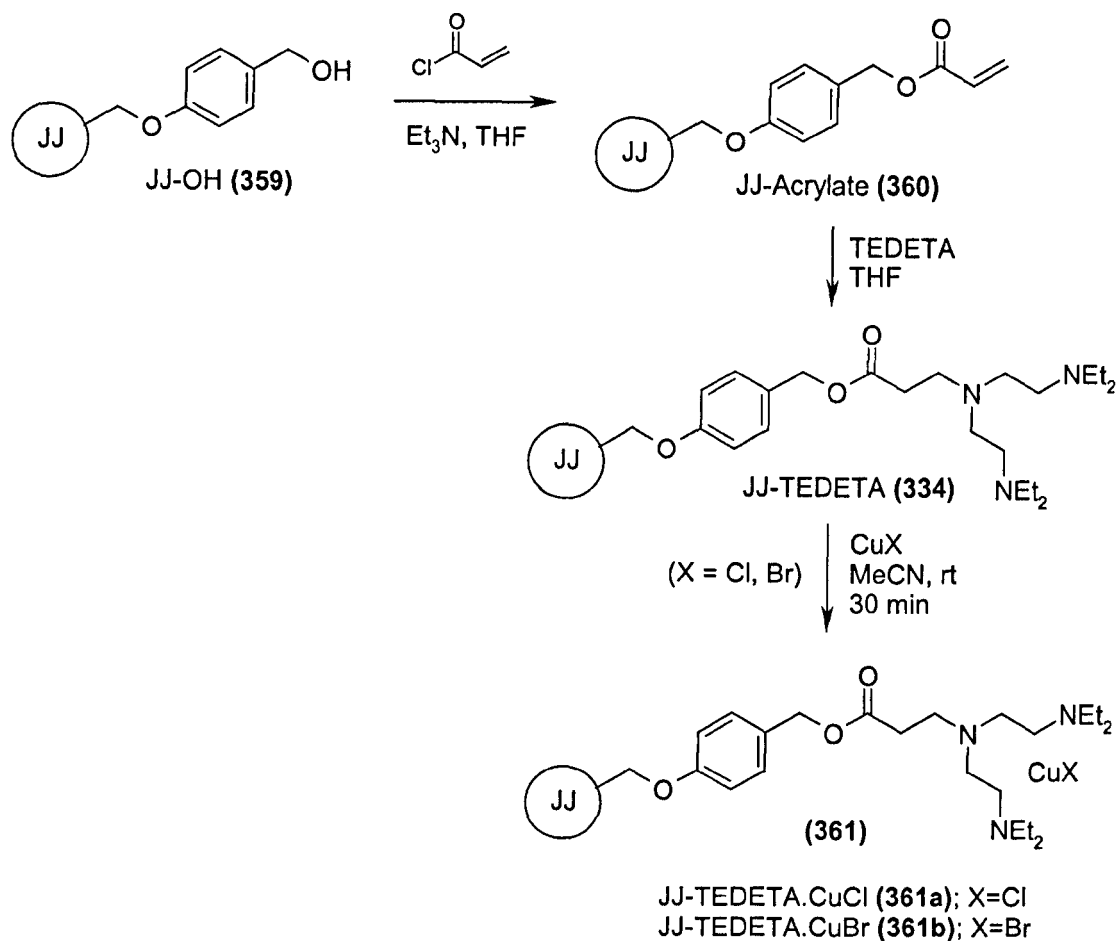
^a All numerical values are the mean of duplicate microanalysis results

Table 10

5.2.3 Synthesis and Characterisation of Solid Supported TEDETA Copper (I) Catalysts

Honigfort and Brittain have recently published the successful application of JandaJel supported TEDETA.CuBr complex (361b) to the controlled polymerisation of methyl methacrylate (Scheme 127).¹⁹¹ Compared to divinylbenzene cross-linked polystyrene resins, JandaJel resins have increased organic solvent compatibility and site accessibility and have shorter reaction times, due to a flexible ether cross-linker.¹⁹⁹ We were keen to investigate whether this JandaJel supported catalyst would be particularly effective in copper (I) mediated ATRC reactions. Therefore, catalysts (361a-b) were prepared in three steps from the commercial resin JandaJel-OH (359) (*ex* Aldrich) (Scheme 127). This sequence involved formation of the acrylate ester (360), followed by conjugate addition of TEDETA to give supported ligand (334), which was complexed with either copper (I) bromide or chloride. The esterification and addition steps required a much larger excess of acryloyl chloride and TEDETA than that reported by Brittain to give a

supported ligand (**334**) with a nitrogen content (2.1% N) comparable to that achieved by Brittain (2.5% N from 1.0 mmol g^{-1} JJ-OH (**359**)) (Scheme 127, Table 11).¹⁹¹



Scheme 127

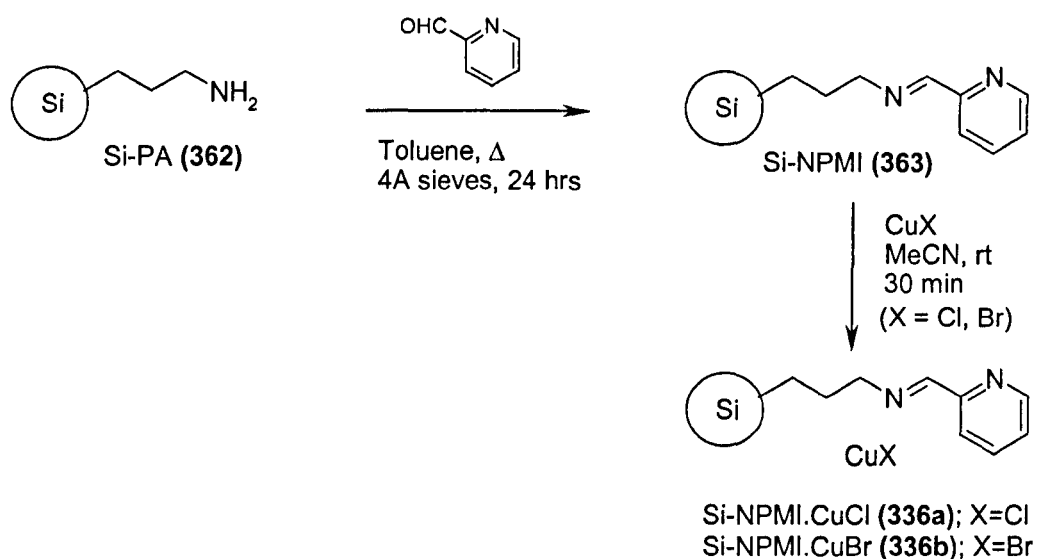
Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cu	Loading Copper (mmol/g)
JJ-OH (359)	89.08	7.91	0.09	0.916	NA	NA
JJ-Acrylate (360)	82.53	7.48	0.72	1.93	NA	NA
JJ-TEDETA (334)	83.97	8.02	2.09	0.497	NA	NA
JJ-TEDETA.CuCl (361a)	79.79	7.47	1.87	0.445	2.70	0.425
JJ-TEDETA.CuBr (361b)	78.29	7.33	1.89	0.449	2.75	0.433

^a All numerical values are the mean of duplicate microanalysis results

Table 11

5.2.4 Synthesis and Characterisation of Solid Supported NPMI Copper (I) Catalysts

The previously reported silica supported NPMI catalysts (**336a-b**) were synthesised to provide a comparison with the novel solid supported Me₆-tren and PMDETA catalysts in various ATRC reactions (Scheme 128, Table 12).³⁵ Surprisingly, the copper (I) bromide catalyst (**336b**) was found to have a stoichiometry of NPMI:Cu of approximately 2:1, whilst the copper (I) chloride catalyst (**336a**) was found to exist as 1:1 complex, despite using 1.2 equivalents of copper (I) halide relative to ligand in both cases. One possible explanation is that the copper chloride complex exists as $\text{Cu}(\text{ligand})_2^+ \text{CuCl}_2^-$, whilst the copper bromide complex exists as $\text{Cu}(\text{ligand})_2^+ \text{Br}^-$.



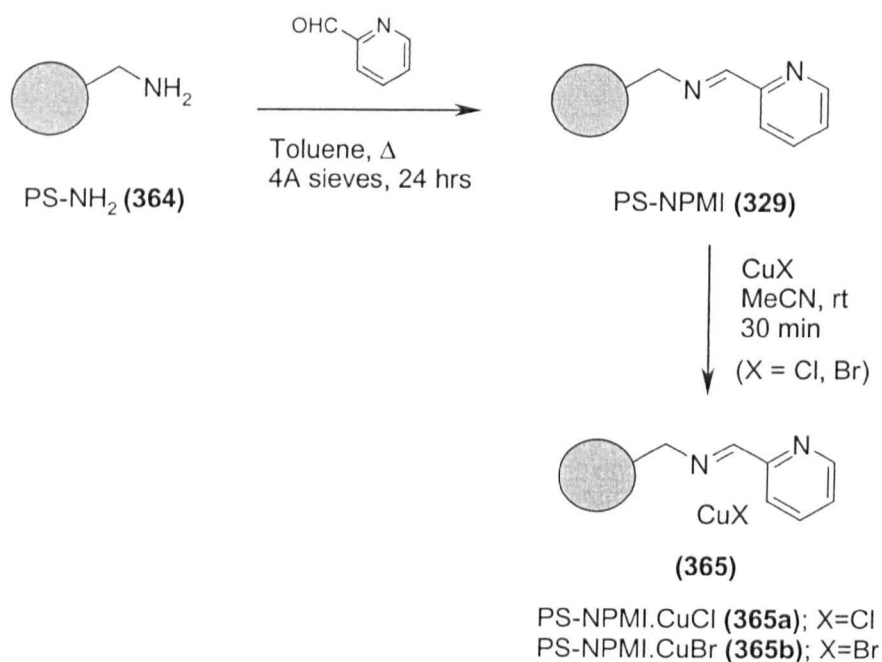
Scheme 128

Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cu	Loading Copper (mmol/g)
Si-PA (362)	7.33	1.81	1.76	1.26	NA	NA
Si-NPMI (363)	15.25	1.78	3.54	1.26	NA	NA
Si-NPMI.CuCl (336a)	13.89	1.72	2.45	0.875	5.16	0.811
Si-NPMI.CuBr (336b)	13.55	1.72	3.25	1.16	4.38	0.689

^a All numerical values are the mean of duplicate microanalysis results

Table 12

We were keen to explore the effect of changing the solid support on catalyst activity for the NPMI ligand, thus the polystyrene catalysts (**365a-b**) and (**367a-b**) were also prepared from commercial amine resins by the same sequence of reactions (Schemes 129 and 130). PS-NPMI.CuX catalysts (**365a-b**) were found to have a 2:1 ratio of ligand to copper suggesting that both catalysts exist as $\text{Cu}(\text{ligand})_2^+ \text{X}^-$ (Table 13).



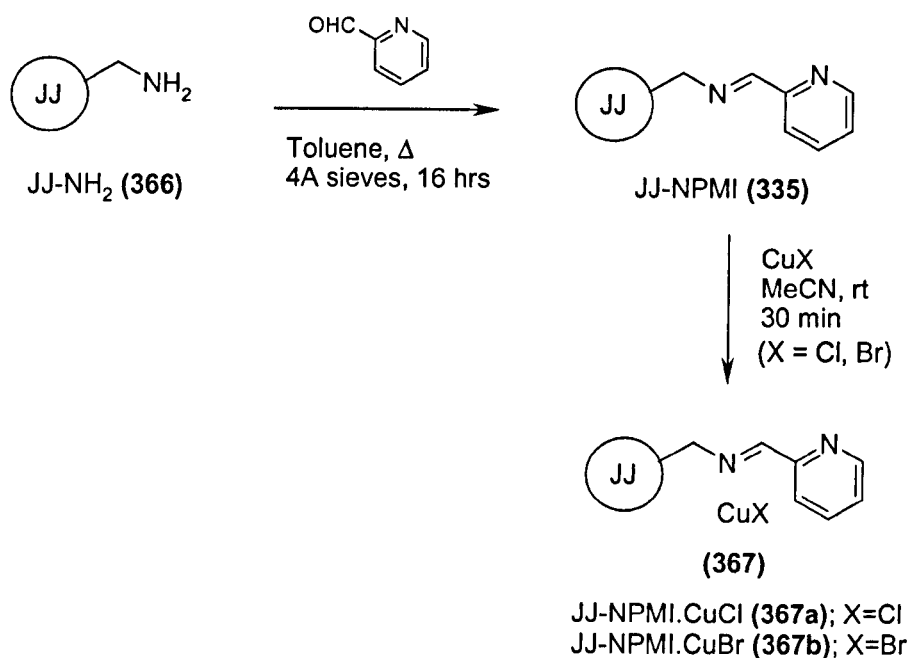
Scheme 129

Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cu	Loading Copper (mmol/g)
PS-NH ₂ (364)	86.42	7.86	2.32	1.66	NA	NA
PS-NPMI (329)	88.13	7.29	3.30	1.18	NA	NA
PS-NPMI.CuCl (365a)	82.06	6.64	3.33	1.19	3.26	0.513
PS-NPMI.CuBr (365b)	78.94	6.39	3.28	1.17	3.34	0.526

^a All numerical values are the mean of duplicate microanalysis results

Table 13

In comparison, JandaJel supported catalysts JJ-NPMI.CuCl (**367a**) and JJ-NPMI.CuBr (**367b**)¹⁹¹ were found to have 2:1 and 1:1 ratios of ligand:Cu respectively (Scheme 130, Table 14). This result is the exact reverse observed for the Si-NPMI.CuX catalysts.



Scheme 130

Resin	%C ^a	%H	%N	Loading Ligand (mmol/g)	%Cu	Loading Copper (mmol/g)
JJ-NH ₂ (366)	89.17	7.87	0.89	0.635	NA	NA
JJ-NPMI (335)	89.10	7.64	1.46	0.521	NA	NA
JJ-NPMI.CuCl (367a)	85.82	7.22	1.48	0.528	1.62	0.255
JJ-NPMI.CuBr (367b)	83.97	7.08	1.46	0.519	2.87	0.452

^a All numerical values are the mean of duplicate microanalysis results

Table 14

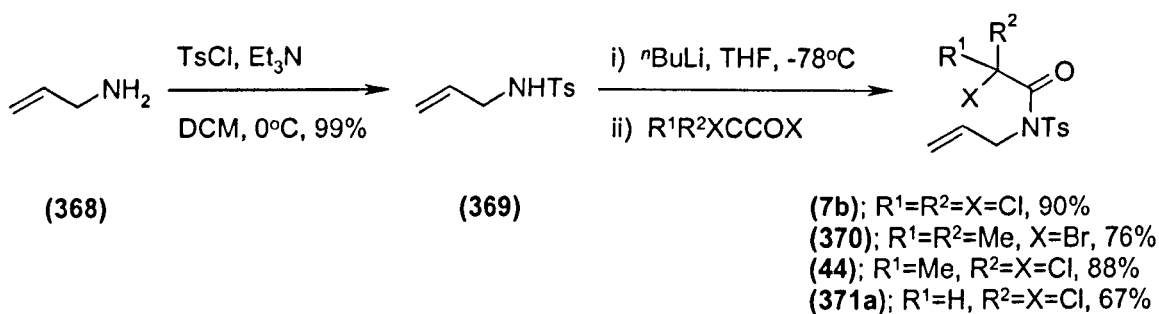
5.3 SYNTHESIS OF RADICAL CYCLISATION SUBSTRATES

A range of α -halo amide radical precursors was selected to enable the evaluation of the solid supported copper (I) catalysts described in Section 5.2 in ATRC reactions. Since the new catalysts could potentially offer a greater rate enhancement for ATRC reactions than previously prepared Si-NPMI.CuX (336a-b), it was important to include substrates which (336a-b) had previously failed to cyclise as well as more activated ones. The ten selected substrates include *mono*-, *di*- and *tri*- α -halo amides, tertiary and secondary

halides, and both *N*-protected and *N*-unprotected amides. This covers a broad range of reactivity to radical generation and cyclisation. The substrates also vary in their likely modes of cyclisation; some substrates are expected to undergo 5-*exo* cyclisation onto double and triple carbon-carbon bonds, and others 5-*endo* or 4-*exo* cyclisation.

5.3.1 Synthesis of Substrates amenable to 5-*Exo* Trig Cyclisation

N-Allyl-*N*-tosyl- α -halo amides (**7b**), (**370**), (**44**) and (**371a**) were synthesised in two steps by the route outlined in Scheme 131. Treatment of allylamine (**368**) with *p*-toluenesulfonyl chloride in the presence of triethylamine gave common sulfonamide intermediate (**369**) in excellent yield. Subsequent N-H deprotonation with *n*-butyl lithium in THF, followed by trapping of the intermediate nitrogen anion with a range of acid halides gave the desired substrates in moderate yield.¹³ In all cases, purification of the crude products by chromatography or recrystallisation was required.



Scheme 131

The modest yield of (**371a**) reflects the formation of an unidentified by-product (**371b**) in 13% yield in the final step (Figure 25). Column chromatography gave the major product (**371a**) as a white crystalline solid and also the minor product (**371b**) as a colourless oil. Mass spectrometry confirmed both (**371a**) and (**371b**) to have identical mass, but significant differences in chemical shifts of the (1H, s) and (2H, dt) signals are observed in the proton NMR (Figure 25). Interestingly, the minor product (**371b**) was found to convert to the major product (**371a**) on heating in hexane, or in the presence of silica gel (6 days, DCM, silica). The identity of crystalline product (**371a**) has been confirmed by

X-ray crystallography to be the desired *N*-allyl-*N*-(2,2-dichloro-acetyl)-4-methylbenzenesulfonamide (Figure 24, Tables 27-28, Appendix). However, the minor product (**371b**) was not crystalline and its structure remains undetermined. Rotational isomerism for this type of structure has been reported, and it is possible that (**371a**) and (**371b**) are simply rotational isomers of each other.¹³

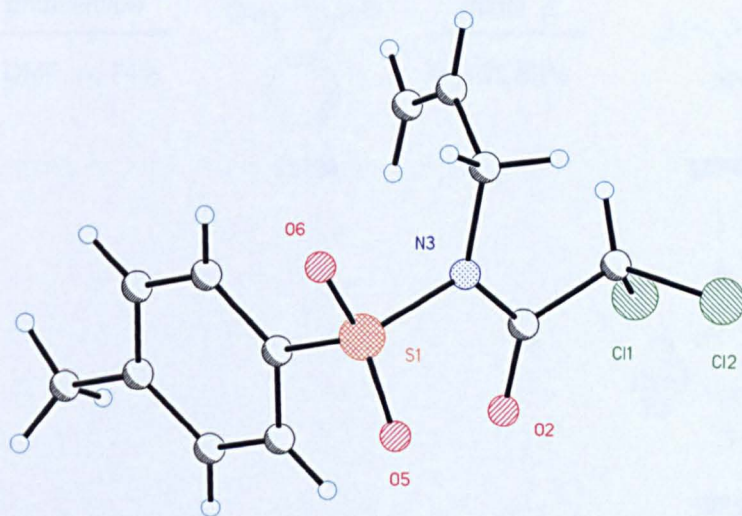


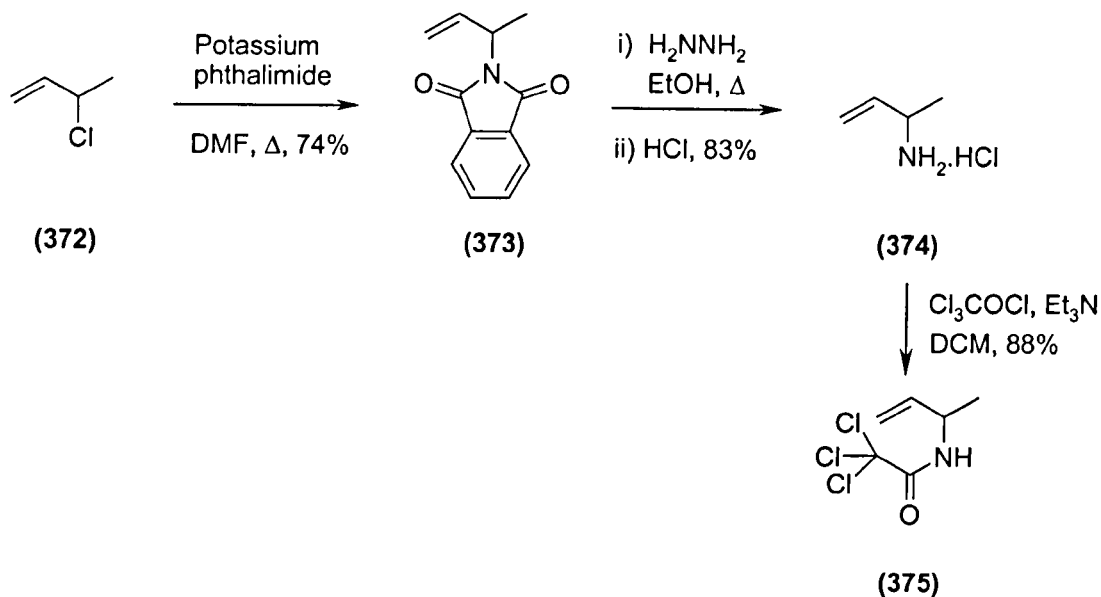
Figure 24: X-ray crystal structure of (371a)

δ_{H} (300MHz, CDCl ₃) Major (371a)	δ_{H} (300MHz, CDCl ₃) Minor (371b)
7.81 (2H, d, J 8.5 Hz)	7.79 (2H, d, J 8.5 Hz)
7.34 (2H, d, J 8.5 Hz)	7.33 (2H, d, J 8.5 Hz)
6.82 (1H, s)	5.97 (1H, s)
5.77 (1H, ddt, J 17.3, 10.2, 5.3 Hz)	5.80 (1H, ddt, J 17.0, 10.2, 6.6 Hz)
5.20 (1H, dd, J 10.2, 0.9 Hz)	5.25 (1H, ddt, J 10.2, 1.1, 1.1 Hz)
5.19 (1H, dd, J 17.3, 0.9 Hz)	5.20 (1H, ddt, J 10.2, 1.1, 1.1 Hz)
4.39 (2H, dt, J 5.3, 0.9 Hz)	3.97 (2H, dt, J 6.6, 1.1 Hz)
2.42 (3H, s)	2.44 (3H, s)

Figure 25

2,2,2-Trichloro-*N*-(1-methyl-allyl)-acetamide (**375**), a cyclisation substrate without a nitrogen protecting group, was synthesised in three steps from 3-chloro-1-butene (**372**)

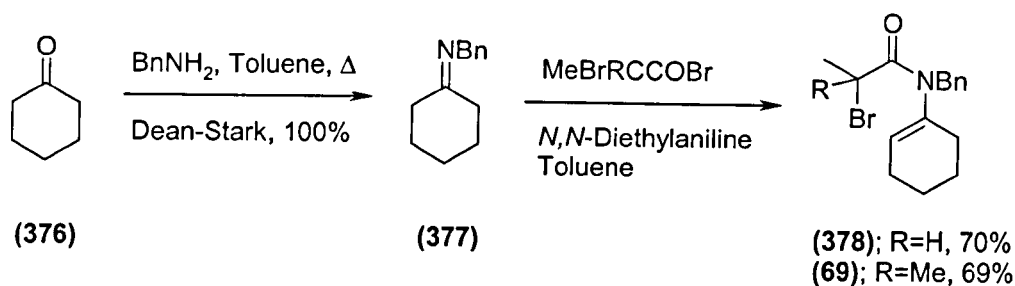
(Scheme 132).²⁰⁰ Chloride displacement of (372) with phthalimide ion gave imide (373), which was subsequently deprotected using hydrazine in ethanol. The amine (374) was isolated as its hydrochloride salt, and subsequently reacted with trichloroacetyl chloride to give (375) in good yield.



Scheme 132

5.3.2 Synthesis of Substrates amenable to 5-Endo Trig Cyclisation

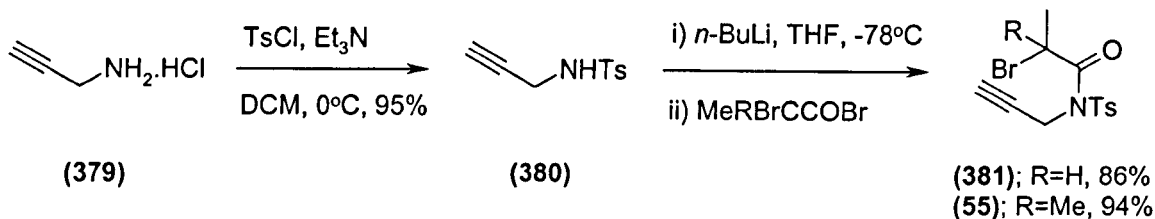
N-Benzyl-2-bromo-*N*-cyclohex-1-enyl-propionamides (378) and (69) are known to undergo 5-*endo* cyclisation in the presence of certain copper (I) halide ligand systems (Scheme 133).⁴⁰ Treatment of cyclohexanone (376) with a molar equivalent of benzylamine in toluene under Dean-Stark conditions gave benzyl imine (377) in quantitative yield. It was found to be essential to use freshly distilled benzylamine to ensure high purity of the imine product, since (377) was not amenable to purification by chromatography or distillation. Acylation of (377) with either 2-bromopropionyl bromide or 2-bromoisobutyryl bromide in the presence of *N,N*-diethylaniline gave desired enamides (378) and (69) in good yield.^{25,35}



Scheme 133

5.3.3 Synthesis of Substrates amenable to 5-*Exo* Dig Cyclisation

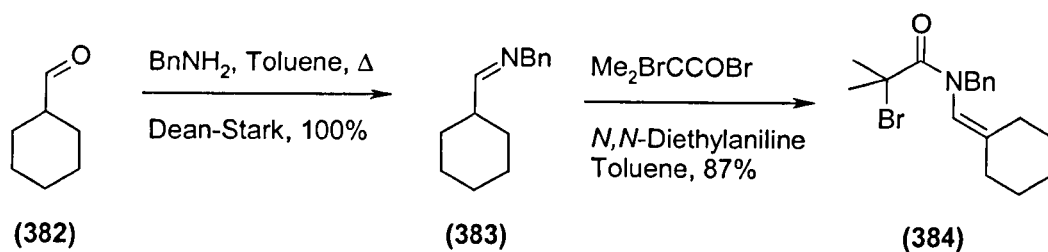
An approach similar to that described in Section 5.3.1 was utilised to synthesise *N*-propargyl-*N*-tosyl- α -halo amides (**381**) and (**55**) from propargylamine hydrochloride (**379**) (Scheme 134).²⁰



Scheme 134

5.3.4 Synthesis of Substrate amenable to 4-*Exo* Trig Cyclisation

Finally, *N*-benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**384**), which is amenable to 4-*exo* atom transfer radical cyclisation, was made from cyclohexanecarboxaldehyde (**382**) (Scheme 135). Treatment of (**382**) with one equivalent of distilled benzylamine under Dean-Stark conditions gave imine (**383**) in high purity, which was subsequently reacted with 2-bromoisobutyryl bromide to furnish enamide (**384**) in excellent yield.³⁶



Scheme 135

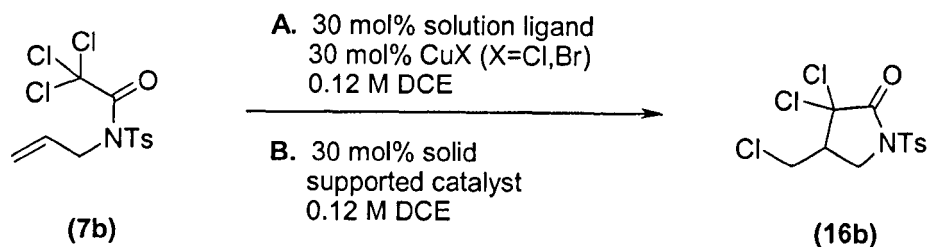
5.4 RADICAL CYCLISATION USING SOLID SUPPORTED COPPER (I) CATALYSTS

The solid supported copper (I) catalysts described in Section 5.2 were screened *via* the cyclisation of the ten α -halo amide substrates described in Section 5.3. Hence, to a 0.12 M solution of the α -halo amides in DCE was added 30 mol % (Cu) of the solid supported catalysts. In most cases this was also approximately 30 mol % of the supported ligand (refer to the microanalysis results in Section 5.2). Reactions were performed at room temperature (or reflux where necessary) under a nitrogen atmosphere and were monitored by tlc and/or ^1H NMR at regular intervals to determine the relative rates of reaction. The rates and outcome of each reaction was compared with the solution ligand/copper (I) halide (30 mol %) systems at the same concentration of substrate in DCE. After reaction completion, the solid supported catalysts were simply filtered, and the solution ligand/copper (I) halide systems were removed by filtration through a short silica plug. Cyclisation products were purified by flash column chromatography where necessary.

5.4.1 Cyclisation of *N*-allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide

Trichloroacetamide (**7b**) is highly amenable to atom transfer radical cyclisation (Scheme 136).^{13,19} The tertiary radical formed by atom transfer to the copper (I) catalyst is stabilised by two chlorine atoms, and may readily undergo 5-*exo* cyclisation onto the allyl double bond. Protection of the amide nitrogen with the bulky tosyl group ensures that

(7b) adopts predominantly the *anti* conformer. Indeed, cyclisation of (7b) with active solution ligands Me₆-tren (43) and PMDETA (42) at room temperature was found to be complete within 5 minutes to give pyrrolidinone (16b) in excellent yield (Table 15).



Scheme 136

Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (7b):(16b) ^a	Yield (16b) (%)
Me ₆ -tren (43)	A	14	0.0833	0 : 1	93 ^b
PS-Me ₆ -tren.CuCl (341a)	B	17	40	1 : 13.8	93 ^a
PS-Me ₆ -tren.CuCl (341a)	B	83	0.5	0 : 1	100 ^a
PS(CL)-Me ₆ -tren.CuCl (346a)	B	15	42	1 : 19	95 ^a
PS(CL)-Me ₆ -tren.CuCl (346a)	B	83	0.5	0 : 1	100 ^b
PMDETA (42)	A	18	0.0833	0 : 1	93 ^b
PS-PMDETA.CuCl (350a)	B	16	120	1 : 4	80 ^a
PS-PMDETA.CuCl (350a)	B	83	0.5	0 : 1	100 ^b
Si-PMDETA.CuCl (357a)	B	18	80	1 : 0	0
Si-DETA.CuCl (358a)	B	18	80	1 : 0	0
JJ-TEDETA.CuCl (361a)	B	18	72	1 : 1.6	61 ^a
JJ-TEDETA.CuCl (361a)	B	83	0.5	0 : 1	100 ^b
Si-NPMI.CuCl (336a) ³⁵	B	RT	3	0 : 1	92 ^b
PS-NPMI.CuCl (365a)	B	22	3	0 : 1	98 ^b
JJ-NPMI.CuCl (367a)	B	22	3	0 : 1	100 ^b

^a ratio or yield determined by ¹H NMR, ^b isolated yield

Table 15

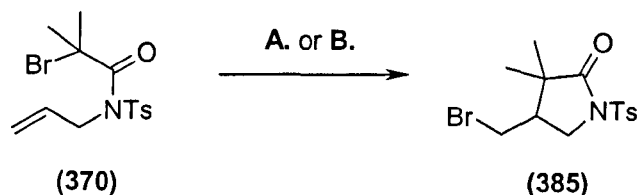
Solid supported catalysts PS-Me₆-tren.CuCl (341a), PS(CL)-Me₆-tren.CuCl (346a) and PS-PMDETA.CuCl (350a) were all found to be considerably less active than their solution counterparts, cyclising (7b) very slowly at room temperature (Table 15). The most active of these (341a) was found to cyclise (7b) in a total of 40 hours at 17°C.

There existed some concern that the activity of complex **(341a)** was due to uncomplexed Cu(I) since the loading of copper on the catalyst exceeds that of the ligand (Section 5.2.2). However, when the cyclisation was conducted at the same temperature and concentration using the equivalent amount of “free” Cu(I)Cl only, no cyclisation was observed. Catalyst **(341a)** possessed similar activity to **(346a)**, but PS-PMDETA.CuCl **(350a)** required 120 hours to convert only 80% of **(7b)** to **(16b)**. This result compares disappointingly with Si-NPMI.CuCl **(336a)** which has been reported to cyclise **(7b)** in only 3 hours at room temperature.³⁵ However, all three catalysts **(341a)**, **(346a)** and **(350a)** were found to cyclise **(7b)** within 30 minutes at reflux in DCE (83°C). The reusability of these catalysts for the cyclisation of **(7b)** is discussed in Section 5.5. The activity of Si-NPMI.CuCl **(336a)** in this reaction was also demonstrated by the polystyrene supported NPMI catalysts PS-NPMI.CuCl **(365a)** and JJ-NPMI.CuCl **(367a)**. Changing the solid support from a silica to a polystyrene structure did not alter the reaction time. As anticipated, the Si-PMDETA.CuCl **(357a)** and Si-DETA.CuCl **(358a)** catalysts both failed to cyclise **(7b)** at room temperature after 80 hours. Since **(7b)** is the most activated radical precursor of the ten selected amides, these catalysts were not investigated further.

5.4.2 Cyclisation of *N*-Allyl-*N*-(2-bromo-2-methyl-propionyl)-4-methyl-benzene sulfonamide

Mono-bromide **(370)** is also activated towards atom transfer radical cyclisation. Atom transfer of Br· from **(370)** to the Cu(I)Br catalyst results in the formation of a stable tertiary radical whose *anti* conformer can cyclise in the 5-*exo* mode onto the allyl double bond give pyrrolidinone **(385)** (Scheme 137).²⁰ Again Me₆-tren **(43)** and PMDETA **(42)** were found to effect ATRC in less than 5 minutes at room temperature (Table 16). As before, the solid supported catalysts **(341b)**, **(346b)** and **(350b)** showed reduced activity, and also the same order of reactivity. The most active of these **(341b)** completely cyclised **(370)** after 92 hours at 15°C, whereas the least active catalyst PS-PMDETA.CuBr **(350b)** failed to cyclise **(370)** at all after 48 hours at 16°C. PS(CL)-Me₆-tren.CuBr **(346b)** showed intermediate activity converting 30% of **(370)** to **(385)** after 92

hours. Again treatment of (370) with the new catalysts at reflux gave the desired pyrrolidinone (385) within 30 minutes in all three cases. The JandaJel catalyst JJ-TEDETA.CuBr (361b), which has been used in ATRP, was found to give a longer reaction time at reflux than the novel catalysts.¹⁹¹ JJ-NPMI.CuBr (367b) with its flexible cross-linker provided no advantage over the analogous polystyrene catalyst PS-NPMI.CuBr (365b) at room temperature.¹⁹¹



Scheme 137

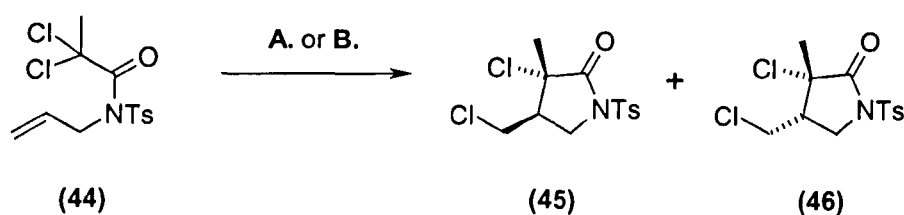
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (370):(385) ^a	Yield (385) (%)
Me ₆ -tren (43)	A	14	0.083	0 : 1	97 ^b
PS-Me ₆ -tren.CuBr (341b)	B	15	92	0 : 1	95 ^b
PS-Me ₆ -tren.CuBr (341b)	B	83	0.5	0 : 1	95 ^b
PS(CL)-Me ₆ -tren.CuBr (346b)	B	15	92	7 : 3	30 ^a
PS(CL)-Me ₆ -tren.CuBr (346b)	B	83	0.5	0 : 1	99 ^b
PMDETA (42)	A	18	0.083	0 : 1	99 ^b
PS-PMDETA.CuBr (350b)	B	16	48	1 : 0	0
PS-PMDETA.CuBr (350b)	B	83	0.5	0 : 1	95 ^b
JJ-TEDETA.CuBr (361b)	B	83	3	0 : 1	100 ^b
Si-NPMI.CuBr (336b) ³⁵	B	83	24	0 : 1	92 ^b
PS-NPMI.CuBr (365b)	B	22	24	2.1 : 1	30 ^a
JJ-NPMI.CuBr (367b)	B	22	24	2.7 : 1	27 ^a
JJ-NPMI.CuBr (367b)	B	83	0.5	0 : 1	100 ^b

^a ratio or yield determined by ¹H NMR, ^b isolated yield

Table 16

5.4.3 Cyclisation of *N*-Allyl-*N*-(2,2-dichloro-propionyl)-4-methyl-benzene sulfonamide

α -Dichloro-*N*-tosyl amide (**44**), which also forms a stable tertiary radical on atom transfer to the copper (I) catalyst, may cyclise to form two diastereomeric pyrrolidinones (**45**) and (**46**) (Scheme 138).^{22,34,201-202} Me₆-tren (**43**) and PMDETA (**42**) were found to cyclise (**44**) at room temperature in less than one hour to give *trans* diastereoisomer (**45**) in 75% and 73% de respectively (Table 17). The diastereomeric ratios were determined by ¹H NMR; the diastereotopic chloromethyl protons appear in an ABX pattern between δ 1.4-2.1 in C₆D₆ and can be used to measure the isomeric ratios.²⁰¹



Scheme 138

Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (44):(45):(46) ^a	de (45) (%)	Yield (45),(46) (%)
Me ₆ -tren (43)	A	20	1	0 : 7 : 1	75	88 ^b
PS-Me ₆ -tren.CuCl (341a)	B	83	1	0 : 4.7 : 1	65	91 ^b
PS(CL)-Me ₆ -tren.CuCl (346a)	B	83	1	0 : 4.3 : 1	62	85 ^b
PMDETA (42)	A	18	0.083	0 : 6.5 : 1	73	98 ^b
PS-PMDETA.CuCl (350a)	B	83	44	0 : 4.4 : 1	63	93 ^b
JJ-TEDETA.CuCl (361a)	B	83	19	1 : 0.8 : 0.6	31	58 ^a
Si-NPMI.CuCl (336a) ³⁵	B	83	18	0 : 4.4 : 1	64	94 ^b
JJ-NPMI.CuCl (367a)	B	83	19	0.4 : 4.0 : 1	60	93 ^b

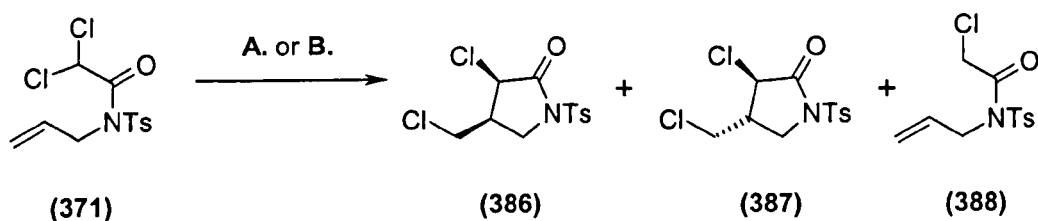
^a ratio or yield determined by ¹H NMR, ^b isolated yield

Table 17

Experience with substrates (**7b**) and (**370**) suggested that the solid supported catalysts were highly unlikely to cyclise (**44**) at room temperature within a reasonable time frame. Consequently, reactions with these catalysts were performed at reflux. PS-Me₆-tren.CuCl

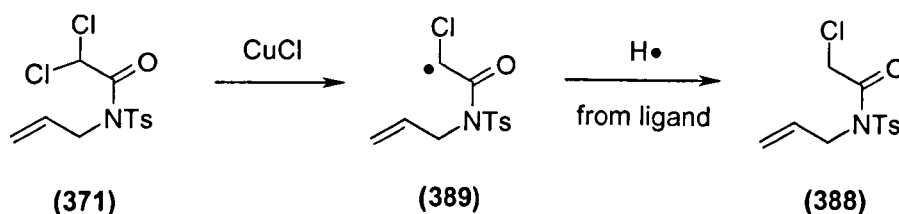
(**341a**) and PS(CL)-Me₆-tren.CuCl (**346a**) was found to cyclise (**44**) within one hour to give predominantly the *trans* isomer (**45**) in 65% and 62% de respectively (Table 17). Therefore, use of solid supported Me₆-tren gives a slightly lower de than solution phase Me₆-tren (**43**). Reaction of (**44**) with PS-PMDETA.CuCl (**350a**) at reflux took a considerable longer time of 44 hours to reach completion, and also gave a lower de of 63% compared with PMDETA (**42**) (73% de). These solid supported ATRC catalysts were all found to give a similar diastereoselectivity to that reported for Si-NPMI.CuCl (**336a**).³⁵ The JandaJel catalyst JJ-TEDETA.CuCl (**361a**) was found to have a lower activity than the novel catalysts at reflux giving only 58% conversion to (**45**) and (**46**) with a low de of 31%. The result obtained for JJ-NPMI.CuCl (**367a**) after 19 hours was found to be similar to that obtained for Si-NPMI.CuCl (**336a**) indicating again that changing the solid support for this ligand did not influence catalyst activity.

5.4.4 Cyclisation of *N*-Allyl-*N*-(2,2-dichloro-acetyl)-4-methyl-benzenesulfonamide



Scheme 139

Atom transfer radical cyclisation of radical precursor (**371**) with Me₆-tren and PMDETA based catalytic systems leads to the formation of three products (**386**), (**387**) and (**388**) (Scheme 139).²⁰¹⁻²⁰² Unlike substrates (**7b**), (**370**) and (**44**), atom transfer of Cl· from (**371**) to the Cu(I)Cl catalyst gives a secondary radical (**389**) which is less stable (than a tertiary radical) and more reactive to H· transfer from the ligand system to give reduced product (**388**) (Scheme 140).



Scheme 140

The results for the eight catalytic systems are shown in Table 18. Cyclisation of **(371)** with both Me₆-tren (**43**) and PMDETA (**42**) was found to be incomplete after 24 hours at room temperature, and of the products formed, 38% and 40% of the isolated material was found to be reduced compound **(388)**. The *cis* diastereoselectivity of the cyclisation (which was determined from the ¹H NMR)²⁰¹ was found to be greater for Me₆-tren (70%) than PMDETA (49%). The solid supported catalysts **(341a)**, **(346a)**, **(350a)** and **(361a)** (reflux, 48 hrs) were found to give reduced *cis* selectivity (35-49% de), but less reduction to **(388)** (22-31% of reacted material). Again starting material **(371)** remained after this period. The silica supported NPMI catalyst **(336a)** has been reported to completely cyclise **(371)** to give **(386)** in modest 55% de after 24 hours at reflux with no reduction to **(388)**.³⁵ This de and low level of reduction was also achieved by JJ-NPMI.CuCl (**367a**) although starting material still remained after 48 hours at reflux.

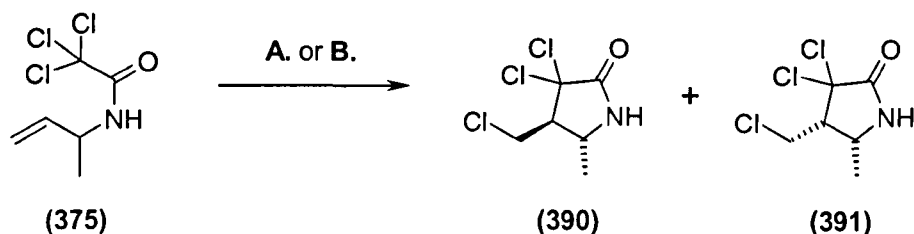
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (371):(386):(387):(388) ^a	de (386) (%)	% (388) ^c
Me ₆ -tren (43)	A	20	24	1 : 6.6 : 1.1 : 4.7	70	38
PS-Me ₆ -tren.CuCl (341a)	B	83	48	1 : 3.3 : 1.3 : 1.3	44	22
PS(CL)-Me ₆ -tren.CuCl (346a)	B	83	48	1 : 3 : 1.4 : 2	35	31
PMDETA (42)	A	20	24	3.5 : 13 : 4.5 : 11.5	49	40
PS-PMDETA.CuCl (350a)	B	83	44	1 : 1.1 : 0.4 : 0.5	43	25
JJ-TEDETA.CuCl (361a)	B	83	48	1.1 : 2.9 : 1 : 1.2	49	23
Si-NPMI.CuCl (336a) ³⁵	B	83	24	0 : 3.4 : 1 : 0	55	0
JJ-NPMI.CuCl (367a)	B	83	48	1.4 : 3.8 : 1 : 0.5	58	6

^a ratio or yield determined by ¹H NMR, ^c % of reacted material

Table 18

5.4.5 Cyclisation of 2,2,2-Trichloro-*N*-(1-methyl-allyl)-acetamide

Although substrate (**375**) is a trichloro-acetamide, and readily forms a stable tertiary radical, the lack of protecting group on the amide nitrogen means that the predominant conformer of (**375**) is *anti* (not as drawn) which means that the generated radical intermediate cannot cyclise readily (Scheme 141).^{13,203-204}



Scheme 141

Despite this, it has been reported that Si-NPMI.CuCl (**336a**) cyclises (**375**) at reflux to give isomeric pyrrolidinones (**390**) and (**391**) in 75% yield with a de of 72% (Table 19).³⁵ Neither solution nor solid supported Me₆-tren or PMDETA ligands were found to be effective in cyclising (**375**). Interestingly, Me₆-tren (**43**) and PMDETA (**42**) were found to give mixtures of rotational isomers of (**375**). Furthermore, JJ-NPMI.CuCl (**367a**), which was expected to have activity comparable to Si-NPMI.CuCl (**336a**), gave no cyclisation after 48 hours at reflux. JJ-TEDETA.CuCl (**361a**) was surprisingly found to be reasonably effective in the cyclisation of (**375**) giving (**390**) and (**391**) in a total isolated yield of 58% with a 70% de.

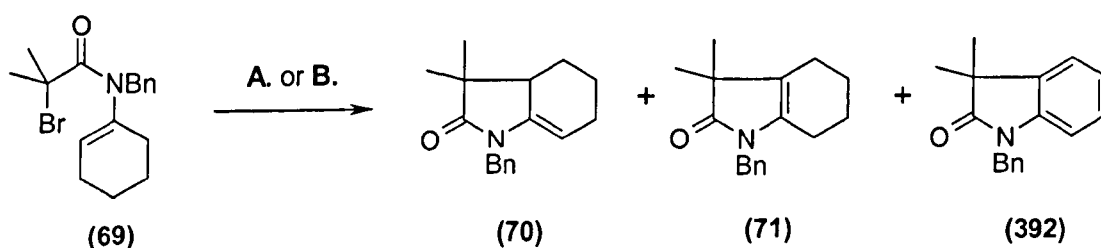
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (375):(390):(391) ^a	de (390) (%)	Yield (390),(391) (%)
Me ₆ -tren (43)	A	83	62	Isomer of (375)	NA	0
PS-Me ₆ -tren.CuCl (341a)	B	83	40	1 : 0	NA	0
PS(CL)-Me ₆ -tren.CuCl (346a)	B	83	48	1 : 0	NA	0
PMDETA (42)	A	83	48	(375) and isomer	NA	0
PS-PMDETA.CuCl (350a)	B	83	48	1 : 0	NA	0
JJ-TEDETA.CuCl (361a)	B	83	48	1 : 1.1 : 0.3	70	58 ^a
Si-NPMI.CuCl (336a) ³⁵	B	83	48		72	75 ^b
JJ-NPMI.CuCl (367a)	B	83	48	1 : 0	NA	0

^a ratio determined by ¹H NMR, ^b isolated yield

Table 19

5.4.6 Cyclisation of *N*-Benzyl-2-bromo-*N*-cyclohex-1-enyl-2-methyl-propionamide

Tertiary bromo enamide (69) has been reported to undergo rapid radical-polar crossover reactions to furnish unsaturated pyrrolidinone derivatives (70) and (71) at room temperature with the activated copper complex derived from Cu(I)Br and Me₆-tren (43) (Scheme 142).^{25,35,40} A proposed mechanism for this process is outlined in Scheme 27 (Chapter 1).



Scheme 142

As can be seen in Table 20, conversion of (69) to (70) and (71) is incomplete with Me₆-tren (43) at room temperature after 24 hours and (70) is the major product. At reflux (24 hrs) all starting material is consumed, and (70) and (71) are isolated in an equimolar ratio. Interestingly, cyclisation of (69) (0.12 mmol) with PS-Me₆-tren.CuBr (341b) (reflux, 48

hrs) gave indol-2-one (**392**) in 31% isolated yield, with no evidence of alkenes (**70**) and (**71**). This result, however, did not reproduce on scale up (0.4 mmol), where (**70**) and (**71**) were isolated in 50% combined yield, with no evidence of (**392**). PS(CL)-Me₆-tren.CuBr (**346b**), Si-NPMI.CuBr (**336b**) and JJ-NPMI.CuBr (**367b**) all failed to cyclise (**69**). Previously prepared Si-NPMI.CuBr has been reported to effect the 5-*endo* cyclisation of (**69**) to give the two alkene derivatives (**70**) and (**71**) in 78% yield as a 1:1 mixture of double bond regioisomers.³⁵ PS-PMDETA.CuBr (**350b**), which is usually the least active catalyst, was found to convert 42% of (**69**) to (**70**) and (**71**), and JJ-TEDETA.CuBr (**361b**) was found to be an extremely effective solid supported catalyst for this cyclisation giving a combined quantitative yield of (**70**) and (**71**) after 48 hours at reflux.

Ligand/Catalyst	Scale (69) (mmol)	A or B	Temp (°C)	Time (hr)	Ratio (69):(70):(71):(392) ^a	Yield (70) (%)	Yield (71) (%)	Yield (392) (%)
Me ₆ -tren (43)	0.12	A	20	24	0.6 : 2 : 1 : 0	50 ^b	25 ^b	0
Me ₆ -tren (43)	0.12	A	83	24	0 : 1 : 1 : 0	44 ^b	40 ^b	0
PS-Me ₆ -tren.CuBr (341b)	0.12	B	83	48	2 : 0 : 0 : 1	0	0	31 ^b
PS-Me ₆ -tren.CuBr (341b)	0.40	B	83	48	2 : 1 : 1 : 0	24 ^b	26 ^b	0
PS(CL)-Me ₆ -tren.CuBr (346b)	0.12	B	83	48	1 : 0 : 0 : 0	0	0	0
PMDETA (42)	0.12	A	18	24	1 : 3.7 : 3.5 : 0	45 ^a	43 ^a	0
PS-PMDETA.CuBr (350b)	0.12	B	83	48	3 : 1.2 : 1 : 0	23 ^a	19 ^a	0
JJ-TEDETA.CuBr (361b)	0.12	B	83	48	0 : 1.1 : 1 : 0	52 ^a	48 ^a	0
Si-NPMI.CuBr (336b) ³⁵	0.12	B	83	48	1 : 0 : 0 : 0	0	0	0
JJ-NPMI.CuBr (367b)	0.12	B	83	48	1 : 0 : 0 : 0.2	0	0	15 ^a

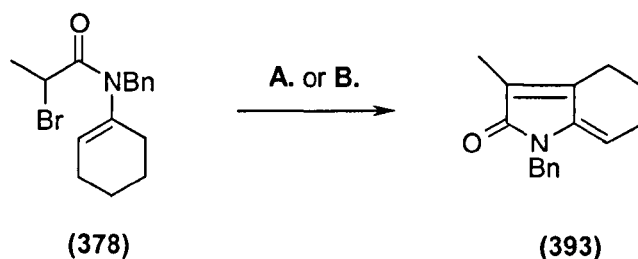
^a ratio or yield determined by ¹H NMR, ^b isolated yield

Table 20

5.4.7 Cyclisation of *N*-Benzyl-2-bromo-*N*-cyclohex-1-enyl-propionamide

Treatment of secondary bromo-enamide (**378**) with TPA (**58**)/CuBr (1 eq.) in refluxing DCE gives bicyclic lactam (**393**) in 42% yield, presumably by oxidation and proton loss of an intermediate similar to (**72**) (Schemes 27 and 143, Table 21).⁴⁰ Attempts to cyclise

(378) using all Me₆-tren, PMDETA and NPMI based catalytic systems gave only starting material in all cases. PMDETA (42) and PS-PMDETA.CuBr (350b) caused isomerisation of bromide (378). Limited cyclisation (21% conversion to (393)) was achieved using JJ-TEDETA.CuBr (361b).¹⁹¹



Scheme 143

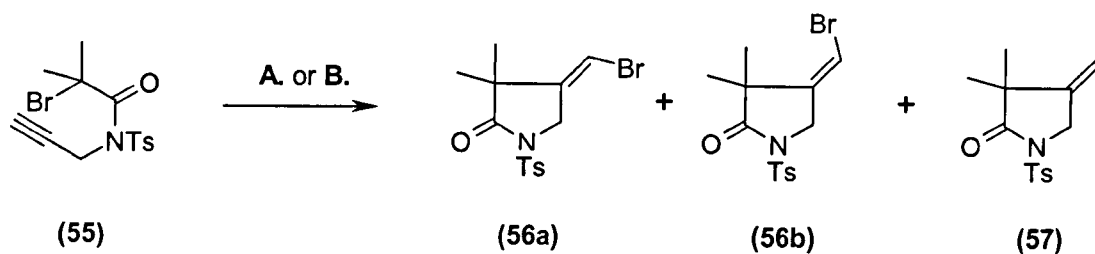
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (378):(393) ^a	Yield (393) (%)
Me ₆ -tren (43)	A	83	62	1 : 0	0
PS-Me ₆ -tren.CuBr (341b)	B	83	48	1 : 0	0
PS(CL)-Me ₆ -tren.CuBr (346b)	B	83	48	1 : 0	0
PMDETA (42)	A	83	48	(378) and isomer	0
PS-PMDETA.CuBr (350b)	B	83	48	(378) and isomer	0
JJ-TEDETA.CuBr (361b)	B	83	48	1 : 0.3	21 ^b
Si-NPMI.CuBr (336b)	B	83	48	1 : 0	0
JJ-NPMI.CuBr (367b)	B	83	48	1 : 0	0
TPA (58) ⁴⁰	A	83	2		42 ^b

^a ratio determined by ¹H NMR, ^b isolated yield

Table 21

5.4.8 Cyclisation of *N*-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide

5-*Exo* cyclisation of radical precursor (55) with a range of catalytic systems was found to give an inseparable mixture of isomeric vinyl bromides (56a) and (56b), and also alkene (57), which is presumably formed by reduction of the intermediate vinyl radical by the ligand system (Scheme 144, Table 22).^{20,24}



Scheme 144

The stereochemistry of each of the vinyl bromides (**56a**) and (**56b**) was determined by a ^1H NMR nOe experiment. In the major *Z* isomer (**56a**) a measurable nOe was observed between the peak at 6.16 ppm (1H, m, $\text{CH}=\text{C}$) and the peak at 1.21 ppm (6H, s, 2 x CH_3). In the minor *E* isomer (**56b**) a measurable nOe was observed between the peak at 6.19 ppm (1H, m, $\text{CH}=\text{C}$) and the peak at 4.40 ppm (2H, d, CH_2N).²⁰⁵

Solution ligands $\text{Me}_6\text{-tren}$ (**43**) and PMDETA (**42**) were found to give the highest *Z/E* selectivity (3.7:1 and 3.8:1 respectively) for vinyl bromide formation, but also the highest levels of reduction to alkene (**57**) (29%) (Table 22). In contrast, the solid supported catalysts gave reduced stereoselectivity in the cyclisation of (**55**) (2.2-2.6:1, *Z/E*), but a diminished level of reduction to (**57**). Si-NPMI.CuBr (**336b**) gave no (**57**), whilst the most selective solid supported catalyst, PS(CL)- $\text{Me}_6\text{-tren.CuBr}$ (**346b**), gave 7% of the reduced product. The results follow a trend where reduction increases as *Z/E* selectivity increases.

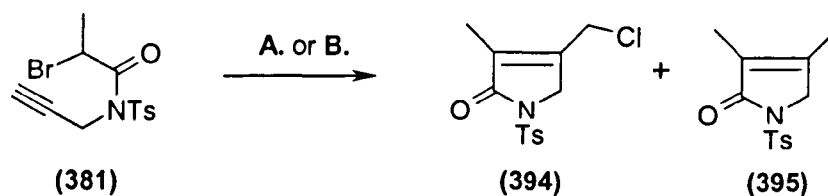
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (55):(56a):(56b):(57) ^a	% (57) ^c
$\text{Me}_6\text{-tren}$ (43)	A	20	0.5	0 : 3.7 : 1 : 1.9	29
PS- $\text{Me}_6\text{-tren.CuBr}$ (341b)	B	83	48	0 : 2.4 : 1 : 0.2	6
PS(CL)- $\text{Me}_6\text{-tren.CuBr}$ (346b)	B	83	48	0 : 2.6 : 1 : 0.3	7
PMDETA (42)	A	18	24	0 : 3.8 : 1 : 2.0	29
PS-PMDETA.CuBr (350b)	B	83	48	0 : 2.3 : 1 : 0.4	11
JJ-TEDETA.CuBr (361b)	B	83	19	0 : 2.4 : 1 : 0.3	8
Si-NPMI.CuBr (336b)	B	83	48	0 : 2.2 : 1 : 0	0
JJ-NPMI.CuBr (367b)	B	83	19	0 : 2.2 : 1 : 0.2	6

^a ratio or yield determined by ^1H NMR, ^c % of reacted material

Table 22

5.4.9 Cyclisation of *N*-(2-Bromo-propionyl)-4-methyl-*N*-prop-2-ynyl-benzene sulfonamide

Secondary bromide (**381**) was found to undergo ATRC in DCE to give primary chloride (**394**) and reduced product (**395**) in low yield using 30 mol % Me₆-tren/CuBr (reflux, 24 hours) (Scheme 145, Table 23).²⁴ The formation of a chloride as opposed to the expected bromide product suggests that atom transfer of a chlorine radical from the solvent to the radical formed on cyclisation is faster than transfer of a bromine radical from copper (II) bromide. Solution ligand PMDETA/CuBr gave only starting material (**381**), reflecting the activity order Me₆-tren > PMDETA. Four of the solid supported catalysts proved unable to cyclise (**381**), and PS(CL)-Me₆-tren.CuBr (**346b**) surprisingly gave a complex mixture. Isomerisation of the starting material was again observed in certain cases. JJ-TEDETA.CuBr (**361b**) was found to be the only solid supported catalyst which could cyclise (**381**) to give (**394**) and (**395**) in 10% and 41% yields.¹⁹¹



Scheme 145

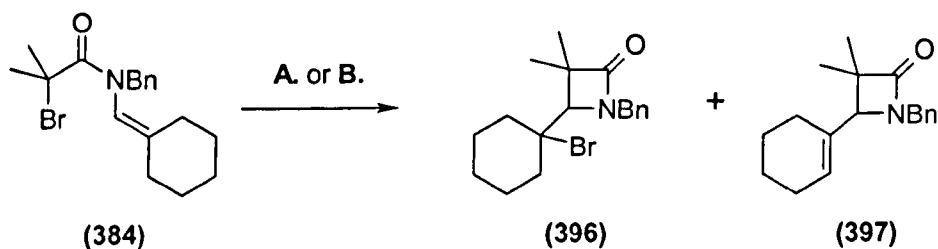
Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (381):(394):(395) ^a	Yield (394) (%)	Yield (395) (%)
Me ₆ -tren (43)	A	20	24	6.8 : 0 : 1	0	13 ^b
Me ₆ -tren (43)	A	83	24	5 : 4.5 : 3.3	g ^b	6 ^b
PS-Me ₆ -tren.CuBr (341b)	B	83	48	(381) and isomer	0	0
PS(CL)-Me ₆ -tren.CuBr (346b)	B	83	48	Complex mixture	0	0
PMDETA (42)	A	18	24	1 : 0 : 0	0	0
PS-PMDETA.CuBr (350b)	B	83	48	(381) and isomer	0	0
JJ-TEDETA.CuBr (361b)	B	83	48	1 : 0.2 : 0.8	10 ^a	41 ^a
Si-NPMI.CuBr (336b)	B	83	48	(381) and isomer	0	0
JJ-NPMI.CuBr (367b)	B	83	48	(381) and isomer	0	0

^a ratio determined by ¹H NMR, ^b isolated yield

Table 23

5.4.10 Cyclisation of *N*-Benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methylpropionamide

Enamide (**384**) which is disubstituted at the terminal end of the alkene, may undergo 4-*exo* ATRC to furnish β -lactams (**396**) and (**397**) (Scheme 146, Table 24).³⁶ Cyclisation of (**384**) with 30 mol % Me₆-tren/Cu(I)Br at room temperature gave bromide (**396**) in 73% isolated yield after 24 hours. Quite remarkably, the solid supported Me₆-tren catalysts display quite different activities in the cyclisation of (**384**). At reflux, after 48 hours, PS(CL)-Me₆-tren.CuBr (**346b**) was found to convert (**384**) to alkene (**397**) in 98% yield, which is presumably formed by elimination of intermediate bromide (**396**). In contrast, PS-Me₆-tren.CuBr (**341b**) gave only starting material under the same conditions. As with substrate (**381**), PMDETA (**42**) shows less activity than Me₆-tren (**43**) in the cyclisation of (**384**); after 24 hours starting material still remained. Solid supported catalysts (**341b**), (**350b**), (**336b**) and (**367b**) did not cyclise bromide (**384**). JJ-TEDETA.CuBr (**361b**) achieved limited cyclisation of (**384**) (alkene (**397**) was isolated in 49% yield), although the activity of the catalyst was found to be less than PS(CL)-Me₆-tren.CuBr (**346b**).



Scheme 146

Ligand/Catalyst	A or B	Temp (°C)	Time (hr)	Ratio (384):(396):(397) ^a	Yield (396) (%)	Yield (397) (%)
Me ₆ -tren (43)	A	20	24	0 : 1 : 0	73 ^b	0
PS-Me ₆ -tren.CuBr (341b)	B	83	48	1 : 0 : 0	0	0
PS(CL)-Me ₆ -tren.CuBr (346b)	B	83	48	0 : 0 : 1	0	98 ^b
PMDETA (42)	A	18	24	1 : 2.4 : 0	71 ^a	0
PS-PMDETA.CuBr (350b)	B	83	48	1 : 0 : 0	0	0
JJ-TEDETA.CuBr (361b)	B	83	48	1.1 : 0 : 1	0	49 ^a
Si-NPMI.CuBr (336b)	B	83	48	1 : 0 : 0	0	0
JJ-NPMI.CuBr (367b)	B	83	48	1 : 0 : 0	0	0

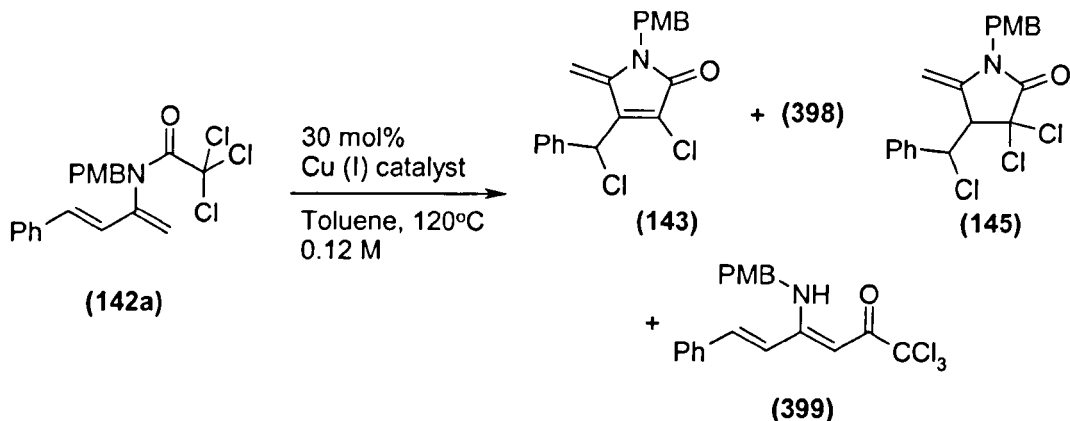
^a ratio or yield determined by ¹H NMR, ^b isolated yield

Table 24

5.4.11 Cyclisation of 2,2,2-Trichloro-*N*-(4-methoxy-benzyl)-*N*-(1-methylene-3-phenyl-allyl)-acetamide

We decided to explore the application of our solid supported catalysts to the novel cyclisation of trichloro dienamide (**142a**) (Chapter 2, Section 2.5). The results are summarised in Table 25. Compared with the copper (I) chloride/TPA solution phase catalytic system, the two JandaJel catalysts (**361a**) and (**367a**) were found to effect the cyclisation more quickly in 1 and 2 hours respectively, although an unidentified byproduct (**398**) was formed in the reaction which lowered the isolated yield of the γ -lactam (**143**). This byproduct was also formed using PS-Me₆-tren.CuCl (**341a**) and Si-NPMI.CuCl (**336a**) although to a lesser extent. Both of these reactions took longer than using CuCl/TPA. PS(CL)-Me₆-tren.CuCl (**346a**) was found to effect the cyclisation in only 4 hours. No byproduct (**398**) was formed but a small yield of product intermediate (**145**) was isolated, which was found to undergo conversion to (**143**) within 24 hours in CDCl₃. Presumably if the reaction had been left longer product (**143**) would have been formed exclusively. PS-PMDETA.CuCl (**350a**) proved to be the least effective solid supported catalyst for this reaction, as encountered in previously discussed cyclisation reactions. The reaction took a day to reach completion and gave γ -lactam (**143**) in a low

yield of 33%. Unknown byproduct (**398**) was also formed together with a further product believed to be (**399**).



Scheme 147

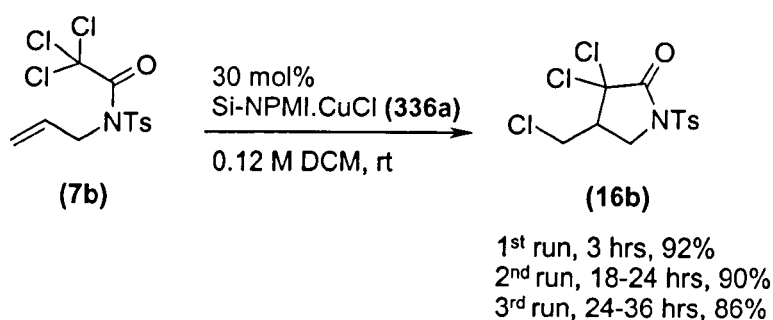
Catalyst	Time (hrs)	Yield (143) (%)	Ratio (143):(398):(145):(399)
TPA, CuCl (58)	3	71	1 : 0 : 0 : 0
PS-Me ₆ -tren.CuCl (341a)	5	62	7 : 1 : 0 : 0
PS(CL)-Me ₆ -tren.CuCl (346a)	4	64	9 : 0 : 1 : 0
PS-PMDETA.CuCl (350a)	23	33	6 : 1 : 0 : 6
JJ-TEDETA.CuCl (361a)	2	60	6 : 1 : 0 : 0
Si-NPMI.CuCl (336a)	9	63	8 : 1 : 0 : 0
JJ-NPMI.CuCl (367a)	1	61	6 : 1 : 0 : 0

Table 25

5.5 RECYCLABILITY OF NOVEL SOLID SUPPORTED COPPER (I) CATALYSTS

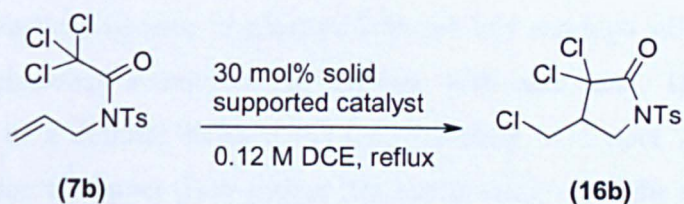
The principal advantage of a solid supported ATRC catalyst over a solution phase system is the potential to re-use the catalyst a number of times. The catalyst, once used to cyclise a particular substrate, may be filtered off, washed dried and then used again. The Si-NPMI.CuCl catalyst (**336a**) has already been reported to be recyclable.³⁵ Reaction of

(**336a**) (30 mol % Cu) with *N*-allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**7b**) in DCM at room temperature for 3 hours gave the expected ATRC product (**16b**) in 92% yield (Scheme 148). The catalyst was reclaimed by filtration from the reaction mixture and was then reused with a new batch of (**7b**) under identical conditions (2nd run; 90% in 18-24 hours). After filtration the catalyst was recycled a third time to give (**16b**) in 86% yield in 24-36 hours. Further runs were found to have excessive reaction times.



Scheme 148

We decided to investigate the reusability of the novel solid supported catalysts PS-Me₆-tren.CuCl (**341a**), PS(CL)-Me₆-tren.CuCl (**346a**) and PS-PMDETA.CuCl (**350a**) in the ATRC of trichloro acetamide (**7b**) (Scheme 149). Reactions were performed using substrate (at least 0.48 mmol) at the usual concentration of 0.12 M in DCE with 30 mol % (Cu) of catalyst at reflux under nitrogen; it had already been established that cyclisation of (**7b**) at room temperature with these catalysts was exceedingly slow (Section 5.4.1). At regular time points (every 30 minutes or every hour depending on the rate), a small aliquot (50 μ l, \sim 6 μ mol) was removed from the reaction mixture, concentrated *in vacuo* and analysed by ¹H NMR to determine the percentage conversion of (**7b**) to (**16b**). Once each reaction had reached completion, the catalyst was filtered, washed well with DCE, dried to constant weight, and then used again with fresh substrate (**7b**). The reaction was repeated a total of seven times for each catalyst. After the final reaction the catalyst was analysed for copper content (ICP analysis).



Scheme 149

The tabulated results for all three catalysts are included in the Appendix (Tables 29-31). These are shown graphically in Figures 26-28.

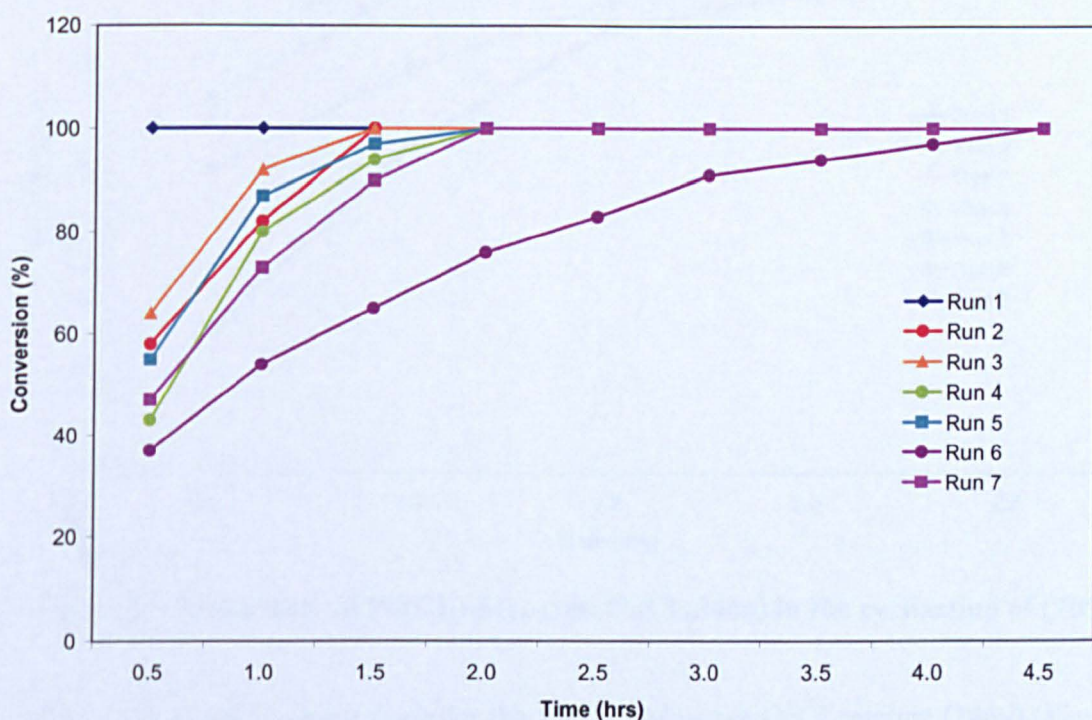


Figure 26: Reusability of PS-Me₆-tren.CuCl (341a) in the cyclisation of (7b)

PS-Me₆-tren.CuCl (**341a**) gives a reasonable reaction time of 4.5 hours even on the sixth run (Figure 26). After each cyclisation it was noted that the catalyst became darker and the resin beads more finely divided. As expected, the second run took longer than the first (1.5 hours compared with 30 minutes). Surprisingly, the initial rate in the third run was found to be higher than the second run. Presumably, the activity of the catalyst is promoted by an increase in surface area as the polymer support is degraded. A similar observation may be noted for subsequent runs. Initial rates (reflected by conversion to

(16b) at 30 minutes) can be seen to alternate between low and high values with a general trend towards decreasing activity of the catalyst with each run. This observation is presumably due to a delicate balance between leaching of copper (I) from the solid support or oxidation of copper (I) to copper (II), and breakdown of the resin beads to give a larger catalytic surface area.

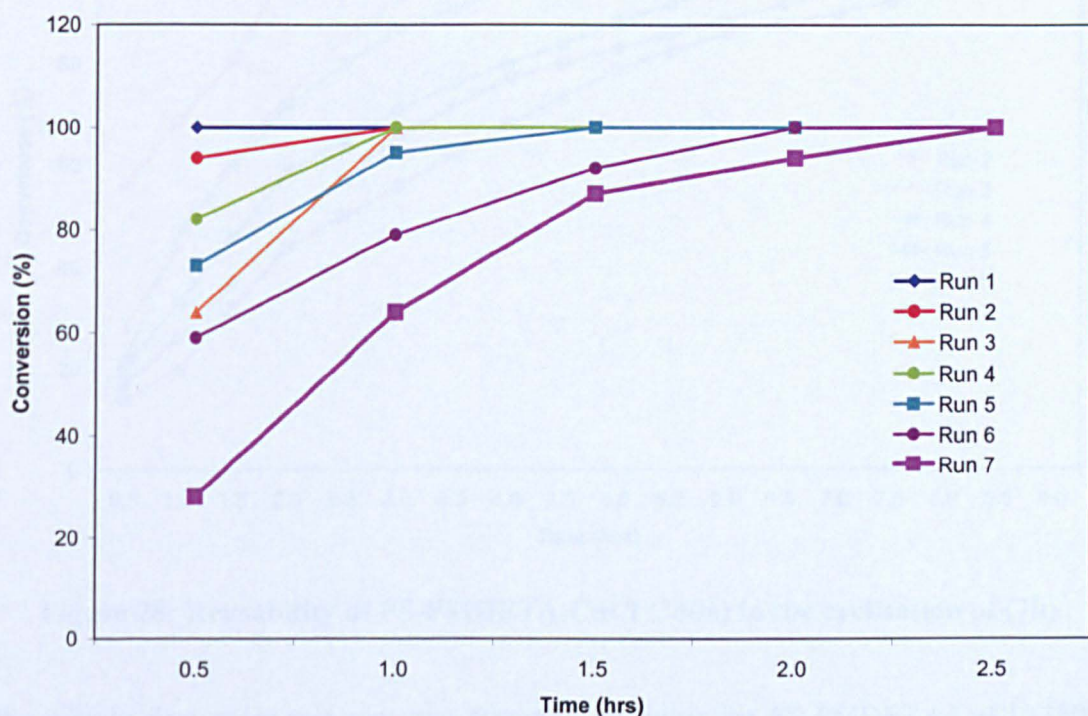


Figure 27: Reusability of PS(CL)-Me₆-tren.CuCl (346a) in the cyclisation of (7b)

A similar observation can be made for the PS(CL)-Me₆-tren.CuCl catalyst (346a) (Figure 27). This same alternating pattern of initial rate is observed until the fifth run of the catalyst. Thereon (sixth and seventh runs) the initial rate is seen to steadily decline. One can deduce that breakdown of the polystyrene support in this case is achieved earlier on the fourth run of the catalyst. PS(CL)-Me₆-tren.CuCl (346a) was found to be the most active of the three catalytic systems after being recycled several times (7th run took only 2.5 hours to reach reaction completion).

Finally, the recyclability of the third catalyst PS-PMDETA.CuCl (350a) is illustrated in Figure 28. The rate is seen to drop off more rapidly compared with the other two

catalysts with each run; on the 7th run a total of 9 hours is required to achieve reaction completion. The resin beads are, however, evidently more stable to degradation since the initial rate declines steadily with each run.

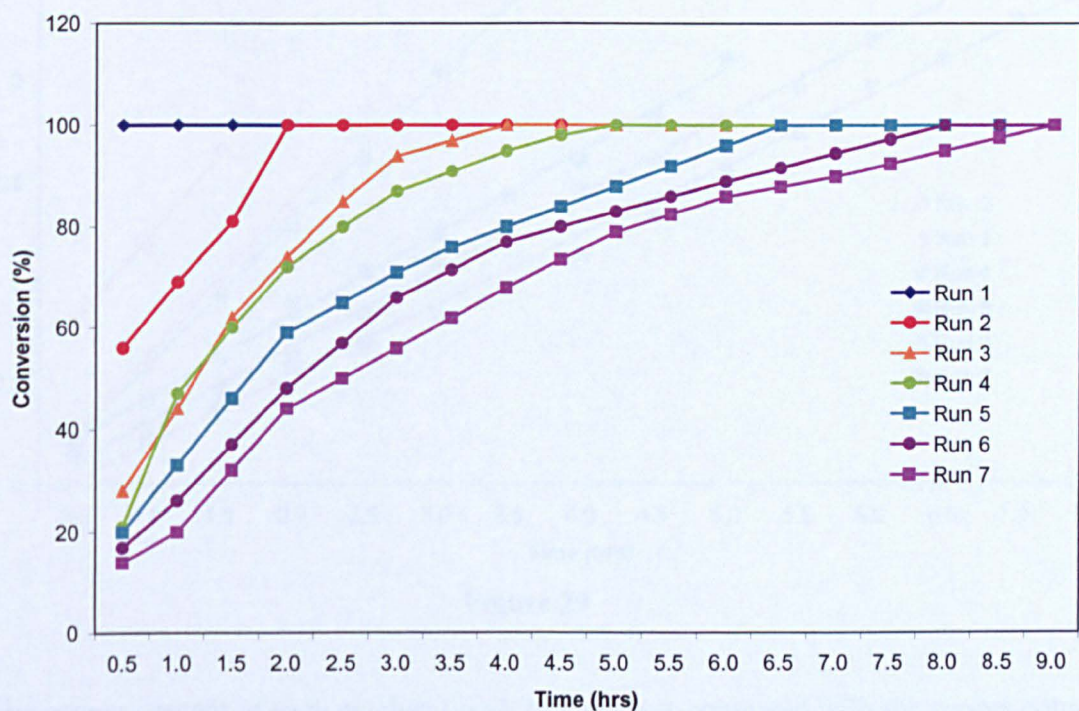


Figure 28: Reusability of PS-PMDETA.CuCl (350a) in the cyclisation of (7b)

The pseudo first order rate plot was found to be linear for PS-PMDETA.CuCl (350a) (Figure 29).

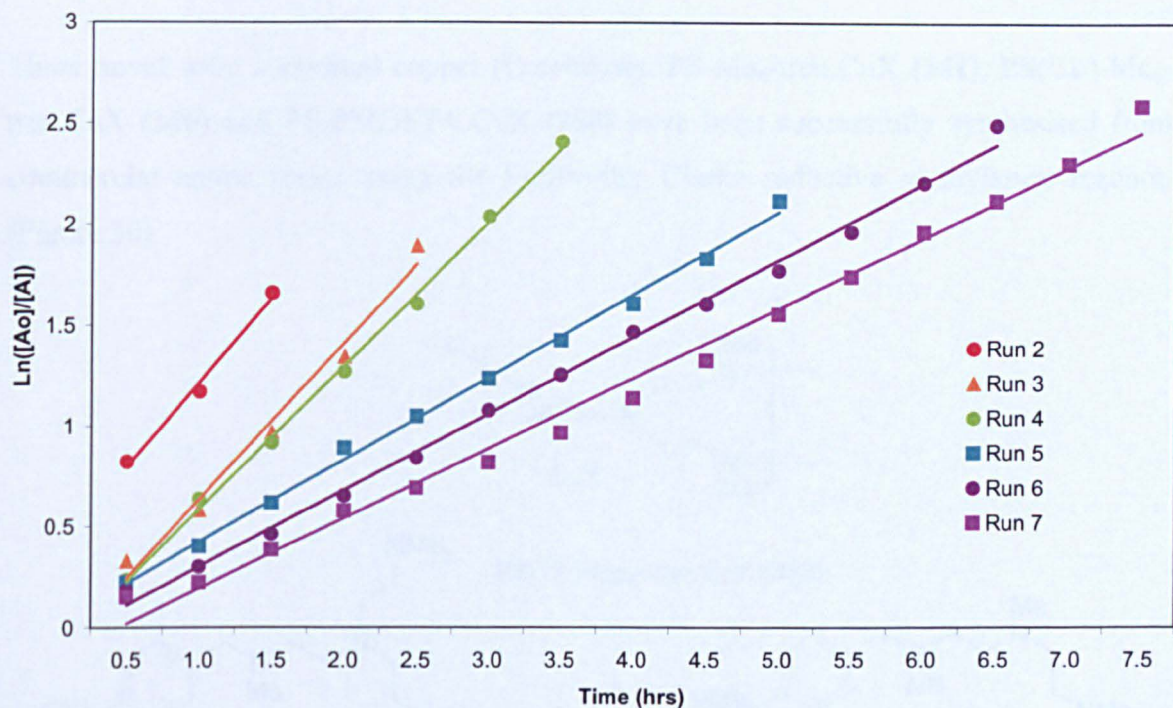


Figure 29

The copper content of each catalyst (used 7 times) was compared with the copper content of the unused catalyst. The results indicate that between 20 and 34% copper had leached out of the catalysts after 7 runs (Table 26). Interestingly, a correlation exists between loss of copper and catalytic activity. PS(CL)-Me₆-tren.CuCl (**346a**) gave the shortest reaction time for run 7 (2.5 hours) and also had the lowest loss of copper (20%), whilst PS-PMDETA.CuCl (**350a**) gave the longest reaction time for run 7 (9 hours) and had the highest loss of copper (34%).

Catalyst	ICP % Cu (unused)	ICP % Cu (used 7 times)	Loss of Cu (%) (after 7 runs)
PS-Me ₆ -tren.CuCl (341a)	8.10	5.91	27
PS(CL)-Me ₆ -tren.CuCl (346a)	6.78	5.45	20
PS-PMDETA.CuCl (350a)	12.59	8.31	34

Table 26

5.6 CONCLUSIONS

Three novel solid supported copper (I) catalysts, PS-Me₆-tren.CuX (**341**), PS(CL)-Me₆-tren.CuX (**346**) and PS-PMDETA.CuX (**350**) have been successfully synthesised from commercial amine resins using the Eschweiler Clarke reductive methylation reaction (Figure 30).

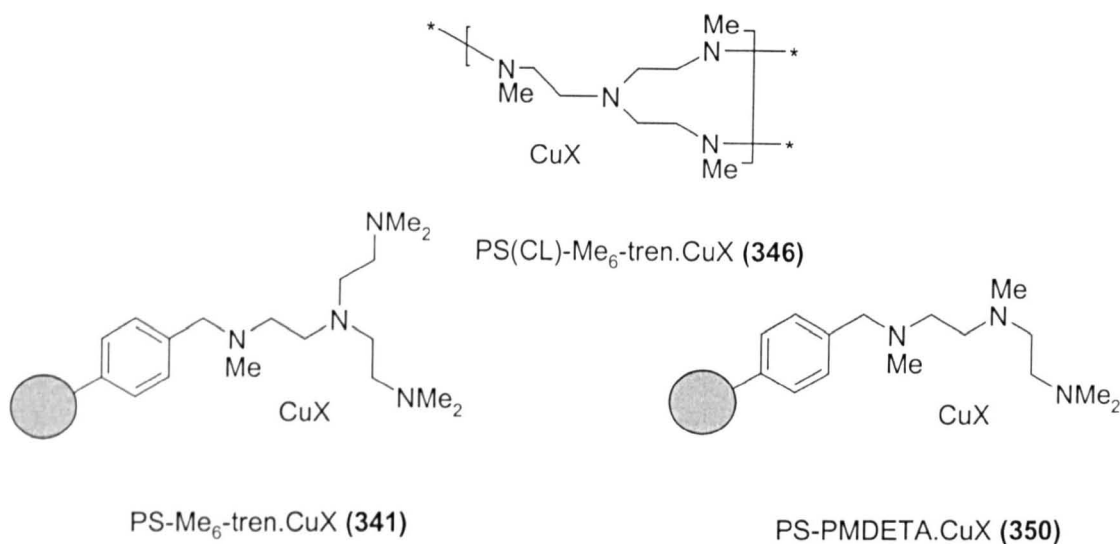


Figure 30

These catalysts were found to be effective in the atom transfer radical cyclisation of a number of activated α -halo acetamide substrates. Compared with their solution counterparts (Me₆-tren and PMDETA/Cu(I)X systems), the solid supported catalysts were found to be less active and less stereoselective. However, reduction of intermediate radicals was observed to a lesser extent with (**341**), (**346**) and (**350**) than with Me₆-tren or PMDETA. The solid supported catalysts follow an approximate hierarchy of reactivity PS-Me₆-tren.CuX > PS(CL)-Me₆-tren.CuX > PS-PMDETA.CuX, although PS(CL)-Me₆-tren.CuBr (**346b**) was the only catalyst within this group which successfully achieves the 4-*exo* cyclisation of *N*-benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methyl-propionamide (**384**) (Scheme 146).

All three catalysts were found to be reusable in the cyclisation of *N*-allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**7b**). After 7 runs, reaction times varied

from only 2.5 to 9 hours at reflux in DCE. Initial rates for each run indicate that the polystyrene supports of PS-Me₆-tren.CuCl (**341a**) and PS(CL)-Me₆-tren.CuCl (**346a**) probably undergo degradation. PS(CL)-Me₆-tren.CuCl (**346a**) proved to be the most reusable catalyst for this particular cyclisation.

The JandaJel supported catalysts JJ-TEDETA.CuX (**361**), which have been reported as effective ATRP catalysts, were shown to provide equivalent or in some cases enhanced activity for ATRC reactions compared with novel catalysts (**341**), (**346**) and (**350**).

Comparison of the activities of Si-NPMI.CuX (**336**) and JJ-NPMI.CuX (**367**) for eleven cyclisation reactions indicated that changing the solid support from silica to polystyrene either maintained, reduced or slightly improved catalytic activity depending on the reaction.

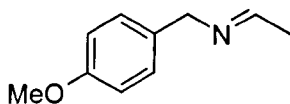
6. EXPERIMENTAL

6.1 Experimental Notes

^1H NMR spectra were recorded in CDCl_3 , unless otherwise stated, at either 300, 400 or 500 MHz on a Bruker DPX300, DPX400 and DPX500 spectrometer respectively. Chemical shifts (δ) are quoted in parts per million (ppm) with residual protic solvent CHCl_3 ($\delta_{\text{H}}=7.26$ ppm) used as internal reference. Coupling constants were measured in hertz. ^{13}C NMR spectra were recorded in CDCl_3 , unless otherwise stated, at 75.5, 100.6 and 125.8 MHz on a Bruker DPX300, DPX400 and DPX500 spectrometer respectively. Infra-red spectra were recorded on a Golden Gate spectrometer. Mass spectra were recorded using a Micromass Autospec at the University of Warwick. Only molecular ions (M^+ or MH^+) and major peaks are reported. Microanalyses were determined in the micro analytical laboratories of Warwick Analytical Services, University of Warwick Science Park. Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Chemicals and solvents used were purchased from Fisher, Lancaster, Aldrich or Jones Chromatography, and were purified, when needed, by literature methods. Flash chromatography was performed on silica gel (Merck Kieselgel 60F₂₅₄, 230-4-mesh). Analytical thin layer chromatography was carried out using aluminium backed plates pre-coated with silica (0.2 mm, 60F₂₅₄) and visualised by ultra-violet radiation (254 nm), acidic ammonium molybdate or potassium permanganate. Preparative thin layer chromatography was performed on glass backed silica gel plates (Whatman Partisil PK6F, 60 Å, 1000 μm , 20 x 20 cm). All reactions were carried out under nitrogen other otherwise stated. Petrol refers to petroleum ether b.p. 40-60°C.

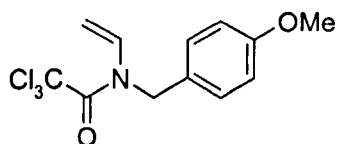
6.2 Experimental for Chapter 2

Ethylidene-(4-methoxybenzyl)-amine (107)



Acetaldehyde (2.24 ml, 40.0 mmol) was added dropwise to stirred 4-methoxybenzylamine (5.23 ml, 40.0 mmol) at 0°C. After 2 hours at 0°C and then 1 hour at room temperature, sodium hydroxide pellets were added and the reaction mixture was allowed to sit for 16 hours. Filtration gave *ethylidene-(4-methoxybenzyl)-amine (107)* as a yellow oil (6.36 g, 97%), which was used without further purification, ν_{\max} (film)/cm⁻¹ 2908, 2833, 1668 (C=N), 1610, 1584, 1439, 1358, 1296, 1241, 1173, 1106, 1032, 812; δ_{H} (300 MHz, CDCl₃) 7.80 (1H, qt, J 4.7, 1.3 Hz, N=CHCH₃), 7.18 (2H, d, J 8.7 Hz, Ar C-H), 6.86 (2H, d, J 8.7 Hz, Ar C-H), 4.49 (2H, br s, CH₂N), 3.78 (3H, s, OCH₃), 2.00 (3H, dt, J 4.7, 1.1 Hz, N=CHCH₃); δ_{C} (75.5 MHz, CDCl₃) 161.2 (N=CHCH₃), 158.4 and 131.2 (Ar quat.), 129.0 and 113.7 (Ar C-H), 64.3 (CH₂N), 55.0 (OCH₃), 22.1 (N=CHCH₃); m/z (EI) 163 (M)⁺, 136, 121, 106, 91, 78, 63, 55; [Found: (M)⁺, 163.0989, C₁₀H₁₃NO requires (M)⁺, 163.0997].

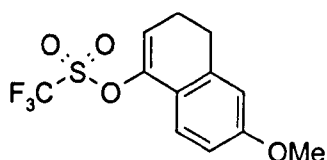
2,2,2-Trichloro-N-(4-methoxybenzyl)-N-vinylacetamide (108)



Trichloroacetyl chloride (2.23 ml, 20.0 mmol) was added dropwise over 10 minutes to a stirred solution of ethylidene-(4-methoxybenzyl)-amine (**107**) (3.26 g, 20.0 mmol) and *N,N*-diethylaniline (3.18 ml, 20.0 mmol) in anhydrous DCM (100 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was

washed with 1M HCl (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) to give *2,2,2-trichloro-N-(4-methoxybenzyl)-N-vinylacetamide (108)* as an off-white crystalline solid (3.27 g, 53%), R_f (5:1 petrol:ethyl acetate) 0.33; m.p. 53.8-54.1°C; ν_{\max} (film)/cm⁻¹ 2931, 2836, 1764, 1684 (C=O), 1628, 1512, 1448, 1421, 1347, 1292, 1245, 1200, 1176, 1112, 1033, 953, 913, 843, 803, 754, 659; δ_{H} (300 MHz, CDCl₃) 7.44 (1H, dd, J 15.4, 9.2 Hz, NCH=CH₂), 7.14 (2H, d, J 8.7 Hz, Ar C-H), 6.87 (2H, d, J 8.7 Hz, Ar C-H), 4.97 (2H, br s, CH₂N), 4.68 (1H, br d, J 15.4 Hz, NCH=CH_aH_b), 4.56 (1H, dd, J 9.2, 1.7 Hz, NCH=CH_aH_b), 3.79 (3H, s, OCH₃); δ_{C} (75.5 MHz, CDCl₃) 159.6 and 159.3 (C=O and Ar quat.), 133.9 (NCH=CH₂), 128.2 (Ar C-H), 128.1 (Ar quat.), 114.6 (Ar C-H), 98.8 (NCH=CH₂), 93.2 (CCl₃), 55.7 (OCH₃), 49.8 (CH₂N); m/z (EI) 307 (M)⁺, 272, 246, 210, 161, 134, 121, 91, 78, 65; [Found: (M)⁺, 308.9901, C₁₂H₁₂NO₂³⁵Cl₂³⁷Cl requires (M)⁺, 308.9904]; [Found: C, 46.61, 46.55; H, 3.90, 3.90; N, 4.46, 4.49. C₁₂H₁₂NO₂Cl₃ requires C, 46.71; H, 3.92; N, 4.54].

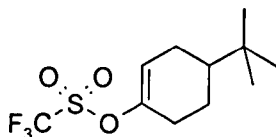
Trifluoromethanesulfonic acid 6-methoxy-3,4-dihydronaphthalen-1-yl ester (109)⁸³



Trifluoromethanesulfonic anhydride (3.36 ml, 20.0 mmol) was added dropwise over 10 minutes to a mixture of 6-methoxy-1-tetralone (1.76 g, 20.0 mmol) and sodium carbonate (1.70 g, 16.0 mmol) in anhydrous DCM (15 ml). After 24 hours, the mixture was filtered. The organic filtrate was washed with saturated NaHCO₃ solution (2 x 10 ml) and water (10 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 19:1 petrol:ethyl acetate) to give *trifluoromethanesulfonic acid 6-methoxy-3,4-dihydronaphthalen-1-yl ester (109)* as a pale yellow oil (489 mg, 16%), R_f (19:1 petrol:ethyl acetate) 0.24; δ_{H} (400 MHz, CDCl₃) 7.27

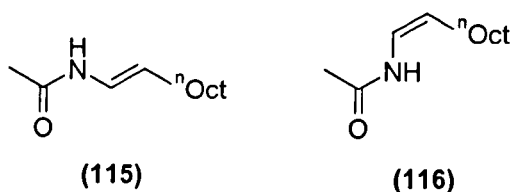
(1H, d, J 8.5 Hz, Ar C-H), 6.77 (1H, dd, J 8.5, 2.8 Hz, Ar C-H), 6.73 (1H, d, J 2.8 Hz, Ar C-H), 5.86 (1H, dd, J 4.8, 4.8 Hz, TfO-C=CHCH₂), 3.81 (3H, s OCH₃), 2.84 (2H, dd, J 7.8, 7.8 Hz, C=CHCH₂CH₂), 2.48 (2H, ddd, J 7.8, 7.8, 4.8 Hz, C=CHCH₂CH₂).

Trifluoromethanesulfonic acid 4-tert-butylcyclohex-1-enyl ester (110)⁸⁴



2,6-Di-*tert*-butyl-4-methylpyridine (1.01 g, 4.92 mmol) and trifluoromethanesulfonic anhydride (749 μ l, 4.45 mmol) were added to a stirred solution of 4-*tert*-butylcyclohexanone (362 mg, 2.34 mmol) in anhydrous DCM (12 ml) at 0°C under nitrogen. After 1.5 hours at room temperature, hexane was added and the pyridinium salts were removed by filtration through a pad of celite. The solids were washed with ethyl acetate and the combined organics were concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, petrol) to give *trifluoromethanesulfonic acid 4-tert-butylcyclohex-1-enyl ester (110)* as a pale yellow oil (548 mg, 82%), R_f (9:1 petrol:ethyl acetate) 0.66; ν_{\max} (film)/cm⁻¹ 2962, 2872, 1694 (C=C), 1475, 1416, 1247, 1205, 1142, 1054, 1038, 1013, 869, 611; δ_{H} (300 MHz, CDCl₃) 5.74 (1H, m, OC=CH), 2.48-2.14 (2H, m, CH₂), 2.02-1.88 (2H, m, CH₂), 1.44-1.23 (3H, m, CH₂ and CH^tBu), 0.89 (9H, s, C[CH₃]₃); δ_{C} (75.5 MHz, CDCl₃) 149.6 (TfOC=CH), 118.9 (q, J 339 Hz, CF₃), 118.8 (TfOC=CH), 43.3 (CH^tBu), 32.4 (C[CH₃]₃), 28.9 (CH₂), 27.6 (C[CH₃]₃), 25.7 and 24.4 (2 x CH₂); m/z (EI) 287 (MH)⁺, 250, 221, 170, 157, 141, 105, 91, 77.

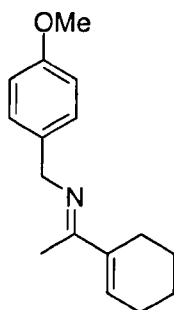
*E-N-Dec-1-enylacetamide (115) and Z-N-dec-1-enylacetamide (116)*⁸¹



Copper (I) iodide (1.1 mg, 0.00601 mmol), acetamide (8.5 mg, 0.144 mmol), cesium carbonate (58.8 mg, 0.180 mmol), *N,N'*-dimethylethylenediamine (1.3 μ l, 0.0120 mmol) and a 3:1 mixture of *E*-1-iododec-1-ene (**112**) and *Z*-1-iododec-1-ene (**113**) (32.0 mg, 0.120 mmol) were stirred at room temperature in dry DMF (0.12 ml) under nitrogen to give a white suspension in a blue solution. After 72 hours, the reaction was partitioned between ethyl acetate (20 ml) and water (20 ml). The layers were separated and the organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 1:1, petrol:ethyl acetate) to give *E-N-dec-1-enylacetamide* (**115**) as a white solid (15.0 mg, 63%), R_f (1:1 petrol:ethyl acetate) 0.20; m.p. 56.6-56.9°C; ν_{max} (film)/ cm^{-1} 3286 (NH), 3210, 3052, 2956, 2917, 2847, 1686 (C=O), 1650 (C=C), 1539, 1459, 1372, 1290, 1266, 1188, 943, 731; δ_{H} (300 MHz, CDCl_3) 7.20-7.05 (1H, br, NH), 6.71 (1H, ddt, J 14.3, 10.6, 1.3 Hz, NHCH=CH), 5.11 (1H, dt, J 14.3, 7.1 Hz, NHCH=CH), 2.01 (3H, s, COCH₃), 2.05-1.94 (2H, m, NHCH=CHCH₂), 1.40-1.20 (12H, m, CH=CHCH₂(CH₂)₆CH₃), 0.87 (3H, t, J 6.4 Hz, CH₂CH₃); δ_{C} (75.5 MHz, CDCl_3) 167.5 (C=O), 122.7 (NHCH=CH), 113.6 (NHCH=CH), 32.3 (CH=CHCH₂), 30.2, 30.0, 29.8, 29.7 and 29.5 (CH=CHCH₂(CH₂)₅CH₂CH₃), 23.6 (COCH₃), 23.1 (CH₂CH₃), 14.5 (CH₂CH₃); m/z (EI) 197 (M)⁺, 182, 168, 154, 138, 126, 112, 98, 82, 70, 60, 56; [Found: (M)⁺, 197.1779, C₁₂H₂₃NO requires (M)⁺, 197.1780], and *Z-N-dec-1-enylacetamide* (**116**) as a colourless oil (4.0 mg, 17%), R_f (1:1 petrol:ethyl acetate) 0.25; ν_{max} (film)/ cm^{-1} 3294 (NH), 3187, 2923, 2854, 1654 (C=O), 1519, 1462, 1372, 1277, 1142, 1093, 749; δ_{H} (300 MHz, CDCl_3) 7.00-6.80 (1H, br, NH), 6.69 (1H, ddt, J 10.7, 9.1, 1.7 Hz, NHCH=CH), 4.72 (1H, dt, J 9.1, 7.4 Hz, NHCH=CH), 2.08 (3H, s, COCH₃), 2.03-1.93 (2H, m, CH=CHCH₂), 1.45-1.20 (12H, m, CH=CHCH₂(CH₂)₆CH₃), 0.88 (3H, t, J 7.0 Hz, CH₂CH₃); δ_{C} (75.5 MHz, CDCl_3) 167.8 (C=O), 122.1 (NHCH=CH), 111.6 (NHCH=CH), 32.3 (CH=CHCH₂), 29.8, 29.7, and

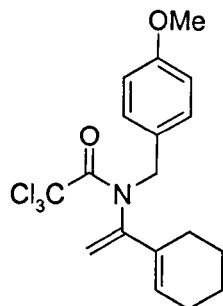
26.1 (CH=CHCH₂(CH₂)₅CH₂CH₃, 3 signals coincident at 29.7), 23.8 (COCH₃), 23.1 (CH₂CH₃), 14.5 (CH₂CH₃); m/z (EI) 197 (M)⁺, 182, 168, 154, 138, 126, 112, 98, 82, 70; [Found: (M)⁺, 197.1769, C₁₂H₂₃NO requires (M)⁺, 197.1780].

(1-Cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (118)

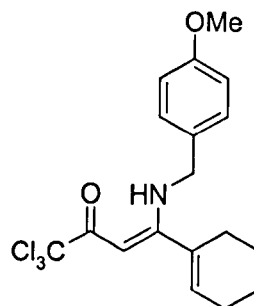


A mixture of 1-acetyl-1-cyclohexene (1.91 g, 15.4 mmol), 4-methoxybenzylamine (2.01 ml, 15.4 mmol) and zinc chloride (100 mg) in toluene (60 ml) were refluxed for 16 hours with azeotropic removal of water *via* a Dean-Stark trap. The reaction was cooled, the catalyst filtered and the filtrate concentrated *in vacuo* to give *(1-cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (118)* as an orange oil (3.63 g, 97%, >95% purity) which was used without further purification; ν_{\max} (film)/cm⁻¹ 2925, 2855, 1662 (C=N), 1609 (C=C), 1509, 1442, 1347, 1299, 1240, 1171, 1033, 813; δ_{H} (300 MHz, CDCl₃) 7.26 (2H, d, J 8.6 Hz, Ar C-H), 6.85 (2H, d, J 8.6 Hz, Ar C-H), 6.34 (1H, m, N=C-C=CH), 4.54 (2H, s, CH₂N), 3.76 (3H, s, OCH₃), 2.45-2.35 (2H, m, CH₂), 2.26-2.14 (2H, m, CH₂), 1.99 (3H, s, N=C-CH₃), 1.70-1.50 (4H, m, 2 x CH₂); δ_{C} (75.5 MHz, CDCl₃) 167.3 (C=N), 158.6 and 140.6 (Ar quat.), 133.6 (N=C-C=CH), 131.0 (N=C-C=CH), 129.0 and 114.1 (Ar C-H), 55.6 (OCH₃), 55.2 (CH₂N), 27.3, 25.9, 23.1 and 22.7 (4 x CH₂), 14.2 (CH₃); m/z (EI) 243 (M)⁺, 200, 136, 121, 106, 91, 78, 65.

2,2,2-Trichloro-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-acetamide (119a) and 2,2,2-trichloro-4-cyclohex-1-enyl-4-(4-methoxybenzylamino)-but-3-en-2-one (120a)



(119a)

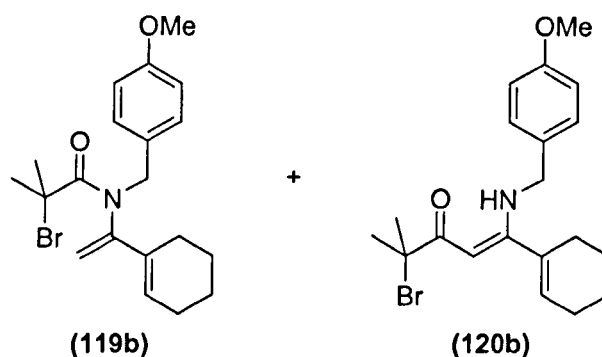


(120a)

Trichloroacetyl chloride (446 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (1-cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (**118**) (973 mg, 4.00 mmol) and *N,N*-diethylaniline (636 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with 1M HCl (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2,2,2-trichloro-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-acetamide (**119a**) as a pale yellow oil (434 mg, 28%), *R_f* (9:1 petrol:ethyl acetate) 0.39; ν_{\max} (film)/cm⁻¹ 2929, 2835, 1671 (C=O), 1610 (C=C), 1511, 1438, 1302, 1245, 1175, 1114, 1033, 906, 842, 806, 759, 732, 662; δ_{H} (400 MHz, CDCl₃) 7.17 (2H, d, *J* 8.5 Hz, Ar C-H), 6.73 (2H, d, *J* 8.5 Hz, Ar C-H), 5.84 (1H, br, H₂C=C-C=CH), 5.40-5.10 (1H, br, CH_aH_bN), 5.16 (1H, s, H_aH_bC=C), 4.69 (1H, s, H_aH_bC=C), 3.90-3.55 (1H, br, CH_aH_bN), 3.68 (3H, s, OCH₃), 2.12-1.95 (4H, m, 2 x CH₂), 1.70-1.40 (4H, m, 2 x CH₂); δ_{C} (100.6 MHz, CDCl₃) 160.6 and 159.3 (C=O and Ar quat.), 145.6 (NC=CH₂), 131.3 and 129.0 (Ar quat. and H₂C=C-C=CH), 130.8 (Ar C-H), 127.8 (C=CHCH₂), 115.2 (C=CH₂), 113.6 (Ar C-H), 93.2 (CCl₃), 55.2 (OCH₃), 54.7 (CH₂N), 25.6, 25.3, 22.5 and 21.9 (4 x CH₂); *m/z* (EI) 387 (M)⁺, 352, 340, 316, 281, 270, 231, 121, 91, 77, 65; [Found: (M)⁺, 387.0552, C₁₈H₂₀NO₂³⁵Cl₃ requires (M)⁺, 387.0560], and 2,2,2-trichloro-4-cyclohex-1-enyl-4-(4-methoxybenzylamino)-but-3-en-2-one (**120a**) as a pale yellow oil (274 mg, 18%), *R_f* (9:1 petrol:ethyl acetate) 0.20; ν_{\max} (film)/cm⁻¹ 2933, 2862, 2837, 1650 (C=O), 1600 (C=C), 1566, 1513, 1457, 1369, 1320, 1249, 1176,

1108, 1034, 808, 755, 654; δ_{H} (400 MHz, CDCl_3) 10.70 (1H, br NH), 7.18 (2H, d, J 8.8 Hz, Ar C-H), 6.87 (2H, d, J 8.8 Hz, Ar C-H), 5.90 (1H, m, $\text{C}=\text{C}[\text{NH}]\text{C}=\text{CH}$), 5.66 (1H, s, $\text{Cl}_3\text{C}[\text{CO}]\text{CH}=\text{C}$), 4.45 (2H, d, J 6.0 Hz, CH_2N), 3.79 (3H, s, OCH_3), 2.20-2.10 (4H, m, 2 x CH_2), 1.75-1.57 (4H, m, 2 x CH_2); δ_{C} (100.6 MHz, CDCl_3) 180.9 ($\text{C}=\text{O}$), 172.5 ($\text{CH}=\text{C}-\text{NH}$), 159.3 and 133.1 (Ar quat.), 130.5 ($\text{C}=\text{C}[\text{NH}]\text{C}=\text{CH}$), 129.0 ($\text{C}=\text{C}[\text{NH}]\text{C}=\text{CH}$), 128.6 and 114.4 (Ar C-H), 97.5 (CCl_3), 85.6 ($\text{Cl}_3\text{C}[\text{CO}]\text{CH}=\text{C}$), 55.3 (OCH_3), 48.1 (CH_2NH), 27.8, 24.9, 22.1 and 21.5 (4 x CH_2); m/z (EI) 387 (M)⁺, 352, 316, 270, 242, 202, 135, 121, 91, 77, 65; [Found: (M)⁺, 387.0555, $\text{C}_{18}\text{H}_{20}\text{NO}_2^{35}\text{Cl}_3$ requires (M)⁺, 387.0560].

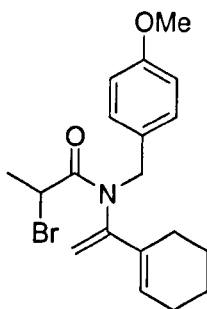
Mixture of 2-bromo-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-2-methylpropionamide (119b) and 4-bromo-1-cyclohex-1-enyl-1-(4-methoxybenzylamino)-4-methylpent-1-en-3-one (120b)



Triethylamine (558 μl , 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (1-cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (**118**) (973 mg, 4.00 mmol) and 2-bromoisobutyryl bromide (494 μl , 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 9:1, petrol:ethyl acetate) to give 2-bromo-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-2-methylpropionamide (**119b**) and 4-bromo-1-cyclohex-1-enyl-1-(4-methoxybenzylamino)-4-methylpent-1-en-3-one (**120b**) as an

inseparable 1:1 mixture (709 mg, 45%), R_f (9:1 petrol:ethyl acetate) 0.30; ν_{\max} (film)/ cm^{-1} 2927, 1635, 1592, 1510, 1459, 1388, 1365, 1305, 1244, 1173, 1094, 1034, 921, 813, 933, 630; δ_H (400 MHz, CDCl_3 , mixture) 10.8 (1H, br, NH , (**120b**)), 7.25 (2H, d, J 8.5 Hz, Ar C-H, (**119b**)), 7.17 (2H, d, J 8.8 Hz, Ar C-H, (**120b**)), 6.86 (2H, d, J 8.8 Hz, Ar C-H, (**120b**)), 6.82 (2H, d, J 8.5 Hz, Ar C-H, (**119b**)), 5.89 (1H, m, $\text{C}=\text{CHCH}_2$, (**119b**)), 5.83 (1H, m, $\text{C}=\text{CHCH}_2$, (**120b**)), 5.46 (1H, s, $\text{CH}=\text{C}-\text{NH}$, (**120b**)), 5.50-5.20 (<2H, br, CH_2N , (**119b**)), 5.21 (1H, s, $\text{C}=\text{CH}_a\text{H}_b$, (**119b**)), 4.91 (1H, s, $\text{C}=\text{CH}_a\text{H}_b$, (**119b**)), 4.36 (2H, d, J 6.3 Hz, CH_2N , (**120b**)), 3.78 (3H, s, OCH_3 , (**119b**)), 3.78 (3H, s, OCH_3 , (**120b**)), 2.20-2.08 (4H, m, 2 x CH_2 , (**119b**)), 2.20-2.08 (4H, m, 2 x CH_2 , (**120b**)), 2.03-1.90 (6H, br, $\text{BrC}[\text{CH}_3]_2$, (**119b**)), 1.91 (6H, s $\text{BrC}[\text{CH}_3]_2$, (**120b**)), 1.75-1.55 (4H, m, 2 x CH_2 , (**119b**)), 1.75-1.55 (4H, m, 2 x CH_2 , (**120b**)); m/z (EI) 391 (M^+), 312, 270, 242, 190, 121, 77; [Found: (M^+), 391.1152, $\text{C}_{20}\text{H}_{26}\text{NO}_2^{79}\text{Br}$ requires (M^+), 391.1147].

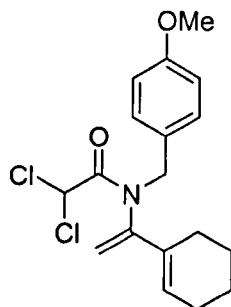
2-Bromo-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-propionamide (119c)



Triethylamine (558 μl , 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (1-cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (**118**) (973 mg, 4.00 mmol) and 2-bromopropionyl bromide (419 μl , 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 9:1, petrol:ethyl acetate) to give 2-bromo-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-propionamide (**119c**) as a colourless oil (714 mg, 47%),

R_f (5:1 petrol:ethyl acetate) 0.26; ν_{\max} (film)/cm⁻¹ 2927, 1659, 1607, 1510, 1441, 1400, 1244, 1174, 1033, 900, 850, 814, 730; δ_{H} (400 MHz, CDCl₃) 7.22 (2H, d, J 8.8 Hz, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 5.83 (1H, br m, C=CHCH₂), 5.17 (1H, s, C=CH_aH_b), 4.73 (1H, br s, C=CH_aH_b), 4.50 (1H, br q, CHBr), 3.78 (3H, s, OCH₃), 2.22-2.05 (4H, m, 2 x CH₂), 1.76 (3H, d, J 6.5 Hz, CHBrCH₃), 1.74-1.67 (2H, m, CH₂), 1.63-1.55 (2H, m, CH₂), CH₂N not visible; δ_{C} (100.6 MHz, CDCl₃) 169.9 (C=O), 159.0 (Ar quat.), 146.2 (N-C=CH), 132.1 and 129.7 (Ar quat. and N-C-C=CH), 130.5 (Ar C-H), 128.2 (N-C-C=CHCH₂), 113.6 (Ar C-H), 113.0 (C=CH₂), 55.2 (OCH₃), 50.5 (CH₂N), 40.2 (CHBr), 25.6, 25.3, 22.5 and 22.0 (4 x CH₂), 22.4 (CH₃); m/z (EI) 378 (MH)⁺, 376 (M-H)⁺, 314, 298, 242, 175, 150, 121, 77; [Found: (M-H)⁺, 376.0906, C₁₉H₂₄NO₂⁷⁹Br requires (M-H)⁺, 376.0912].

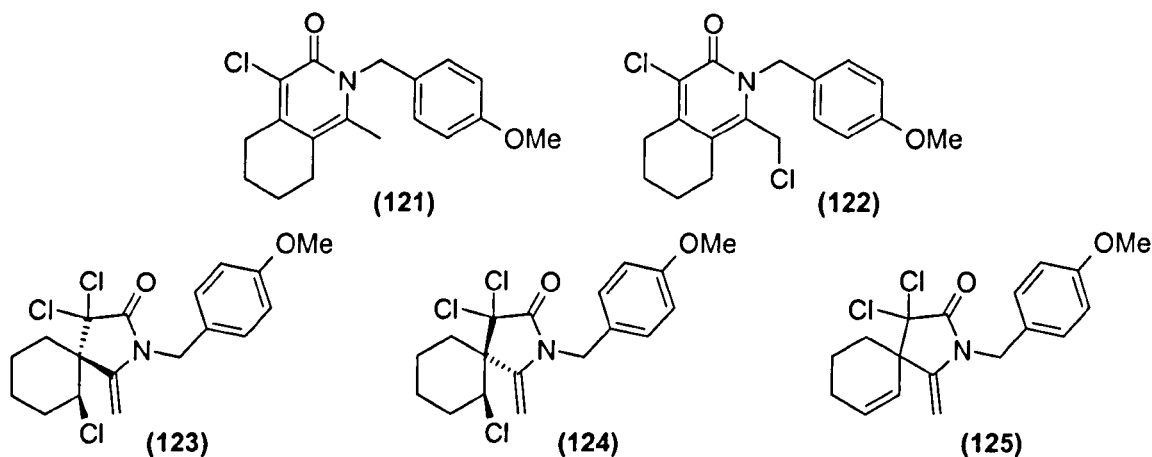
2,2-Dichloro-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-acetamide (119d)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (1-cyclohex-1-enylethylidene)-(4-methoxybenzyl)-amine (**118**) (973 mg, 4.00 mmol) and dichloroacetyl chloride (385 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2,2-dichloro-N-(1-cyclohex-1-enylvinyl)-N-(4-methoxybenzyl)-acetamide (**119d**) as a pale yellow oil (567 mg, 40%), R_f (5:1 petrol:ethyl acetate) 0.29; ν_{\max} (film)/cm⁻¹ 2932, 1781, 1681, 1636, 1611, 1512,

1436, 1398, 1303, 1247, 1196, 1176, 1114, 1034, 908, 848, 805, 668; δ_{H} (400 MHz, CDCl_3) 7.22 (2H, d, J 8.8 Hz, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 6.12 (1H, s, CHCl_2), 5.88 (1H, m, $\text{C}=\text{CHCH}_2$), 5.22 (1H, s, $\text{H}_a\text{H}_b\text{C}=\text{C}$), 4.70 (1H, s, $\text{H}_a\text{H}_b\text{C}=\text{C}$), 3.79 (3H, s, OCH_3), 2.18-2.08 (4H, m, 2 x CH_2), 1.75-1.67 (2H, m, CH_2), 1.64-1.55 (2H, m, CH_2), CH_2N absent; δ_{C} (100.6 MHz, CDCl_3) 164.4 ($\text{C}=\text{O}$), 159.2 (Ar quat.), 145.6 ($\text{NC}=\text{CH}_2$), 131.4 and 128.7 (Ar quat. and $\text{H}_2\text{C}=\text{C}-\text{C}=\text{CH}$), 130.7 (Ar C-H), 129.3 ($\text{C}=\text{CHCH}_2$), 113.9 ($\text{C}=\text{CH}_2$), 113.7 (Ar C-H), 64.4 (CHCl_2), 55.2 (OCH_3), 45.0 (CH_2N), 25.6, 25.1, 22.5 and 21.8 (4 x CH_2); m/z (EI) 353 (M^+), 318, 282, 232, 197, 121, 109, 77, 67; [Found: ($\text{M}-\text{H}$) $^+$, 352.0853, $\text{C}_{18}\text{H}_{21}\text{NO}_2^{35}\text{Cl}_2$ requires ($\text{M}-\text{H}$) $^+$, 352.0871].

4-Chloro-2-(4-methoxybenzyl)-1-methyl-5,6,7,8-tetrahydro-2H-isoquinolin-3-one (121), **4-chloro-1-chloromethyl-2-(4-methoxybenzyl)-5,6,7,8-tetrahydro-2H-isoquinolin-3-one (122)**, (**5R*,6S***) **4,4,6-trichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (123)**, (**5S*,6S***) **4,4,6-trichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (124)** and **4,4-dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]dec-6-en-3-one (125)**

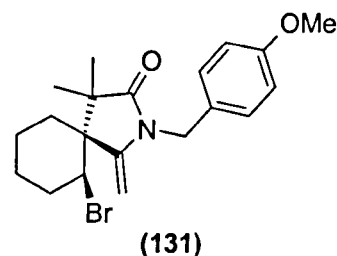
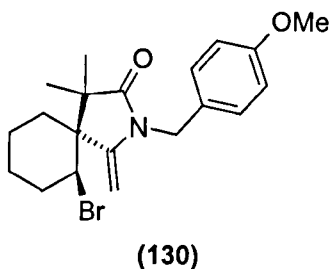
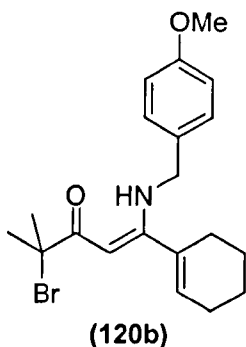


A stirred solution of 2,2,2-trichloro-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-acetamide (**119a**) (313 mg, 0.805 mmol), copper (I) chloride (24.0 mg, 0.242 mmol) and TPA (70.1 mg, 0.242 mmol) in anhydrous toluene (6.70 ml) were heated to reflux under nitrogen for 5 hours. The reaction mixture was cooled and filtered through a small plug

of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) and preparative thin layer chromatography (SiO₂, 5:1, petrol:ethyl acetate) to give *4-chloro-2-(4-methoxybenzyl)-1-methyl-5,6,7,8-tetrahydro-2H-isoquinolin-3-one* (**121**) as a pale yellow oil (74.2 mg, 29%), R_f (1:1 petrol:ethyl acetate) 0.28; ν_{\max} (film)/cm⁻¹ 2936, 2865, 1721, 1644, 1586, 1512, 1441, 1344, 1248, 1178, 1033, 941, 818, 730, 653, 610; δ_{H} (400 MHz, CDCl₃) 7.13 (2H, d, J 8.8 Hz, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 5.38 (2H, br, CH₂N), 3.76 (3H, s, OCH₃), 2.78-2.72 (2H, m, CH₂), 2.48-2.42 (2H, m, CH₂), 2.21 (3H, s, N-C[CH₃]), 1.77-1.69 (4H, m, 2 x CH₂); δ_{C} (100.6 MHz, CDCl₃) 158.9 and 158.8 (C=O and Ar quat.), 147.7, 140.7, 128.5, 122.0 and 114.2 (4 x olef. quat. and Ar quat.), 128.2 and 114.2 (Ar C-H), 55.3 (OCH₃), 48.3 (CH₂N), 28.8, 26.3, 22.8 and 21.8 (4 x CH₂), 16.1 (N-C[CH₃]); m/z (EI) 317 (M)⁺, 121, 91; [Found: (M)⁺, 317.1179, C₁₈H₂₀NO₂³⁵Cl requires (M)⁺, 317.1183], *4-chloro-1-chloromethyl-2-(4-methoxybenzyl)-5,6,7,8-tetrahydro-2H-isoquinolin-3-one* (**122**) as a pale yellow oil (58.8 mg, 21%), R_f (1:1 petrol:ethyl acetate) 0.45; ν_{\max} (film)/cm⁻¹ 2935, 2864, 1640, 1578, 1511, 1446, 1247, 1177, 1033, 921, 732; δ_{H} (400 MHz, CDCl₃) 7.14 (2H, d, J 8.5 Hz, Ar C-H), 6.84 (2H, d, J 8.5 Hz, Ar C-H), 5.51 (2H, br, CH₂N), 4.45 (2H, s, CH₂Cl), 3.77 (3H, s, OCH₃), 2.80-2.73 (2H, m, CH₂), 2.67-2.60 (2H, m, CH₂), 1.80-1.73 (4H, m, 2 x CH₂); δ_{C} (100.6 MHz, CDCl₃) 159.2 and 158.6 (C=O and Ar quat.), 147.6, 137.6, 128.7, 126.2 and 117.5 (4 x olef. quat. and Ar. quat.), 127.9 and 114.4 (Ar C-H), 55.3 (OCH₃), 47.5 (CH₂N), 38.0 (CH₂Cl), 28.7, 25.0, 22.3 and 21.6 (4 x CH₂); m/z (EI) 352 (M)⁺, 351 (M)⁺, 121, 77; [Found: (M)⁺, 352.0826, C₁₇¹³CH₁₉NO₂³⁵Cl₂ requires (M)⁺, 352.0826]; [Found: (M)⁺, 351.0808, C₁₈H₁₉NO₂³⁵Cl₂ requires (M)⁺, 351.0793], (*5R**,*6S**) *4,4,6-trichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one* (**123**) as a pale yellow oil (40.9 mg, 13%), R_f (5:1 petrol:ethyl acetate) 0.27; ν_{\max} (film)/cm⁻¹ 2942, 1746 (C=O), 1647 (C=C), 1612, 1514, 1444, 1389, 1354, 1298, 1249, 1178, 1033, 946, 833; δ_{H} (400 MHz, CDCl₃) 7.19 (2H, d, J 8.6 Hz, Ar C-H), 6.85 (2H, d, J 8.6 Hz, Ar C-H), 5.12 (1H, d, J 15.4 Hz, CH_aH_bN), 4.71 (1H, d, J 3.0 Hz, C=CH_aH_b), 4.67 (1H, d, J 3.0 Hz, C=CH_aH_b), 4.26 (1H, d, J 15.4 Hz, CH_aH_bN), 4.24 (1H, dd, J 11.6, 4.3 Hz, CHCl, H_{1a}), 3.78 (3H, s, OCH₃), 2.60-2.50 (1H, m, H_{5e}), 2.10-1.95 (2H, m, H_{2e} and H_{2a}), 1.90-1.80 (2H, m, H_{3c} and H_{4e}), 1.78-1.60 (2H, m, H_{4a} and H_{5a}), 1.50-1.35 (1H,

m, H_{3a}); δ_C (100.6 MHz, $CDCl_3$) 166.5 ($C=O$), 159.1 (Ar quat.), 145.5 ($N-C=CH_2$), 128.4 (Ar $C-H$), 127.1 (Ar quat.), 114.1 (Ar $C-H$), 93.9 ($C=CH_2$), 90.4 (CCl_2), 63.8 ($CHCl$), 55.5 (aliph. quat.), 55.3 (OCH_3), 44.6 (CH_2N), 32.7, 30.7, 25.4 and 22.6 (4 x CH_2); m/z (EI) 387 (M)⁺, 352, 318, 281, 155, 135, 121, 91, 77, 65; [Found: (M)⁺, 387.0546, $C_{18}H_{20}NO_2^{35}Cl_3$ requires (M)⁺, 387.0560], (*5S**,*6S**) *4,4,6-trichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one* (**124**) as a pale yellow oil (21.8 mg, 7%), R_f (5:1 petrol:ethyl acetate) 0.23; ν_{max} (film)/ cm^{-1} 2989, 1744 ($C=O$), 1648 ($C=C$), 1614, 1514, 1446, 1393, 1353, 1298, 1248, 1179, 1032, 827; δ_H (500 MHz, $CDCl_3$, 323 K) 7.18 (2H, d, J 8.2 Hz, Ar $C-H$), 6.84 (2H, d, J 8.2 Hz, Ar $C-H$), 4.87 (1H, d, J 15.2 Hz, CH_aH_bN), 4.60 (1H, d, J 3.3 Hz, $C=CH_aH_b$), 4.55 (1H, d, J 15.2 Hz, CH_aH_bN), 4.49 (1H, br d, $C=CH_aH_b$), 4.43-4.37 (1H, br m, $CHCl$, H_1), 3.78 (3H, s, OCH_3), 2.65-2.50 (2H, br m, H_{2e} and H_{5e}), 2.17-2.05 (1H, m, H_{2a}), 1.97-1.90 (1H, m, H_{3e}), 1.82-1.69 (1H, m, H_{4e}), 1.60-1.42 (3H, m, H_{3a} , H_{4a} and H_{5a}); δ_C (125.8 MHz, $CDCl_3$, 323 K) 166.7 ($C=O$), 159.7 (Ar quat.), 148.5 ($N-C=CH_2$), 129.1 (Ar $C-H$), 127.2 (Ar quat.), 114.6 (Ar $C-H$), 91.3 ($C=CH_2$), 88.3 (CCl_2), 64.9 ($CHCl$), 56.4 (aliph. quat.), 55.6 (OCH_3), 45.3 (CH_2N), 33.6, 33.5, 23.8 and 21.1 (4 x CH_2); m/z (EI) 387 (M)⁺, 352, 318, 121, 77; [Found: (M)⁺, 387.0557, $C_{18}H_{20}NO_2^{35}Cl_3$ requires (M)⁺, 387.0560], and *4,4-dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]dec-6-en-3-one* (**125**) as a pale yellow oil (13.3 mg, 5%), R_f (5:1 petrol:ethyl acetate) 0.28; ν_{max} (film)/ cm^{-1} 2931, 1781, 1742 ($C=O$), 1653 ($C=C$), 1612, 1513, 1445, 1385, 1346, 1299, 1249, 1178, 1094, 1032, 842, 805, 676, 643; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, d, J 8.6 Hz, Ar $C-H$), 6.84 (2H, d, J 8.6 Hz, Ar $C-H$), 6.15 (1H, dt, J 10.3, 3.4 Hz, $CH_2CH=CH$), 5.76 (1H, br d, J 10.3 Hz, $CH_2CH=CH$), 4.71 (1H, d, J 15.3 Hz, CH_aH_bN), 4.66 (1H, d, J 15.3 Hz, CH_aH_bN), 4.54 (1H, d, J 2.3 Hz, $C=CH_aH_b$), 4.36 (1H, d, J 2.3 Hz, $C=CH_aH_b$), 3.79 (3H, s, OCH_3), 2.15-2.04 (2H, m, CH_2), 1.88-1.72 (1H, m, CH), 1.67-1.50 (3H, m, CH_2 and CH); δ_C (125.8 MHz, $CDCl_3$) 165.6 ($C=O$), 158.2 (Ar quat.), 146.9 ($N-C=CH_2$), 133.5 ($CH_2CH=CH$), 127.7 (Ar $C-H$), 126.0 (Ar quat.), 122.6 ($CH_2CH=CH$), 113.1 (Ar $C-H$), 90.6 ($C=CH_2$), 88.7 (CCl_2), 54.2 (OCH_3), 52.7 (aliph. quat.), 43.7 (CH_2N), 29.8, 23.7 and 18.0 (3 x CH_2); m/z (EI) 351 (M)⁺, 316, 290, 280, 250, 155, 121, 91, 78, 65; [Found: (M)⁺, 351.0791, $C_{18}H_{19}NO_2^{35}Cl_2$ requires (M)⁺, 351.0793].

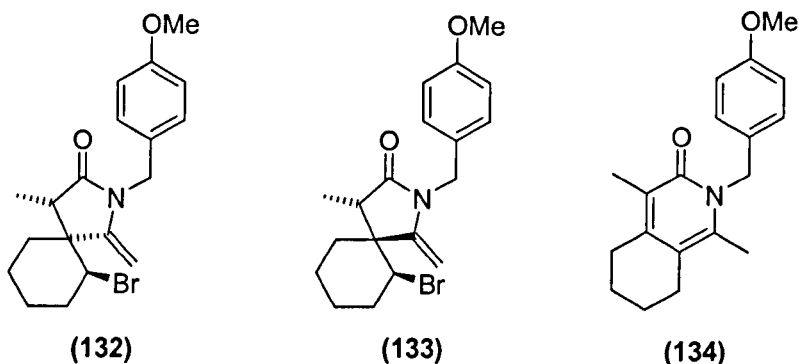
4-Bromo-1-cyclohex-1-enyl-1-(4-methoxybenzylamino)-4-methylpent-1-en-3-one (120b), (5S*,6S*) 6-bromo-2-(4-methoxybenzyl)-4,4-dimethyl-1-methylene-2-aza-spiro[4.5]decan-3-one (130) and (5R*,6S*) 6-bromo-2-(4-methoxybenzyl)-4,4-dimethyl-1-methylene-2-aza-spiro[4.5]decan-3-one (131)



A stirred solution of 2-bromo-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-2-methylpropionamide (**119b**) and 4-bromo-1-cyclohex-1-enyl-1-(4-methoxybenzylamino)-4-methylpent-1-en-3-one (**120b**) (1:1 mixture, 394 mg, 1.00 mmol), copper (I) bromide (43.2 mg, 0.301 mmol) and TPA (87.5 mg, 0.301 mmol) in anhydrous toluene (8.37 ml) were heated to reflux under nitrogen for 3 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) and preparative thin layer chromatography (SiO₂, 5:1, petrol:ethyl acetate) to give 4-bromo-1-cyclohex-1-enyl-1-(4-methoxybenzylamino)-4-methylpent-1-en-3-one (**120b**) as a pale yellow oil (24.0 mg, 12% of reacted (**120b**) recovered), *R*_f (9:1 petrol:ethyl acetate) 0.30; ν_{max} (film)/cm⁻¹ 2931, 1565, 1513, 1458, 1310, 1248, 1175, 1094, 1034, 819, 735; δ_{H} (400 MHz, CDCl₃) 10.8 (1H, br, NH), 7.17 (2H, d, *J* 8.8 Hz, Ar C-H), 6.86 (2H, d, *J* 8.8 Hz, Ar C-H), 5.83 (1H, m, C=CHCH₂), 5.51 (1H, s, CH=C-NH), 4.36 (2H, d, *J* 6.0 Hz, CH₂N), 3.79 (3H, s, OCH₃), 2.17-2.07 (4H, m, 2 x CH₂), 1.73 (6H, s, BrC[CH₃]₂), 1.73-1.60 (4H, m, 2 x CH₂); δ_{C} (100.6 MHz, CDCl₃) 195.3 (C=O), 167.0 (C=C-NH), 159.0 and 133.7 (Ar quat.), 130.2 (C=CHCH₂), 129.2 (C=CHCH₂), 128.5 and 114.2 (Ar C-H), 89.3 (CH=C-NH), 70.8 (CBr), 55.3 (OCH₃), 47.6 (CH₂N), 30.7 (BrC[CH₃]₂), 28.1, 24.9, 22.3 and 21.6 (4 x CH₂); *m/z* (EI) 311 (M-HBr)⁺, 296, 270, 242, 162, 135, 121, 91, 77, 65; [Found: (M-

HBr^+ , 311.1876, $\text{C}_{20}\text{H}_{26}\text{NO}_2^{79}\text{Br}$ requires $(\text{M}-\text{HBr})^+$, 311.1885], (*5S**,*6S**) *6-bromo-2-(4-methoxybenzyl)-4,4-dimethyl-1-methylene-2-aza-spiro[4.5]decan-3-one (130)* as a pale yellow oil (103.0 mg, 52% from (**119b**)), R_f (5:1 petrol:ethyl acetate) 0.20; ν_{max} (film)/ cm^{-1} 2934, 2865, 1715 (C=O), 1660 (C=C), 1630, 1513, 1444, 1398, 1347, 1298, 1246, 1175, 1108, 1031, 918, 818; δ_{H} (400 MHz, CDCl_3) 7.16 (2H, d, J 8.5 Hz, Ar C-H), 6.82 (2H, d, J 8.5 Hz, Ar C-H), 4.96 (1H, br d, J 15.1 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.37 (1H, br s, C= CH_aH_b), 4.26 (1H, br d, J 15.1 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.32-4.15 (1H, br m, CHBr , H_1), 4.24 (1H, br s, C= CH_aH_b), 3.76 (3H, s, OCH_3), 2.41-2.27 (1H, br m, H_{2a}), 2.25-2.15 (1H, br m, H_{2e}), 2.14-2.06 (1H, br m, H_{5e}), 1.89-1.81 (1H, br m, H_{3e}), 1.66-1.58 (1H, br m, H_{4e}), 1.56-1.43 (3H, br m, H_{3a} , H_{4a} and H_{5a}), 1.59 (3H, br s, $\text{C}[\text{CH}_3][\text{CH}_3]$), 1.21 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (125.8 MHz, d^8 -toluene, 343K) 178.9 (C=O), 159.9 (Ar quat.), 154.9 (olef. quat.), 137.6 (Ar quat.), 129.4 (Ar C-H), 114.8 (Ar C-H), 88.6 (C= CH_2), 61.8 (CHBr), 55.1 (OCH_3), 52.3 and 47.8 (2 x aliph. quat.), 44.7 (CH_2N), 35.4 (CH_2 , C_2), 32.3 (CH_2 , C_5), 25.7 (CH_2 , C_3), 22.8 (CH_2 , C_4), 21.8 and 21.7 ($\text{C}[\text{CH}_3][\text{CH}_3]$); m/z (FAB) 394 (MH^+), 392 (MH^+), 312, 154, 121; [Found: (MH^+), 394.1197, $\text{C}_{20}\text{H}_{26}\text{NO}_2^{81}\text{Br}$ requires (MH^+), 394.1204], and (*5R**,*6S**) *6-bromo-2-(4-methoxybenzyl)-4,4-dimethyl-1-methylene-2-aza-spiro[4.5]decan-3-one (131)* as a pale yellow oil (39.0 mg, 20% from (**119b**)), R_f (5:1 petrol:ethyl acetate) 0.13; ν_{max} (film)/ cm^{-1} 2938, 2874, 1718 (C=O), 1662, 1631, 1513, 1447, 1397, 1355, 1304, 1247, 1173, 1109, 1031, 821; δ_{H} (400 MHz, CDCl_3) 7.16 (2H, d, J 8.5 Hz, Ar C-H), 6.83 (2H, d, J 8.5 Hz, Ar C-H), 5.13 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.56 (1H, d, J 2.5 Hz, C= CH_aH_b), 4.51 (1H, d, J 2.5 Hz, C= CH_aH_b), 4.06 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.97 (1H, dd, J 12.0, 4.0 Hz, CHBr , H_{1a}), 3.78 (3H, s, OCH_3), 2.32-2.06 (3H, m, H_{2a} , H_{2e} and H_{5e}), 1.82-1.68 (3H, m, H_{3e} , H_{4e} and H_{4a}), 1.49-1.32 (2H, m, H_{5a} and H_{3a}), 1.28 (3H, s, CH_3), 1.12 (3H, s, CH_3); δ_{C} (100.6 MHz, CDCl_3) 179.7 (C=O), 158.7 (Ar quat.), 150.4 (N-C= CH_2), 128.9 (Ar quat.), 128.5 and 114.0 (Ar C-H), 91.0 (C= CH_2), 57.7 (CHBr), 55.2 (OCH_3), 50.9 and 47.6 (aliph. quat.), 43.6 (CH_2N), 34.1 (CH_2 , C_2), 30.1 (CH_2 , C_5), 27.0 (CH_2 , C_3), 22.7 (CH_2 , C_4), 24.8 and 18.3 ($\text{C}[\text{CH}_3][\text{CH}_3]$); m/z (EI) 391 (M^+), 312, 121, 77; [Found: (M^+), 391.1151, $\text{C}_{20}\text{H}_{26}\text{NO}_2^{79}\text{Br}$ requires (M^+), 391.1147].

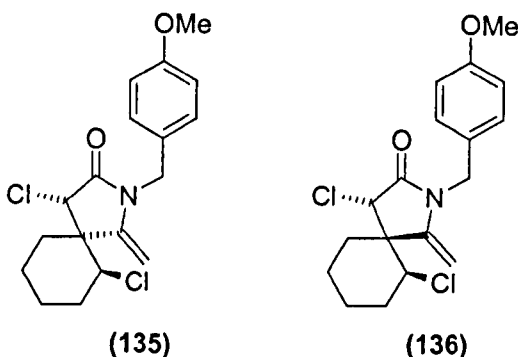
(4*S**,5*S**,6*S**) 6-Bromo-2-(4-methoxybenzyl)-4-methyl-1-methylene-2-aza-spiro[4.5]decan-3-one (132), (4*S**,5*R**,6*S**) 6-Bromo-2-(4-methoxybenzyl)-4-methyl-1-methylene-2-aza-spiro[4.5]decan-3-one (133), and 2-(4-methoxybenzyl)-1,4-dimethyl-5,6,7,8-tetrahydro-2*H*-isoquinolin-3-one (134)



A stirred solution of 2-bromo-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-propionamide (**119c**) (265 mg, 0.700 mmol), copper (I) bromide (30.1 mg, 0.210 mmol) and TPA (61.0 mg, 0.210 mmol) in anhydrous toluene (5.83 ml) were heated to reflux under nitrogen for 2.5 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1, petrol:ethyl acetate, then ethyl acetate) to give (4*S**,5*S**,6*S**) 6-bromo-2-(4-methoxybenzyl)-4-methyl-1-methylene-2-aza-spiro[4.5]decan-3-one (**132**) as a pale yellow oil (119.3 mg, 45%), *R*_f (5:1 petrol:ethyl acetate) 0.15; ν_{\max} (film)/cm⁻¹ 2939, 2681, 1716 (C=O), 1661 (C=C), 1633, 1513, 1460, 1397, 1348, 1299, 1247, 1215, 1178, 1032, 818; δ_{H} (400 MHz, CDCl₃) 7.17 (2H, d, *J* 8.5 Hz, Ar C-H), 6.82 (2H, d, *J* 8.5 Hz, Ar C-H), 4.82 (1H, d, *J* 15.0 Hz, CH_aH_bN), 4.38 (1H, d, *J* 15.0 Hz, CH_aH_bN), 4.29 (1H, d, *J* 2.8 Hz, C=CH_aH_b), 4.16 (1H, d, *J* 2.8 Hz, C=CH_aH_b), 4.11 (1H, dd, *J* 12.6, 3.8 Hz, CHBr, H_{1a}), 3.78 (3H, s, OCH₃), 2.84 (1H, q, *J* 7.4 Hz, CHCH₃), 2.28-2.20 (1H, m, H_{2c}), 2.03-1.96 (1H, m, H_{5e}), 1.96-1.87 (1H, m, H_{2a}), 1.83-1.77 (1H, m, H_{4e}), 1.74-1.68 (1H, m, H_{3e}), 1.64-1.54 (1H, m, H_{5a}), 1.50-1.40 (2H, m, H_{4a} and H_{3a}), 1.37 (3H, d, *J* 7.4 Hz, CHCH₃); δ_{C} (125.8 MHz, CDCl₃) 177.9 (C=O), 158.8 (Ar quat.), 154.5 (N-C=CH₂), 128.8 (Ar C-H), 128.1 (Ar quat.), 113.9 (Ar C-H), 84.9 (C=CH₂), 64.3 (CHBr), 60.4 (OCH₃), 48.4 (aliph. quat.), 43.6 (CH₂N), 40.7 (CHCH₃), 34.9 (CH₂, C₂), 33.3 (CH₂, C₅),

27.1 ($\underline{\text{C}}\text{H}_2$, C_4), 22.9 ($\underline{\text{C}}\text{H}_2$, C_3), 14.5 ($\text{CH}\underline{\text{C}}\text{H}_3$); m/z (EI) 377 (M)⁺, 298, 149, 121, 91, 78; [Found: ($\text{M}-\text{H}$)⁺, 376.0905, $\text{C}_{19}\text{H}_{24}\text{NO}_2$ ⁷⁹Br requires ($\text{M}-\text{H}$)⁺, 376.0912], (*4S**,*5R**,*6S**) 2-(4-methoxybenzyl)-4-methyl-1-methylene-2-aza-spiro[4.5]decan-3-one (**133**) as a pale yellow oil (58.3 mg, 22%), R_f (5:1 petrol:ethyl acetate) 0.13; ν_{max} (film)/ cm^{-1} 2937, 1717 ($\text{C}=\text{O}$), 1662, 1630, 1513, 1444, 1392, 1356, 1296, 1247, 1181, 1033, 821; δ_{H} (400 MHz, CDCl_3) 7.20 (2H, d, J 8.8 Hz, Ar C- $\underline{\text{H}}$), 6.83 (2H, d, J 8.8 Hz, Ar C- $\underline{\text{H}}$), 4.95 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.57 (1H, d, J 2.5 Hz, $\text{C}=\text{CH}_a\text{H}_b$), 4.46 (1H, d, J 2.5 Hz, $\text{C}=\text{CH}_a\text{H}_b$), 4.29 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.93 (1H, dd, J 12.3, 4.2 Hz, CHBr , $\underline{\text{H}}_{1a}$), 3.78 (3H, s, OCH_3), 2.37 (1H, q, J 7.5 Hz, CHCH_3), 2.31-2.19 (1H, m, $\underline{\text{H}}_{2a}$), 2.16-2.08 (1H, m, $\underline{\text{H}}_{2e}$), 2.06-1.99 (1H, m, $\underline{\text{H}}_{5e}$), 1.85-1.74 (2H, m, $\underline{\text{H}}_{3e}$ and $\underline{\text{H}}_{4e}$), 1.74-1.61 (2H, m, $\underline{\text{H}}_{5a}$ and $\underline{\text{H}}_{4a}$), 1.43-1.33 (1H, m, $\underline{\text{H}}_{3a}$), 1.34 (3H, d, J 7.5 Hz, CHCH_3); δ_{C} (125.8 MHz, CDCl_3) 175.7 ($\text{C}=\text{O}$), 158.8 (Ar quat.), 151.0 ($\text{N}-\underline{\text{C}}=\text{CH}_2$), 129.1 (Ar $\underline{\text{C}}-\text{H}$), 128.4 (Ar quat.), 113.8 (Ar $\underline{\text{C}}-\text{H}$), 89.7 ($\text{C}=\underline{\text{C}}\text{H}_2$), 55.3 (CHBr), 55.2 (OCH_3), 47.9 (aliph. quat.), 47.6 (CHCH_3), 43.6 (CH_2N), 36.5 ($\underline{\text{C}}\text{H}_2$, C_5), 32.9 ($\underline{\text{C}}\text{H}_2$, C_2), 26.7 ($\underline{\text{C}}\text{H}_2$, C_3), 22.1 ($\underline{\text{C}}\text{H}_2$, C_4), 7.6 (CHCH_3); m/z (EI) 377 (M)⁺, 376 ($\text{M}-\text{H}$)⁺, 298, 162, 121, 91, 78 ; [Found: ($\text{M}-\text{H}$)⁺, 376.0920, $\text{C}_{19}\text{H}_{24}\text{NO}_2$ ⁷⁹Br requires ($\text{M}-\text{H}$)⁺, 376.0912], and 2-(4-methoxybenzyl)-1,4-dimethyl-5,6,7,8-tetrahydro-2H-isoquinolin-3-one (**134**) as a pale yellow oil (14.0 mg, 7%), R_f (1:1 petrol:ethyl acetate) 0.16; ν_{max} (film)/ cm^{-1} 2932, 2862, 1632, 1574, 1532, 1512, 1445, 1246, 1177, 1033, 811; δ_{H} (300 MHz, CDCl_3) 7.10 (2H, d, J 8.6 Hz, Ar C- $\underline{\text{H}}$), 6.82 (2H, d, J 8.6 Hz, Ar C- $\underline{\text{H}}$), 5.36 (2H, br, CH_2N), 3.77 (3H, s, OCH_3), 2.63-2.55 (2H, m, CH_2), 2.50-2.42 (2H, m, CH_2), 2.18 (3H, s, CH_3), 2.12 (3H, s, CH_3), 1.75-1.68 (4H, m, 2 x CH_2); δ_{C} (125.8 MHz, CDCl_3) 162.6 ($\text{C}=\text{O}$), 158.6 (Ar quat.), 146.8, 138.9, 129.5, 121.4 and 113.7 (4 x olef. quat. and Ar quat.), 127.0 and 114.1 (Ar $\underline{\text{C}}-\text{H}$), 55.3 (OCH_3), 48.5 (CH_2N), 28.4, 27.0, 23.3 and 22.5 (4 x CH_2), 15.7 and 12.4 (2 x CH_3); m/z (EI) 297 (M)⁺, 242, 176, 161, 121, 91, 77; [Found: (M)⁺, 297.1740, $\text{C}_{19}\text{H}_{23}\text{NO}_2$ requires (M)⁺, 297.1729].

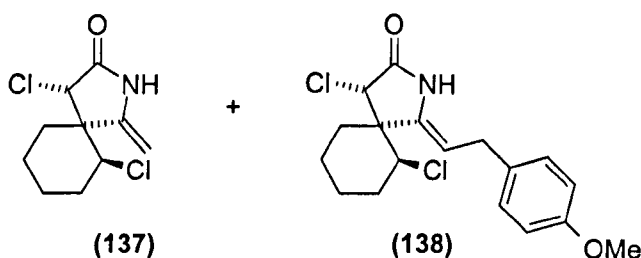
(4*S**,5*S**,6*S**) 4,6-Dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (135), and (4*S**,5*R**,6*S**) 4,6-dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (136)



A stirred solution of 2,2-dichloro-*N*-(1-cyclohex-1-enylvinyl)-*N*-(4-methoxybenzyl)-acetamide (**119d**) (248 mg, 0.700 mmol), copper (I) chloride (20.8 mg, 0.210 mmol) and TPA (61.0 mg, 0.210 mmol) in anhydrous toluene (5.83 ml) were heated to reflux under nitrogen for 2.5 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1, petrol:ethyl acetate, then ethyl acetate) to give (4*S**,5*S**,6*S**) 4,6-dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (**135**) as a pale yellow oil (67.0 mg, 27%), *R*_f (5:1 petrol:ethyl acetate) 0.20; ν_{\max} (film)/cm⁻¹ 2940, 2865, 1727 (C=O), 1644 (C=C), 1514, 1446, 1396, 1349, 1299, 1248, 1177, 1030, 835, 739; δ_{H} (400 MHz, CDCl₃) 7.19 (2H, d, *J* 8.8 Hz, Ar C-H), 6.84 (2H, d, *J* 8.8 Hz, Ar C-H), 4.81 (1H, d, *J* 15.1 Hz, CH_aH_bN), 4.60 (1H, s, CHCl[CO]), 4.52 (1H, d, *J* 15.1 Hz, CH_aH_bN), 4.40 (1H, d, *J* 3.0 Hz, C=CH_aH_b), 4.28 (1H, d, *J* 3.0 Hz, C=CH_aH_b), 4.00 (1H, dd, *J* 12.3, 4.0 Hz, CHClCH₂, H_{1a}), 3.78 (3H, s, OCH₃), 2.31-2.25 (1H, m, H_{5c}), 2.21-2.11 (1H, m, H_{2e}), 1.91-1.74 (3H, m, H_{3e}, H_{2a} and H_{4c}), 1.72-1.55 (2H, m, H_{5a} and H_{4a}), 1.54-1.35 (1H, m, H_{3a}); δ_{C} (100.6 MHz, CDCl₃) 170.4 (C=O), 159.0 (Ar quat.), 151.5 (N-C=CH₂), 128.7 (Ar C-H), 127.2 (Ar quat.), 114.0 (Ar C-H), 87.0 (C=CH₂), 68.5 (CHClCH₂), 57.2 ([CO]CHCl), 55.2 (OCH₃), 49.7 (aliph. quat.), 44.0 (CH₂N), 34.1 (CH₂, C₅), 34.0 (CH₂, C₂), 25.7 (CH₂, C₃) and 22.2 (CH₂, C₄); *m/z* (EI) 353 (M)⁺, 318, 282, 240, 136, 136, 121, 91, 77, 65; [Found: (M)⁺, 353.0952, C₁₈H₂₁NO₂³⁵Cl₂ requires (M)⁺, 353.0949], and

(4*S**,5*R**,6*S**) 4,6-dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (**136**) as a pale yellow oil (5.0 mg, 2%), R_f (5:1 petrol:ethyl acetate) 0.14; ν_{\max} (film)/ cm^{-1} 2938, 1734 (C=O), 1640 (C=C), 1513, 1445, 1391, 1344, 1297, 1248, 1182, 1033, 832; δ_H (400 MHz, CDCl_3) 7.19 (2H, d, J 8.8 Hz, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 4.82 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.77 (1H, d, J 2.8 Hz, C= CH_aH_b), 4.59 (1H, d, J 2.8 Hz, C= CH_aH_b), 4.49 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.38 (1H, s, $\text{CHCl}[\text{CO}]$), 4.30 (1H, dd, J 9.6, 5.5 Hz, CHClCH_2 , H_{1a}), 3.78 (3H, s, OCH_3), 2.10-1.97 (3H, m, H_{2e} , H_{2a} and H_{5e}), 1.92-1.83 (1H, m, H_{3e}), 1.81-1.64 (3H, m, H_{4a} , H_{4e} and H_{5a}), 1.51-1.38 (1H, m, H_{3a}); δ_C (125.8 MHz, CDCl_3) 169.5 (C=O), 159.0 (Ar quat.), 147.8 (N-C=CH₂), 129.0 (Ar C-H), 127.4 (Ar quat.), 114.0 (Ar C-H), 91.9 (C=CH₂), 64.0 ([CO]CHCl), 61.4 (CHClCH₂), 55.2 (OCH₃), 49.6 (aliph. quat.), 44.2 (CH₂N), 34.2 (CH₂, C₅), 31.2 (CH₂, C₂), 24.2 (CH₂, C₃) and 22.3 (CH₂, C₄); m/z (EI) 353 (M)⁺, 335, 318, 292, 256, 201, 176, 157, 136, 121, 91, 77, 65; [Found: (M)⁺, 355.0920, C₁₈H₂₁NO₂³⁵Cl³⁷Cl requires (M)⁺, 355.0920].

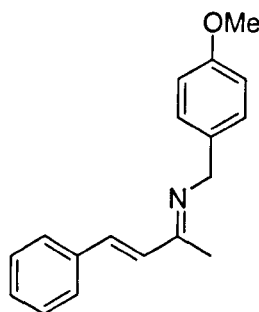
1:1 Mixture of (4*S**,5*S**,6*S**) 4,6-dichloro-1-methylene-2-aza-spiro[4.5]decan-3-one (**137**) and (4*S**,5*S**,6*S**) 4,6-dichloro-1-[2-(4-methoxyphenyl)-ethylidene]-2-aza-spiro[4.5]decan-3-one (**138**)



(4*S**,5*S**,6*S**) 4,6-Dichloro-2-(4-methoxybenzyl)-1-methylene-2-aza-spiro[4.5]decan-3-one (**135**) (61.0 mg, 0.172 mmol) and trifluoroacetic acid (2.0 ml) were heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the residue was purified by preparative thin layer chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give an inseparable 1:1 mixture of (4*S**,5*S**,6*S**) 4,6-dichloro-1-methylene-2-aza-spiro[4.5]decan-3-one (**137**) and (4*S**,5*S**,6*S**) 4,6-dichloro-1-[2-(4-methoxyphenyl)-

ethylidene]-2-aza-spiro[4.5]decan-3-one (138) (11.0 mg), R_f (1:1 petrol:ethyl acetate) 0.51 and 0.56; ν_{\max} (film)/ cm^{-1} 3200 (NH), 2940, 2864, 1720 (C=O), 1691, 1663, 1610, 1510, 1449, 1367, 1300, 1245, 1177, 1033, 909, 837, 733; δ_H (400 MHz, CDCl_3) 8.56 (1H, br, NH, (137) or (138)), 8.41 (1H, br, NH, (137) or (138)), 7.12 (2H, d, J 8.8 Hz, Ar C-H, (138)), 6.84 (2H, d, J 8.8 Hz, Ar C-H, (138)), 4.79 (1H, t, J 7.3 Hz, C=CHCH₂, (138)), 4.58 (1H, d, J 2.8 Hz, C=CH_aH_b, (137)), 4.52 (1H, s, CHCl[CO], (137) or (138)), 4.51 (1H, s, CHCl[CO], (137) or (138)), 4.31 (1H, d, 2.8 Hz, C=CH_aH_b, (137)), 4.04 (1H, dd, J 12.3, 4.3 Hz, CHClCH₂, (137) or (138)), 4.03 (1H, dd, J 12.3, 4.3 Hz, CHClCH₂, (137) or (138)), 3.78 (3H, s, OCH₃, (138)), 3.39 (1H, dd, J 15.9, 7.3 Hz, C=CHCH_aH_b, (138)), 3.34 (1H, dd, J 15.9, 7.3 Hz, C=CHCH_aH_b, (138)), 2.35-1.30 (8H, m, 4 x CH₂, (137)), 2.35-1.30 (8H, m, 4 x CH₂, (138)); m/z (EI) 353 (M)⁺ (138), 318, 282, 233 (M)⁺ (137), 198, 162, 157, 145, 121, 91, 77, 65; [Found: (M)⁺ (137), 233.0393, C₁₀H₁₃NO₂³⁵Cl₂ requires (M)⁺, 233.0374]; [Found: (M)⁺ (138), 353.0960, C₁₈H₂₁NO₂³⁵Cl₂ requires (M)⁺, 353.0949].

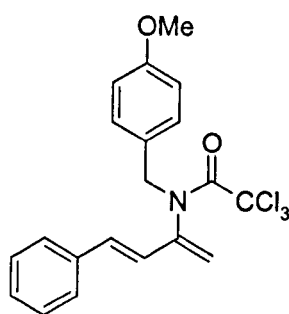
(4-Methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine (141)



A mixture of *trans*-4-phenyl-3-but-2-one (2.92 g, 20.0 mmol), 4-methoxybenzylamine (2.61 ml, 20.0 mmol) and zinc chloride (130 mg) in benzene (64 ml) were refluxed for 4 hours with azeotropic removal of water *via* a Dean-Stark trap. The reaction was cooled, the catalyst filtered and the filtrate concentrated *in vacuo* to give crude (4-methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine (141) as a brown oil (5.22 g, ~60% purity) which was used without further purification, ν_{\max} (film)/ cm^{-1} 3025, 2906, 2833, 1666 (C=N), 1608, 1584, 1509, 1450, 1356, 1299, 1242, 1172, 1107, 1031, 969, 813,

749, 692; δ_{H} (400 MHz, CDCl_3) 7.40-7.15 (7H, m, Ar C-H), 7.02 (1H, d, J 16.6 Hz, $\text{CH}=\text{CH}-\text{C}=\text{N}$), 6.94 (1H, d, J 16.6 Hz, $\text{CH}=\text{CH}-\text{C}=\text{N}$), 6.87 (2H, d, J 8.8 Hz, Ar C-H), 4.57 (2H, s, CH_2N), 3.75 (3H, s, OCH_3), 2.11 (3H, s, CH_3); δ_{C} (100.6 MHz, CDCl_3) 166.3 ($\text{C}=\text{N}$), 158.6, 136.1 and 132.7 (Ar quat.), 134.9 ($\text{CH}=\text{CH}-\text{C}=\text{N}$), 133.0 ($\text{CH}=\text{CH}-\text{C}=\text{N}$), 130.6 (Ar C-H), 129.0-127.0 (3 x Ar C-H), 114.0 (Ar C-H), 55.5 (CH_2N), 55.3 (OCH_3), 14.4 (CH_3); m/z (EI) 266 (MH)⁺, 226, 178, 162, 136, 121, 106, 91, 78.

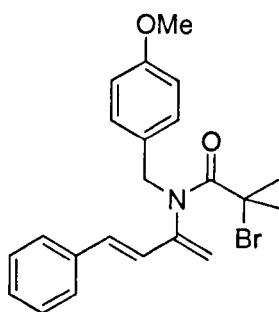
2,2,2-Trichloro-N-(4-methoxybenzyl)-N-(1-methylene-3-phenylallyl)-acetamide (142a)



N,N-Diethylaniline (636 μl , 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine (**141**) (1.06 g, ~60% purity) and trichloroacetyl chloride (446 μl , 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with 1M HCl (100 ml) and then brine (100ml). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 9:1, petrol:ethyl acetate) to give 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-(1-methylene-3-phenylallyl)-acetamide (**142a**) as a pale yellow oil (517 mg, 31% from *trans*-4-phenyl-3-but-2-one), R_f (9:1 petrol:ethyl acetate) 0.28; ν_{max} (film)/ cm^{-1} 3031, 2953, 2836, 1673 (C=O), 1635, 1611, 1517, 1448, 1391, 1249, 1176, 1113, 1033, 965, 908, 839, 813, 757, 693, 667; δ_{H} (400 MHz, CDCl_3) 7.43 (2H, d, J 7.3 Hz, Ar C-H), 7.32-7.21 (5H, m, Ar C-H), 6.83 (2H, d, J 8.5 Hz, Ar C-H), 6.67 (1H, d, J 16.3 Hz, $\text{CH}=\text{CH}-\text{C}=\text{N}$), 6.60 (1H, d, J 16.3 Hz, $\text{CH}=\text{CH}-\text{C}=\text{N}$), 5.60-5.20 (1H, br, $\text{CH}_a\text{H}_b\text{N}$), 5.44 (1H, s, $\text{C}=\text{CH}_a\text{H}_b$), 4.99 (1H, s, $\text{C}=\text{CH}_a\text{H}_b$), 4.20-3.80 (1H, br, $\text{CH}_a\text{H}_b\text{N}$),

3.76 (3H, s, OCH₃); δ_c (100.6 MHz, CDCl₃) 161.4 (C=O), 159.5 (Ar quat.), 143.6 (N=C=CH₂), 135.8 and 128.3 (Ar quat.), 131.1 (CH=C-N), 130.9, 128.9, 128.6 and 127.0 (Ar C-H), 124.6 (CH=CH-C-N), 122.1 (C=CH₂), 113.8 (Ar C-H), 93.2 (CCl₃), 55.2 (OCH₃), 54.0 (CH₂N); m/z (EI) 409 (M)⁺, 374, 338, 288, 253, 223, 197, 176, 155, 131, 121, 91, 77, 67; [Found: (M-Cl)⁺, 374.0717, C₂₀H₁₈NO₂³⁵Cl₃ requires (M-Cl)⁺, 374.0715].

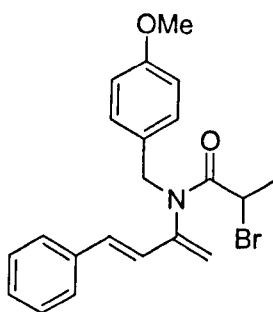
2-Bromo-N-(4-methoxybenzyl)-2-methyl-N-(1-methylene-3-phenylallyl)-propionamide (142b)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine) (**141**) (1.06 g, ~60% purity) and 2-bromoisobutyryl bromide (446 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2-bromo-N-(4-methoxybenzyl)-2-methyl-N-(1-methylene-3-phenylallyl)-propionamide (**142b**) as a colourless oil (178 mg, 11% from *trans*-4-phenyl-3-but-2-one), R_f (9:1 petrol:ethyl acetate) 0.25; ν_{\max} (film)/cm⁻¹ 3029, 2932, 2836, 1636, 1512, 1463, 1391, 1298, 1249, 1175, 1108, 1034, 968, 911, 817, 758, 696; δ_H (400 MHz, CDCl₃) 7.44-7.24 (7H, m, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 6.72 (1H, d, J 16.0 Hz, CH=CH-C-N), 6.56 (1H, d, J 16.0 Hz, CH=CH-C-N), 5.40 (1H, s, C=CH_aH_b), 5.13 (1H, s, C=CH_aH_b), 3.76 (3H, s, OCH₃), 2.03 (6H, s, BrC[CH₃]₂), CH₂N not visible; δ_c (100.6 MHz, CDCl₃) 170.7 (C=O),

159.0 (Ar quat.), 144.8 (N-C=CH₂), 135.9 and 129.7 (Ar quat.), 131.3 (CH=CH-C-N), 130.4, 128.9, 128.5 and 126.9 (Ar C-H), 125.7 (CH=CH-C-N), 121.0 (C=CH₂), 113.7 (Ar C-H), 58.5 (BrC[CH₃]₂), 55.2 (OCH₃), 52.8 (CH₂N), 31.0 (BrC[CH₃]₂); m/z (EI) 413 (M)⁺, 373, 333, 306, 264, 213, 172, 131, 121, 91, 78, 65; [Found: (M-HBr)⁺, 333.1730, C₂₂H₂₄NO₂⁷⁹Br requires (M-HBr)⁺, 333.1729], [Found: C, 63.54; H, 5.83; N, 3.17. C₂₂H₂₄NO₂Br requires C, 63.77; H, 5.84; N, 3.38].

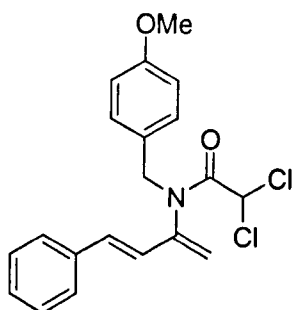
2-Bromo-N-(4-methoxybenzyl)-N-(1-methylene-3-phenylallyl)-propionamide (142c)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine (**141**) (1.06 g, ~60% purity) and 2-bromopropionyl bromide (419 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2-bromo-N-(4-methoxybenzyl)-N-(1-methylene-3-phenylallyl)-propionamide (**142c**) as a pale yellow oil (224 mg, 14% from *trans*-4-phenyl-3-but-2-one), R_f (9:1 petrol:ethyl acetate) 0.24; ν_{\max} (film)/cm⁻¹ 3030, 3001, 2930, 2836, 1662, 1631, 1611, 1511, 1447, 1402, 1296, 1248, 1176, 1113, 1033, 968, 904, 843, 758, 695; δ_{H} (400 MHz, CDCl₃) 7.39-7.23 (7H, m, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 6.74 (1H, d, J 16.0 Hz, CH=CH-C-N), 6.46 (1H, d, J 16.0 Hz, CH=CH-C-N), 5.35 (1H, s, C=CH_aH_b), 4.95 (1H, s, C=CH_aH_b), 4.60 (1H, br q, J 6.5 Hz, CHBr[CH₃]), 3.73 (3H, s, OCH₃), 1.77 (3H, d, J 6.5 Hz, CHBr[CH₃]), CH₂N not

visible; δ_C (100.6 MHz, $CDCl_3$) 169.8 ($\underline{C}=\underline{O}$), 159.2 (Ar quat.), 144.5 ($\underline{N}-\underline{C}=\underline{CH}_2$), 135.6 (Ar quat.), 130.5 ($\underline{CH}=\underline{CH}-\underline{C}-\underline{N}$), 129.5 (Ar quat.), 128.9 and 128.7 (4 x Ar $\underline{C}-\underline{H}$, coincident signals), 127.0 ($\underline{C}\underline{H}=\underline{CH}-\underline{C}-\underline{N}$), 120.0 ($\underline{C}=\underline{CH}_2$), 113.8 (Ar $\underline{C}-\underline{H}$), 55.2 (\underline{OCH}_3), 50.4 ($\underline{CH}_2\underline{N}$), 39.8 ($\underline{CHBr}[\underline{CH}_3]$), 22.3 ($\underline{CHBr}[\underline{CH}_3]$); m/z (FAB) 400 (\underline{MH})⁺, 320, 289, 154, 121; [Found: (\underline{MH})⁺, 400.0923, $C_{21}H_{22}NO_2^{79}Br$ requires (\underline{MH})⁺, 400.0912].

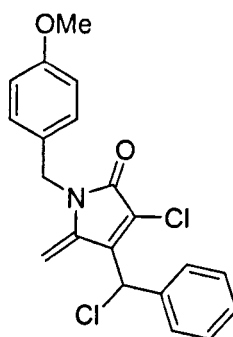
2,2-Dichloro-N-(4-methoxybenzyl)-N-(1-methylene-3-phenylallyl)-acetamide (142d)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-(1-methyl-3-phenylallylidene)-amine (**141**) (1.06 g, ~60% purity) and dichloroacetyl chloride (385 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 9:1, petrol:ethyl acetate) to give 2,2-dichloro-N-(4-methoxybenzyl)-N-(1-methylene-3-phenylallyl)-acetamide (**142d**) as a yellow oil (289 mg, 19% from *trans*-4-phenyl-3-but-2-one), R_f (9:1 petrol:ethyl acetate) 0.23; ν_{max} (film)/ cm^{-1} 3029, 2934, 2837, 1786, 1680, 1632, 1611, 1512, 1448, 1399, 1357, 1325, 1301, 1246, 1176, 1113, 1031, 967, 906, 806, 756, 694, 666; δ_H (400 MHz, $CDCl_3$) 7.39-7.24 (7H, m, Ar $\underline{C}-\underline{H}$), 6.82 (2H, d, J 8.5 Hz, Ar $\underline{C}-\underline{H}$), 6.72 (1H, d, J 16.0 Hz, $\underline{CH}=\underline{CH}-\underline{C}-\underline{N}$), 6.48 (1H, d, J 16.0 Hz, $\underline{CH}=\underline{CH}-\underline{C}-\underline{N}$), 6.24 (1H, s, \underline{CHCl}_2), 5.39 (1H, s, $\underline{C}=\underline{CH}_a\underline{H}_b$), 4.91 (1H, s, $\underline{C}=\underline{CH}_a\underline{H}_b$), 3.73 (3H, s, \underline{OCH}_3), $\underline{CH}_2\underline{N}$ not visible; δ_C (100.6 MHz, $CDCl_3$) 164.3 ($\underline{C}=\underline{O}$), 159.4 (Ar quat.), 143.6 ($\underline{N}-\underline{C}=\underline{CH}_2$), 135.3 (Ar quat.), 132.6 ($\underline{CH}=\underline{CH}-\underline{C}-\underline{N}$), 130.8 and

129.0 (3 x Ar $\underline{\text{C}}\text{-H}$, coincident signals), 128.6 (Ar quat.), 127.2 (Ar $\underline{\text{C}}\text{-H}$), 124.0 ($\underline{\text{C}}\text{H}=\underline{\text{C}}\text{H}-\underline{\text{C}}\text{-N}$), 120.8 ($\text{C}=\underline{\text{C}}\text{H}_2$), 113.9 (Ar $\underline{\text{C}}\text{-H}$), 64.4 ($\underline{\text{C}}\text{HCl}_2$), 55.2 ($\text{O}\underline{\text{C}}\text{H}_3$), 50.2 ($\underline{\text{C}}\text{H}_2\text{N}$); m/z (FAB) 376 (MH)⁺, 307, 289, 254, 154, 121; [Found: (MH)⁺, 376.0878, $\text{C}_{20}\text{H}_{19}\text{NO}_2^{35}\text{Cl}_2$ requires (MH)⁺, 376.0871].

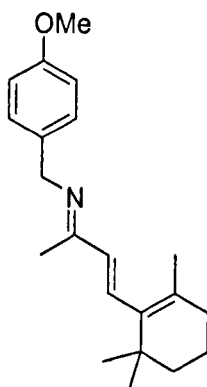
3-Chloro-4-(chlorophenylmethyl)-1-(4-methoxybenzyl)-5-methylene-1,5-dihydropyrrol-2-one (143)



A stirred solution of 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-(1-methylene-3-phenylallyl)-acetamide (**142a**) (327 mg, 0.796 mmol), copper (I) chloride (23.6 mg, 0.239 mmol) and TPA (69.4 mg, 0.239 mmol) in anhydrous toluene (6.63 ml) were heated to reflux under nitrogen for 3 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 5:1, petrol:ethyl acetate) to give 3-chloro-4-(chlorophenylmethyl)-1-(4-methoxybenzyl)-5-methylene-1,5-dihydropyrrol-2-one (**143**) as a pale yellow oil (213 mg, 71%), R_f (5:1 petrol:ethyl acetate) 0.20; ν_{max} (film)/ cm^{-1} 2932, 1708 ($\text{C}=\text{O}$), 1630, 1609, 1512, 1444, 1394, 1349, 1303, 1244, 1175, 1139, 1107, 1030, 959, 813, 733, 700; δ_{H} (400 MHz, CDCl_3) 7.44 (2H, d, J 7.3 Hz, Ar $\underline{\text{C}}\text{-H}$), 7.38-7.28 (3H, m, Ar $\underline{\text{C}}\text{-H}$), 7.13 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}\text{-H}$), 6.83 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}\text{-H}$), 6.30 (1H, s, $\underline{\text{C}}\text{HCl}$), 5.08 (1H, d, J 2.8 Hz, $\text{C}=\underline{\text{C}}\text{H}_a\text{H}_b$), 4.99 (1H, d, J 2.8 Hz, $\text{C}=\underline{\text{C}}\text{H}_a\text{H}_b$), 4.81 (1H, d, J 15.6 Hz, $\underline{\text{C}}\text{H}_a\text{H}_b\text{N}$), 4.73 (1H, d, J 15.6 Hz, $\underline{\text{C}}\text{H}_a\text{H}_b\text{N}$), 3.75 (3H, s, $\text{O}\underline{\text{C}}\text{H}_3$); δ_{C} (100.6 MHz, CDCl_3) 163.1 ($\underline{\text{C}}=\text{O}$), 159.1 (Ar quat.), 140.2, 140.1, 136.9, 128.3 and 129.9 (2 x Ar quat. and 3 x olef. quat.), 128.8, 128.6, 128.5, 126.9 and 114.2 (Ar $\underline{\text{C}}\text{-H}$), 99.5 ($\text{C}=\underline{\text{C}}\text{H}_2$), 55.3 ($\text{O}\underline{\text{C}}\text{H}_3$), 53.4 ($\underline{\text{C}}\text{HCl}$), 43.2

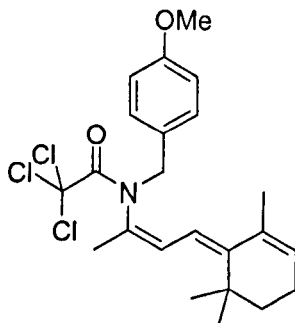
($\underline{\text{C}}\text{H}_2\text{N}$); m/z (EI) 373 (M)⁺, 337, 302, 121, 91, 77; [Found: (M)⁺, 373.0650, $\text{C}_{20}\text{H}_{17}\text{NO}_2^{35}\text{Cl}_2$ requires (M)⁺, 373.0636].

(4-Methoxybenzyl)-[1-methyl-3-(2,6,6-trimethylcyclohex-1-enyl)allylidene]-amine (147)



A mixture of β -ionone (4.07 ml, 20.0 mmol), 4-methoxybenzylamine (2.61 ml, 20.0 mmol) and zinc chloride (130 mg) in benzene (64 ml) were refluxed for 50 hours with azeotropic removal of water *via* a Dean-Stark trap. The reaction was cooled, the catalyst filtered and the filtrate was concentrated *in vacuo* to give *(4-methoxybenzyl)-[1-methyl-3-(2,6,6-trimethylcyclohex-1-enyl)allylidene]-amine (147)* as a yellow oil (6.33 g, ~80% purity) which was used without further purification, ν_{max} (film)/ cm^{-1} 2927, 2862, 1666 ($\text{C}=\text{N}$), 1606, 1510, 1458, 1363, 1297, 1242, 1173, 1034, 971, 731; δ_{H} (400 MHz, CDCl_3) 7.21 (2H, d, J 8.5 Hz, Ar C-H), 6.80 (2H, d, J 8.5 Hz, Ar C-H), 6.63 (1H, d, J 16.6 Hz, $\text{N}=\text{C}-\text{CH}=\text{CH}$), 6.22 (1H, d, J 16.6 Hz, $\text{N}=\text{C}-\text{CH}=\text{CH}$), 4.49 (2H, s, CH_2N), 3.67 (3H, s, OCH_3), 1.99 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 2.00-1.93 (2H, m, CH_2), 1.68 (3H, s, $\text{CH}_2\text{C}=\text{C}-\text{CH}_3$), 1.60-1.50 (2H, m, CH_2), 1.44-1.28 (2H, m, CH_2), 1.01 (6H, s, $\text{C}[\text{CH}_3]_2$); δ_{C} (100.6 MHz, CDCl_3) 165.5 ($\text{C}=\text{N}$), 158.4 (Ar quat.), 137.2 and 134.1 ($\text{N}=\text{C}-\text{CH}=\text{CH}$), 136.7, 132.7 and 131.0 (Ar quat. and 2 x olef. quat.), 129.0 and 113.9 (Ar C-H), 54.1 (CH_2N), 54.0 (OCH_3), 39.6 (CH_2), 34.2 (aliph. quat.), 33.1 (CH_2), 29.0, 29.0 and 21.8 (3 x CH_3), 19.4 (CH_2), 14.6 (CH_3); m/z (EI) 312 (MH)⁺, 296, 190, 177, 161, 136, 121, 105, 91, 77.

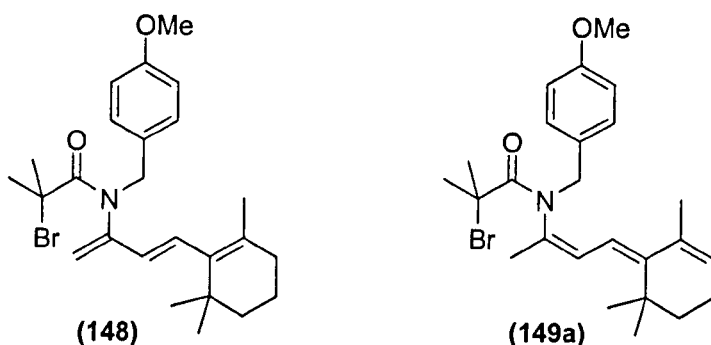
2,2,2-Trichloro-N-(4-methoxybenzyl)-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (149b)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-[1-methyl-3-(2,6,6-trimethylcyclohex-1-enyl)allylidene]-amine (**147**) (1.25 g, 4.00 mmol) and trichloroacetyl chloride (446 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2,2,2-trichloro-N-(4-methoxybenzyl)-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (**149b**) as a yellow oil (555 mg, 30% from β -ionone), R_f (9:1 petrol:ethyl acetate) 0.31; ν_{\max} (film)/cm⁻¹ 2926, 1669 (C=O), 1611, 1512, 1441, 1390, 1302, 1244, 1175, 1111, 1033, 832, 812, 783, 665; δ_{H} (300 MHz, CDCl₃) 7.18 (2H, d, J 8.7 Hz, Ar C-H), 6.73 (2H, d, J 8.7 Hz, Ar C-H), 6.26 (1H, d, J 12.1 Hz, N-C=CH-CH), 5.83 (1H, d, J 12.1 Hz, N-C=CH-CH), 5.69 (1H, t, J 4.1 Hz, C=CHCH₂), 5.30-5.00 (1H, br, CH_aH_bN), 4.10-3.70 (1H, br, CH_aH_bN), 3.67 (3H, s, OCH₃), 2.00-1.89 (2H, m, CH₂), 1.93 (3H, s, N-C-CH₃), 1.76 (3H, s, C[CH₃]=CHCH₂), 1.29 (2H, m, CH₂), 0.89 (3H, br, C[CH₃][CH₃]), 0.68 (3H, br, C[CH₃][CH₃]); δ_{C} (75.5 MHz, CDCl₃) 161.3 (C=O), 159.8 (Ar quat.), 148.9, 136.3, 134.0 and 128.5 (3 x olef. quat. and Ar quat.), 131.9 (N-C=CH-CH), 131.0 (Ar C-H), 130.1 (C=CHCH₂), 117.4 (N-C=CH-CH), 114.4 (Ar C-H), 93.6 (CCl₃), 55.6 (OCH₃), 52.8 (CH₂N), 40.5 (CH₂), 35.1 (aliph. quat.), 29.6 and 28.6 (C[CH₃][CH₃]), 23.2 (CH₂), 22.1 (C[CH₃]=CHCH₂), 17.2 (N-C-CH₃); m/z

(FAB) 457 (M)⁺, 307, 154, 136, 121; [Found: (M)⁺ 455.1195, C₂₃H₂₈NO₂³⁵Cl₃ requires (M)⁺ 455.1186].

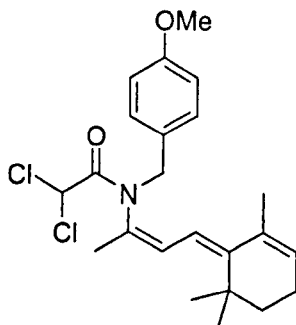
2-Bromo-N-(4-methoxybenzyl)-2-methyl-N-[1-methylene-3-(2,6,6-trimethylcyclohex-1-enyl)-allyl]-propionamide (148) and 2-bromo-N-(4-methoxybenzyl)-2-methyl-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-propionamide (149a)



Triethylamine (558 μ l, 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-[1-methyl-3-(2,6,6-trimethylcyclohex-1-enyl)allylidene]-amine (**147**) (1.25 g, 4.00 mmol) and 2-bromoisobutyryl bromide (494 μ l, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give 2-bromo-N-(4-methoxybenzyl)-2-methyl-N-[1-methylene-3-(2,6,6-trimethylcyclohex-1-enyl)-allyl]-propionamide (**148**) as a yellow oil (550 mg, 30% from β -ionone), R_f (9:1 petrol:ethyl acetate) 0.28; ν_{\max} (film)/cm⁻¹ 2928, 2864, 1638, 1512, 1462, 1390, 1362, 1296, 1248, 1173, 1108, 1035, 975, 900, 816; δ_{H} (400 MHz, CDCl₃) 7.26 (2H, d, J 8.8 Hz, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 6.20 (1H, d, J 16.0 Hz, N-C-CH=CH), 5.97 (1H, d, J 16.0 Hz, N-C-CH=CH), 5.60-5.20 (<2H, br, CH₂N), 5.22 (1H, s, N-C=CH_aH_b), 5.01 (1H, s, N-C=CH_aH_b), 3.79 (3H, s, OCH₃), 2.04 (6H, s, BrC[CH₃]₂), 2.05-2.00 (2H, m, CH₂), 2.05 (3H, s, C=C-CH₃), 1.66-1.58 (2H, m, CH₂), 1.50-1.45 (2H, m, CH₂), 1.02 (6H, s, CH₂C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 170.4 (C=O), 158.9 (Ar quat.), 144.8,

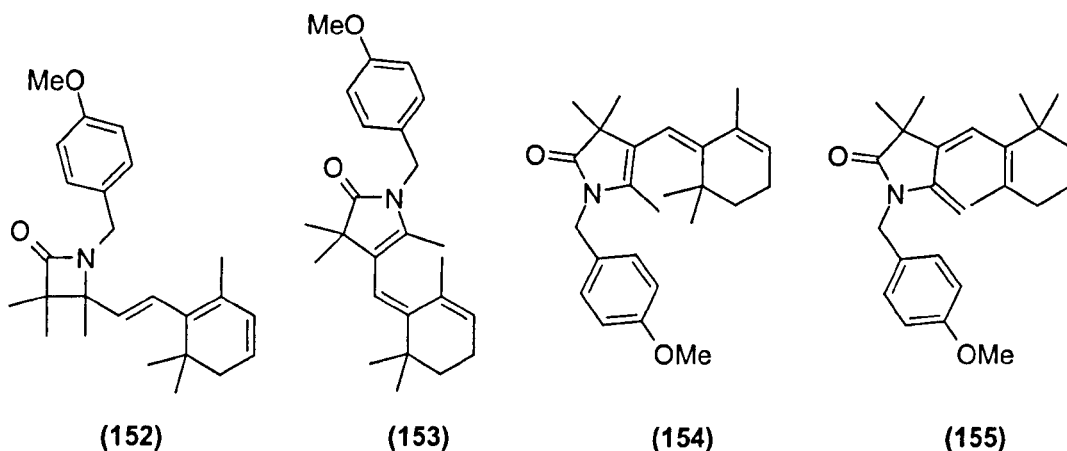
136.6, 135.8 and 130.7 (3 x olef. quat. and Ar quat.), 130.6 and 129.6 (N-CH=CH), 130.6 and 113.6 (Ar C-H), 118.4 (C=CH₂), 58.4 (CBr), 55.1 (OCH₃), 52.4 (CH₂N), 39.4 (CH₂), 34.3 (aliph. quat.), 33.0 (CH₂), 31.0 (BrC[CH₃]₂), 29.0 and 28.8 (CH₂C[CH₃][CH₃]), 21.7 (C=C-CH₃), 18.9 (CH₂); m/z (EI) 461 (M)⁺, 459 (M)⁺, 380, 364, 258, 177, 163, 121, 91, 77; [Found: (M)⁺, 461.1750, C₂₅H₃₄NO₂⁸¹Br requires (M)⁺, 461.1752], and *2-bromo-N-(4-methoxybenzyl)-2-methyl-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-propionamide (149a)* as a yellow oil (218 mg, 12% from β-ionone), R_f (9:1 petrol:ethyl acetate) 0.18; ν_{max} (film)/cm⁻¹ 2927, 2635, 1513, 1463, 1392, 1365, 1304, 1247, 1174, 1110, 1034; δ_H (400 MHz, CDCl₃) 7.24 (2H, d, J 8.5 Hz, Ar C-H), 6.81 (2H, d, J 8.5 Hz, Ar C-H), 6.38 (1H, d, J 12.3 Hz, N-C=CH-CH), 5.95 (1H, d, J 12.3 Hz, N-C=CH-CH), 5.77 (1H, t, J 4.2 Hz, C=CHCH₂), 3.75 (3H, s, OCH₃), 2.08-1.95 (2H, m, CH₂), 2.01 (9H, s, BrC[CH₃]₂ and N-C-CH₃), 1.86 (3H, s, C[CH₃]=CHCH₂), 1.39 (2H, t, J 6.0 Hz, CH₂), 1.00-0.80 (6H, br, CH₂C[CH₃][CH₃]), CH₂N not visible; δ_C (100.6 MHz, CDCl₃) 170.3 (C=O), 159.0 (Ar quat.), 147.9, 134.1, 133.7 and 129.6 (3 x olef. quat. and Ar quat.), 130.3 (Ar C-H), 130.2 (N-C=CH-CH=C), 129.4 (C=CHCH₂), 117.3 (N-C=CH-CH=C), 113.8 (Ar C-H), 60.0 (CBr), 58.7 (CH₂N), 55.2 (OCH₃), 40.2 (CH₂), 34.8 (aliph. quat.), 33.1 (N-C-CH₃), 28.3 (CH₂C[CH₃][CH₃]), 22.9 (CH₂), 21.7 (C=C-CH₃), 17.1 (BrC[CH₃]₂); m/z (EI) 459 (M)⁺, 396, 379, 206, 163, 136, 121, 91, 77.

2,2-Dichloro-N-(4-methoxybenzyl)-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (149c)



Triethylamine (558 μl , 4.00 mmol) was added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-[1-methyl-3-(2,6,6-trimethylcyclohex-1-enyl)allylidene]-amine (**147**) (1.25 g, 4.00 mmol) and dichloroacetyl chloride (385 μl , 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100 ml) and then brine (100ml). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 9:1, petrol:ethyl acetate) to give 2,2-dichloro-N-(4-methoxybenzyl)-N-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (**149c**) as a yellow oil (274 mg, 16% from β -ionone), R_f (9:1 petrol:ethyl acetate) 0.17; ν_{max} (film)/ cm^{-1} 2927, 1680 (C=O), 1612, 1513, 1442, 1400, 1322, 1248, 1179, 1034, 805; δ_{H} (400 MHz, CDCl_3) 7.22 (2H, d, J 8.8 Hz, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 6.35 (1H, s, CHCl_2), 6.31 (1H, d, J 12.3 Hz, N-C=CH-CH), 5.96 (1H, d, J 12.3 Hz, N-C=CH-CH), 5.83 (1H, t, J 4.2 Hz, C=CHCH₂), 5.20-4.20 (2H, br, CH_2N), 3.76 (3H, s, OCH_3), 2.10-2.03 (2H, m, CH_2), 1.96 (3H, s, N-C-CH₃), 1.86 (3H, s, $\text{C}[\text{CH}_3]=\text{CHCH}_2$), 1.41 (2H, m, CH_2), 0.94 (6H, br s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (100.6 MHz, CDCl_3) 163.8 (C=O), 159.3 (Ar quat.), 149.6, 133.4, 132.2 and 128.5 (3 x olef. quat. and Ar quat.), 130.6, 130.5 and 130.4 (N-C=CH-CH, Ar C-H and C=CHCH₂), 116.4 (N-C=CH-CH), 114.0 (Ar C-H), 64.5 (CHCl_2), 55.3 (OCH_3), 49.5 (CH_2N), 40.2 (CH_2), 34.9 (aliph. quat.), 28.7 ($\text{C}[\text{CH}_3][\text{CH}_3]$), 22.8 (CH_2), 21.6 ($\text{C}[\text{CH}_3]=\text{CHCH}_2$), 15.9 (N-C-CH₃); m/z (FAB) 422 (MH)⁺, 421 (M)⁺, 307, 289, 219, 154, 137, 121; [Found: (M)⁺ 421.1586, $\text{C}_{23}\text{H}_{29}\text{NO}_2$ $^{35}\text{Cl}_2$ requires (M)⁺ 421.1575].

1-(4-Methoxybenzyl)-3,3,4-trimethyl-4-[2-(2,6,6-trimethylcyclohexa-1,3-dienyl)-vinyl]-azetidin-2-one (152), *Z-1-(4-methoxybenzyl)-3,3,5-trimethyl-4-(2,6,6-trimethylcyclohex-2-enylidenemethyl)-1,3-dihydropyrrol-2-one (153)*, *E-1-(4-methoxybenzyl)-3,3,5-trimethyl-4-(2,6,6-trimethylcyclohex-2-enylidenemethyl)-1,3-dihydropyrrol-2-one (154)* and *1-(4-methoxybenzyl)-3,3-dimethyl-5-methylene-4-(2,6,6-trimethylcyclohex-1-enylmethylene)-pyrrolidin-2-one (155)*

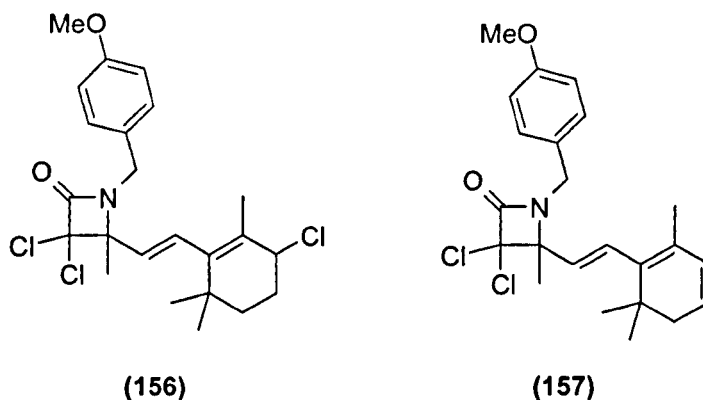


A stirred solution of 2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-[1-methylene-3-(2,6,6-trimethylcyclohex-1-enyl)-allyl]-propionamide (**148**) (330 mg, 0.717 mmol), copper (I) bromide (30.8 mg, 0.215 mmol) and TPA (62.4 mg, 0.215 mmol) in anhydrous toluene (5.97 ml) were heated to reflux under nitrogen for 5 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate, then 1:1, petrol:ethyl acetate) to give *1-(4-methoxybenzyl)-3,3,4-trimethyl-4-[2-(2,6,6-trimethylcyclohexa-1,3-dienyl)-vinyl]-azetidin-2-one (152)* as a pale yellow oil (102 mg, 37%), R_f (1:1 petrol:ethyl acetate) 0.51; ν_{\max} (film)/cm⁻¹ 2958, 1738 (C=O), 1613, 1512, 1462, 1396, 1352, 1303, 1244, 1175, 1109, 1033, 841, 735; δ_{H} (400 MHz, C₆D₆) 7.21 (2H, d, J 8.5 Hz, Ar C-H), 6.70 (2H, d, J 8.5 Hz, Ar C-H), 5.81 (1H, d, J 9.5 Hz, CH=CHCH₂), 5.80 (1H, d, J 16.3 Hz, N-C-CH=CH), 5.65 (1H, ddd, J 9.5, 4.5, 4.5 Hz, CH=CHCH₂), 5.36 (1H, d, J 16.3 Hz, N-C-CH=CH), 4.29 (1H, d, J 15.3 Hz, CH_aH_bN), 4.03 (1H, d, J 15.3 Hz, CH_aH_bN), 3.26 (3H, s, OCH₃), 1.99-1.96 (2H, m, CH₂), 1.68 (3H, s, C=C-CH₃), 1.14

(3H, s, CH_3 lactam), 1.08 (3H, s, CH_3 lactam), 0.99 (3H, s, CH_3 lactam), 0.92 (6H, s, $\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (100.6 MHz, C_6D_6) 173.1 ($\text{C}=\text{O}$), 159.5 (Ar quat.), 137.9 (olef. quat.), 135.3 (N-C-CH= CH), 130.7 (olef. quat.), 130.0 (Ar $\text{C}-\text{H}$), 129.8 ($\text{CH}_2\text{CH}=\text{CH}$), 128.5 (N-C- $\text{CH}=\text{CH}$), 126.1 (Ar quat.), 125.0 ($\text{CH}_2\text{CH}=\text{CH}$), 114.3 (Ar $\text{C}-\text{H}$), 66.0 (N-C- CH_3), 57.9 ($\text{C}[\text{CH}_3]_2$ lactam), 54.8 (OCH_3), 42.7 (CH_2N), 39.8 (CH_2), 33.8 ($\text{CH}_2\text{C}[\text{CH}_3]_2$), 26.8 and 26.6 ($\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$), 20.7, 20.0 and 18.8 (3 x CH_3 lactam), 20.0 (C=C- CH_3); m/z (FAB) 380 (MH)⁺, 341, 307, 289, 273, 219, 154, 137, 121; [Found: (MH)⁺, 380.2577, $\text{C}_{25}\text{H}_{33}\text{NO}_2$ requires (MH)⁺, 380.2590], *Z*-1-(4-methoxybenzyl)-3,3,5-trimethyl-4-(2,6,6-trimethylcyclohex-2-enylidene)methyl)-1,3-dihydropyrrol-2-one (**153**) as a pale yellow oil (72.4 mg, 27%), R_f (5:1 petrol:ethyl acetate) 0.15; ν_{max} (film)/ cm^{-1} 2962, 2920, 1701 (C=O), 1651, 1613, 1513, 1459, 1384, 1360, 1300, 1247, 1175, 1035, 845, 816; δ_{H} (400 MHz, C_6D_6) 7.21 (2H, d, J 8.6 Hz, Ar C-H), 6.82 (2H, d, J 8.6 Hz, Ar C-H), 5.89 (1H, s, C=C- $\text{CH}=\text{C}$), 5.49 (1H, br, C= CHCH_2), 4.72 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.57 (1H, d, J 15.3 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.36 (3H, s, OCH_3), 2.35-2.00 (2H, m, CH_2), 1.79 (3H, s, C=C- CH_3), 1.69 (3H, s, N-C[CH_3]=C), 1.70-1.40 (2H, m, CH_2), 1.52 (3H, s, C[CH_3] [CH_3], lactam), 1.43 (3H, s, C[CH_3] [CH_3], lactam), 1.28 (3H, s, $\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$), 1.20 (3H, s, $\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (125.8 MHz, C_6D_6) 183.0 ($\text{C}=\text{O}$), 159.8 (Ar quat.), 149.7, 133.9, 133.8, 131.4 and 123.0 (4 x olef. quat. and Ar quat.), 129.0 (Ar $\text{C}-\text{H}$), 128.8 (C= CHCH_2), 114.8 (Ar $\text{C}-\text{H}$), 112.5 (N-C=C- $\text{CH}=\text{C}$), 55.1 (OCH_3), 47.5 ($\text{C}[\text{CH}_3]_2$ lactam), 43.3 (CH_2N), 38.4 (CH_2), 36.6 ($\text{CH}_2\text{C}[\text{CH}_3]_2$), 30.0 and 25.9 ($\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$), 24.5 (CH_2), 23.6 and 23.4 (C[CH_3][CH_3], lactam), 22.5 (C=C- CH_3), 12.0 (N-C[CH_3]=C); m/z (EI) 379 (M)⁺, 136, 121; [Found: (M)⁺, 379.2522, $\text{C}_{25}\text{H}_{33}\text{NO}_2$ requires (M)⁺, 379.2511], *E*-1-(4-methoxybenzyl)-3,3,5-trimethyl-4-(2,6,6-trimethylcyclohex-2-enylidene)methyl)-1,3-dihydropyrrol-2-one (**154**) as a pale yellow oil (22.6 mg, 8%), R_f (5:1 petrol:ethyl acetate) 0.14; ν_{max} (film)/ cm^{-1} 2964, 2924, 1701 (C=O), 1614, 1514, 1458, 1386, 1299, 1248, 1176, 1034, 845; δ_{H} (400 MHz, CDCl_3) 7.11 (2H, d, J 8.5 Hz, Ar C-H), 6.84 (2H, d, J 8.5 Hz, Ar C-H), 5.67 (2H, br, C= CHCH_2 and N-C=C- $\text{CH}=\text{C}$), 4.66 (2H, s, CH_2N), 3.79 (3H, s, OCH_3), 2.20-2.08 (2H, m, CH_2), 1.86 (3H, d, J 1.0 Hz, N-C- CH_3), 1.78 (3H, d, J 1.8 Hz, $\text{CH}_2-\text{CH}=\text{C}-\text{CH}_3$), 1.58 (3H, s, C[CH_3] [CH_3], lactam), 1.26 (3H, s, C[CH_3] [CH_3], lactam), 1.45 (2H, t, J 6.3 Hz, CH_2), 1.24 (3H, s, $\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$), 1.05 (3H, s, $\text{CH}_2\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (125.8 MHz, CDCl_3) 183.2 ($\text{C}=\text{O}$), 158.8,

149.4, 133.3, 130.6, 130.3 and 122.9 (2 x Ar quat. and 4 x olef. quat.), 127.9 (Ar $\underline{\text{C}}\text{-H}$), 126.5 ($\text{C}=\underline{\text{C}}\text{HCH}_2$), 114.2 (Ar $\underline{\text{C}}\text{-H}$), 114.1 ($\text{N}-\text{C}=\text{C}-\underline{\text{C}}\text{H}=\text{C}$), 55.3 (OCH_3), 48.4 ($\underline{\text{C}}[\text{CH}_3]_2$ lactam), 42.8 ($\underline{\text{C}}\text{H}_2\text{N}$), 39.3 ($\underline{\text{C}}\text{H}_2$), 35.3 ($\text{CH}_2\underline{\text{C}}[\text{CH}_3]_2$), 25.4 ($\text{CH}_2\underline{\text{C}}[\text{CH}_3]_2$), 23.4 ($\underline{\text{C}}\text{H}_2$), 22.6 ($\text{CH}_2\text{CH}=\text{C}-\underline{\text{C}}\text{H}_3$ and $\text{C}[\underline{\text{C}}\text{H}_3]_2$, lactam), 13.1 ($\text{N}-\text{C}[\underline{\text{C}}\text{H}_3]=\text{C}$); m/z (EI) 379 (M)⁺, 121; [Found: (M)⁺ 379.2522, $\text{C}_{25}\text{H}_{33}\text{NO}_2$ requires (M)⁺ 379.2511], and *1-(4-methoxybenzyl)-3,3-dimethyl-5-methylene-4-(2,6,6-trimethylcyclohex-1-enylmethylene)-pyrrolidin-2-one* (**155**) as a pale yellow oil (34.0 mg, 12%), R_f (5:1 petrol:ethyl acetate) 0.27; ν_{max} (film)/ cm^{-1} 2959, 2926, 2865, 1709 ($\text{C}=\text{O}$), 1613 ($\text{C}=\text{C}$), 1513, 1461, 1393, 1353, 1296, 1246, 1174, 1110, 1035, 818, 734, 619; δ_{H} (400 MHz, C_6D_6) 7.22 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}\text{-H}$), 6.79 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}\text{-H}$), 6.08 (1H, br, $\text{C}=\underline{\text{C}}\text{H}-\text{C}$), 4.97 (1H, d, J 1.3 Hz, $\text{C}=\underline{\text{C}}\text{H}_a\text{H}_b$), 4.80 (1H, d, J 15.3 Hz, $\underline{\text{C}}\text{H}_a\text{H}_b\text{N}$), 4.71 (1H, d, J 15.3 Hz, $\text{C}\text{H}_a\underline{\text{H}}_b\text{N}$), 4.43 (1H, br s, $\text{C}=\text{C}\text{H}_a\underline{\text{H}}_b$), 3.34 (3H, s, OCH_3), 2.00-1.85 (2H, m, $\underline{\text{C}}\text{H}_2$), 1.75-1.60 (2H, m, $\underline{\text{C}}\text{H}_2$), 1.66 (3H, s, $\text{C}=\text{C}-\underline{\text{C}}\text{H}_3$), 1.58-1.50 (2H, m, $\underline{\text{C}}\text{H}_2$), 1.48 (3H, s, $\text{C}[\underline{\text{C}}\text{H}_3]$ [CH_3], lactam), 1.47 (3H, s, $\text{C}[\text{CH}_3]$ [$\underline{\text{C}}\text{H}_3$], lactam), 1.17 (3H, s, $\text{CH}_2\underline{\text{C}}[\text{CH}_3][\text{CH}_3]$), 1.16 (3H, s, $\text{CH}_2\underline{\text{C}}[\text{CH}_3][\underline{\text{C}}\text{H}_3]$); δ_{C} (100.6 MHz, C_6D_6) 159.3 ($\underline{\text{C}}=\text{O}$), 143.0, 140.3, 134.4, 129.5, 128.8 and 128.6 (2 x Ar quat. and 4 x olef. quat.), 128.8 (Ar $\underline{\text{C}}\text{-H}$), 124.6 ($\text{C}=\underline{\text{C}}\text{H}-\text{C}$), 114.4 (Ar $\underline{\text{C}}\text{-H}$), 88.0 ($\text{C}=\underline{\text{C}}\text{H}_2$), 55.7 (OCH_3), 44.1 ($\underline{\text{C}}[\text{CH}_3]_2$ lactam), 42.7 ($\underline{\text{C}}\text{H}_2\text{N}$), 39.4 ($\underline{\text{C}}\text{H}_2$), 35.5 ($\text{CH}_2\underline{\text{C}}[\text{CH}_3]_2$), 32.1 ($\underline{\text{C}}\text{H}_2$), 28.6 and 27.9 ($\text{CH}_2\underline{\text{C}}[\text{CH}_3][\underline{\text{C}}\text{H}_3]$), 26.4 and 25.6 ($\text{C}[\underline{\text{C}}\text{H}_3][\underline{\text{C}}\text{H}_3]$, lactam), 20.8 ($\text{C}=\text{C}-\underline{\text{C}}\text{H}_3$), 19.8 ($\underline{\text{C}}\text{H}_2$); m/z (EI) 379 (M)⁺, 364, 294, 256, 228, 189, 162, 136, 121, 109, 77, 69; [Found: (M)⁺, 379.2525, $\text{C}_{25}\text{H}_{33}\text{NO}_2$ requires (M)⁺, 379.2511].

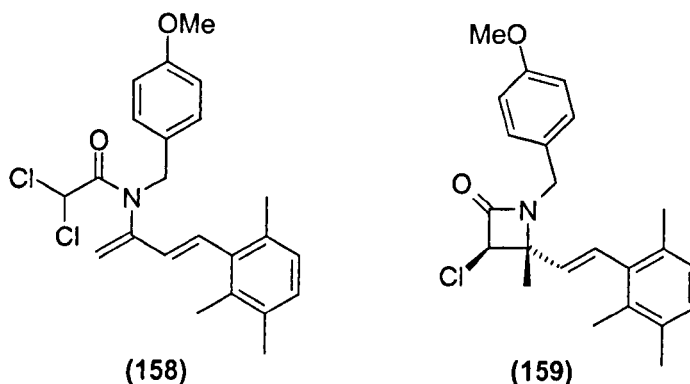
1:1 Mixture of diastereoisomers of 3,3-dichloro-4-[2-(3-chloro-2,6,6-trimethylcyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-4-methylazetidine-2-one (156) and 3,3-dichloro-1-(4-methoxybenzyl)-4-methyl-4-[2-(2,6,6-trimethylcyclohexa-1,3-dienyl)-vinyl]-azetidine-2-one (157)



A stirred solution of 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (**149b**) (260 mg, 0.569 mmol), copper (I) chloride (16.9 mg, 0.171 mmol) and TPA (49.6 mg, 0.171 mmol) in anhydrous toluene (4.74 ml) were heated to reflux under nitrogen for 3 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate, then 3:1, petrol:ethyl acetate, then 1:1, petrol:ethyl acetate) to give a 1:1 mixture of diastereoisomers of 3,3-dichloro-4-[2-(3-chloro-2,6,6-trimethylcyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-4-methylazetidine-2-one (**156**) as a pale yellow oil (76.0 mg, 29%), *R_f* (1:1 petrol:ethyl acetate) 0.46; ν_{\max} (film)/cm⁻¹ 2933, 2862, 1778 (C=O), 1612, 1514, 1448, 1392, 1248, 1177, 1032, 867; δ_{H} (400 MHz, CDCl₃) 7.20 (2H, d, *J* 8.5 Hz, Ar C-H, isomer A), 7.19 (2H, d, *J* 8.5 Hz, Ar C-H, isomer B), 6.85 (2H, d, *J* 8.5 Hz, Ar C-H, isomer A), 6.85 (2H, d, *J* 8.5 Hz, Ar C-H, isomer B), 6.13 (1H, d, *J* 16.3 Hz, N-C-CH=CH, isomer A), 6.13 (1H, d, *J* 16.3 Hz, N-C-CH=CH, isomer B), 5.51 (1H, d, *J* 16.3 Hz, N-C-CH=CH, isomer A), 5.50 (1H, d, *J* 16.3 Hz, N-C-CH=CH, isomer B), 4.56 (1H, d, *J* 15.3 Hz, CH₂H_bN, isomer A), 4.54 (1H, d, *J* 15.3 Hz, CH₂H_aN, isomer B), 4.10 (1H, d, *J* 15.3 Hz, CH₂H_bN, isomer A), 4.10 (1H, d, *J* 15.3 Hz, CH₂H_aN, isomer B), 3.98 (1H, t, *J* 4.5 Hz, CHCl,

isomer A), 3.98 (1H, t, J 4.5 Hz, CHCl , isomer B), 3.80 (3H, s, OCH_3 , isomer A), 3.80 (3H, s, OCH_3 , isomer B), 1.95-1.38 (4H, m, 2 x CH_2 , isomer A), 1.95-1.38 (4H, m, 2 x CH_2 , isomer B), 1.78 (3H, s, $\text{C}=\text{C}-\text{CH}_3$, isomer A), 1.78 (3H, s, $\text{C}=\text{C}-\text{CH}_3$, isomer B), 1.46 (3H, s, $\text{N}-\text{C}-\text{CH}_3$, isomer A), 1.45 (3H, s, $\text{N}-\text{C}-\text{CH}_3$, isomer B), 1.01 (3H, s, $\text{C}[\text{CH}_3]$ [CH_3], isomer A), 0.99 (3H, s, $\text{C}[\text{CH}_3]$ [CH_3], isomer A), 0.97 (3H, s, $\text{C}[\text{CH}_3]$ [CH_3], isomer B), 0.94 (3H, s, $\text{C}[\text{CH}_3]$ [CH_3], isomer B); δ_{C} (125.8 MHz, CDCl_3) 161.5 ($\text{C}=\text{O}$, A and B), 159.5 (Ar quat., A and B), 140.1, 130.8 and 127.3 (2 x olef. quat. and Ar quat., A and B), 133.1 ($\text{N}-\text{C}-\text{CH}=\text{CH}$, A and B), 132.1 ($\text{N}-\text{C}-\text{CH}=\text{CH}$, A), 132.0 ($\text{N}-\text{C}-\text{CH}=\text{CH}$, B), 129.7 (Ar $\text{C}-\text{H}$, A and B), 114.4 (Ar $\text{C}-\text{H}$, A and B), 89.5 (CCl_2 , A and B), 72.7 ($\text{N}-\text{C}-\text{CH}_3$, A and B), 69.9 (CHCl , A), 69.7 (CHCl , B), 55.3 (OCH_3 , A and B), 43.7 (CH_2N , A and B), 34.4 ($\text{C}[\text{CH}_3]_2$, A and B), 34.3 ($\text{CHClCH}_2\text{CH}_2$, A), 34.2 ($\text{CHClCH}_2\text{CH}_2$, B), 28.4 ($\text{CHClCH}_2\text{CH}_2$, A and B), 28.8 and 27.3 ($\text{C}[\text{CH}_3]$ [CH_3], A and B), 20.8 ($\text{N}-\text{C}-\text{CH}_3$, A and B), 18.6 ($\text{C}=\text{C}-\text{CH}_3$, A), 18.4 ($\text{C}=\text{C}-\text{CH}_3$, B); m/z (FAB) 420 ($\text{M}-\text{Cl}$)⁺, 307, 289, 154, 121; [Found: ($\text{M}-\text{Cl}$)⁺ 420.1489, $\text{C}_{23}\text{H}_{28}\text{NO}_2^{35}\text{Cl}_3$ requires ($\text{M}-\text{Cl}$)⁺ 420.1497], and 3,3-dichloro-1-(4-methoxybenzyl)-4-methyl-4-[2-(2,6,6-trimethylcyclohexa-1,3-dienyl)-vinyl]-azetadin-2-one (**157**) as a pale yellow oil (17.0 mg, 7%), R_f (9:1 petrol:ethyl acetate) 0.23; ν_{max} (film)/ cm^{-1} 2959, 2930, 1779 ($\text{C}=\text{O}$), 1612 ($\text{C}=\text{C}$), 1513, 1460, 1389, 1354, 1248, 1177, 1033, 869, 733; δ_{H} (400 MHz, CDCl_3) 7.20 (2H, d, J 8.5 Hz, Ar $\text{C}-\text{H}$), 6.85 (2H, d, J 8.5 Hz, Ar $\text{C}-\text{H}$), 6.12 (1H, d, J 16.3 Hz, $\text{N}-\text{C}-\text{CH}=\text{CH}$), 5.82 (1H, d, J 9.5 Hz, $\text{CH}=\text{CHCH}_2$), 5.96 (1H, ddd, J 9.5, 4.3, 4.3 Hz, $\text{CH}=\text{CHCH}_2$), 5.54 (1H, d, J 16.3 Hz, $\text{N}-\text{C}-\text{CH}=\text{CH}$), 4.53 (1H, d, J 15.0 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.13 (1H, d, J 15.0 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.79 (3H, s, OCH_3), 2.08-2.05 (2H, m, CH_2), 1.79 (3H, s, $\text{C}=\text{C}-\text{CH}_3$), 1.47 (3H, s, CH_3 , lactam), 0.97 (6H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (125.8 MHz, CDCl_3) 161.5 ($\text{C}=\text{O}$), 159.5 (Ar quat.), 136.4 (Olef. quat.), 132.7 ($\text{N}-\text{C}-\text{CH}=\text{CH}$), 130.9 ($\text{N}-\text{C}-\text{CH}=\text{CH}$), 130.7 (Ar $\text{C}-\text{H}$), 130.4 ($\text{CH}=\text{CHCH}_2$), 127.2 and 127.3 (Ar quat. and olef. quat.), 125.9 ($\text{CH}=\text{CHCH}_2$), 114.5 (Ar $\text{C}-\text{H}$), 89.6 (CCl_2), 73.0 ($\text{N}-\text{C}-\text{CH}_3$), 55.1 (OCH_3), 43.6 (CH_2N), 39.5 (CH_2), 33.7 ($\text{C}[\text{CH}_3]_2$), 26.8 and 26.3 ($\text{C}[\text{CH}_3][\text{CH}_3]$), 20.8 (CH_3 , lactam), 19.8 ($\text{C}=\text{C}-\text{CH}_3$); m/z (FAB) 420 (MH)⁺, 307, 289, 154, 137, 121.

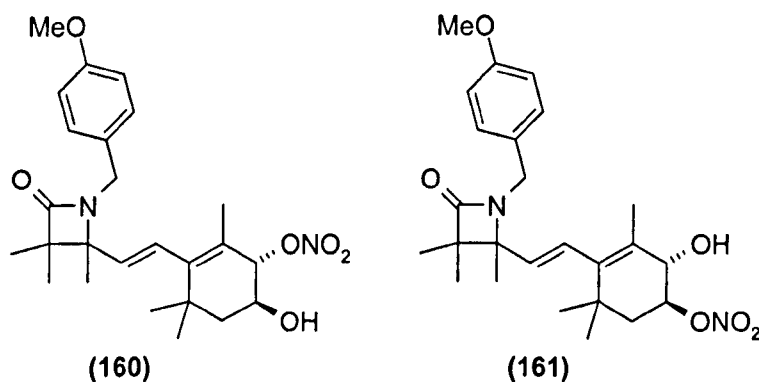
2,2-Dichloro-*N*-(4-methoxybenzyl)-*N*-[1-methylene-3-(2,3,6-trimethylphenyl)-allyl]-acetamide (158) and (3*R,4*R**) 3-chloro-1-(4-methoxybenzyl)-4-methyl-4-[2-(2,3,6-trimethylphenyl)-vinyl]-azetidin-2-one (159)**



A stirred solution of 2,2-dichloro-*N*-(4-methoxybenzyl)-*N*-[1-methyl-3-(2,6,6-trimethylcyclohex-2-enylidene)-propenyl]-acetamide (**149c**) (130 mg, 0.308 mmol), copper (I) chloride (9.1 mg, 92.3 μ mol) and TPA (26.8 mg, 92.3 μ mol) in anhydrous toluene (2.56 ml) were heated to reflux under nitrogen for 6 days. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate, then 3:1, petrol:ethyl acetate, then 1:1, petrol:ethyl acetate) to give 2,2-dichloro-*N*-(4-methoxybenzyl)-*N*-[1-methylene-3-(2,3,6-trimethylphenyl)-allyl]-acetamide (**158**) as a pale yellow oil (13.0 mg, 10%), *R_f* (5:1 petrol:ethyl acetate) 0.35; ν_{\max} (film)/cm⁻¹ 2930, 1684, 1612, 1513, 1461, 1400, 1301, 1248, 1176, 1113, 1033, 808, 663; δ_{H} (400 MHz, CDCl₃) 7.29 (2H, d, *J* 8.8 Hz, Ar C-H), 7.01 (1 H, d, *J* 7.8 Hz, Ar C-H), 6.96 (1 H, d, *J* 7.8 Hz, Ar C-H), 6.85 (2H, d, *J* 8.8 Hz, Ar C-H), 6.65 (1H, d, 16.3 Hz, N-C=CH-CH), 6.33 (1H, s, CHCl₂), 6.18 (1H, d, *J* 16.3 Hz, N-C=CH-CH), 5.54 (1H, s, C=CH_aH_b), 4.92 (1H, s, C=CH_aH_b), 3.80 (3H, s, OCH₃), 2.26 (3H, s, CH₃), 2.22 (3H, s, CH₃), 2.16 (3H, s, CH₃), CH₂N not visible; δ_{C} (125.8 MHz, CDCl₃) 164.7 (C=O), 159.8, 143.7, 135.7, 134.9, 134.7, 133.8 and 128.8 (olef. quat. and 6 x Ar quat.), 132.5, 131.5, 129.9, 129.6 and 127.9 (N-C=CH-CH and 3 x Ar C-H), 120.5 (C=CH₂), 114.3 (Ar C-H), 64.5 (CHCl₂), 55.7 (OCH₃), 49.6 (CH₂N), 21.4, 20.8 and 17.5 (3 x CH₃); *m/z* (FAB) 418 (MH)⁺, 307, 289, 154, 121; [Found: (MH)⁺

418.1333, $C_{23}H_{26}NO_2^{35}Cl_2$ requires $(MH)^+$ 418.1341], and *(3R*,4R*) 3-chloro-1-(4-methoxybenzyl)-4-methyl-4-[2-(2,3,6-trimethylphenyl)-vinyl]-azetidin-2-one (159)* as a pale yellow oil (2.0 mg, 2%), R_f (5:1 petrol:ethyl acetate) 0.24; ν_{max} (film)/ cm^{-1} 2927, 2853, 1765 (C=O), 1612, 1513, 1461, 1388, 1248, 1177, 1033; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, J 8.5 Hz, Ar C-H), 7.00 (1 H, d, J 7.8 Hz, Ar C-H), 6.95 (1 H, d, J 7.8 Hz, Ar C-H), 6.85 (2H, d, J 8.5 Hz, Ar C-H), 6.59 (1H, d, 16.6 Hz, N-C=CH-CH), 5.62 (1H, d, J 16.6 Hz, N-C=CH-CH), 4.71 (1H, s, CHCl), 4.60 (1H, d, J 15.3 Hz, CH_aH_bN), 4.12 (1H, d, J 15.3 Hz, CH_aH_bN), 3.79 (3H, s, OCH_3), 2.25 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.13 (3H, s, CH_3), 1.39 (3H, s, CH_3); δ_C (125.8 MHz, $CDCl_3$) 163.4 (C=O), 159.4, 135.6, 134.4, 134.0, 133.0 and 127.9 (6 x Ar quat.), 134.6 and 131.6 (N-C=CH-CH), 129.8, 128.9, 127.3 and 114.2 (4 x Ar C-H), 66.3 (CHCl), 64.4 (N-C-CH₃), 55.3 (OCH_3), 43.8 (CH_2N), 20.9, 20.4, 19.5 and 16.9 (4 x CH_3); m/z (FAB) 384 $(MH)^+$, 307, 289, 176, 154, 136, 121; [Found: $(MH)^+$ 384.1714, $C_{23}H_{26}NO_2^{35}Cl$ requires $(MH)^+$ 384.1730].

1:1 Mixture of (3S,4S*) 4-[2-(4-hydroxy-2,6,6-trimethyl-3-nitrooxycyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-3,3,4-trimethylazetidin-2-one (160) and 1:1 mixture of (3S*,4S*) 4-[2-(3-hydroxy-2,6,6-trimethyl-4-nitrooxycyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-3,3,4-trimethylazetidin-2-one (161)*

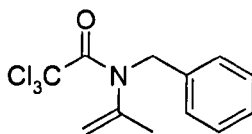


Ceric ammonium nitrate (114 mg, 0.208 mmol) was added to a stirred solution of 1-(4-methoxybenzyl)-3,3,4-trimethyl-4-[2-(2,6,6-trimethylcyclohexa-1,3-dienyl)-vinyl]-azetidin-2-one (**152**) (40.0 mg, 0.105 mmol) in acetone (1 ml) at room temperature. After 1 hour, the reaction mixture was diluted with ethyl acetate (10 ml), washed with water (5

ml), saturated sodium hydrogen carbonate solution (5 ml) and saturated brine (5 ml), dried (MgSO₄), filtered and concentrated to give a yellow residue. Purification by preparative thin layer chromatography (SiO₂, 1:1 petrol:ethyl acetate) gave a 1:1 mixture of (3*S**,4*S**) 4-[2-(4-hydroxy-2,6,6-trimethyl-3-nitrooxycyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-3,3,4-trimethyl-azetidin-2-one (**160**) (11.0 mg, 26%) as a pale yellow oil, R_f (1:1 petrol:ethyl acetate) 0.44; ν_{\max} (film)/cm⁻¹ 3380 (br, OH), 2966, 2932, 1740 (C=O), 1639 (ONO₂), 1514, 1464, 1398, 1282, 1246, 1178, 1112, 1034, 983, 956, 920, 857, 733; δ_{H} (400 MHz, CDCl₃) 7.21 (2H, d, J 8.5 Hz, Ar C-H, isomer A or B), 7.20 (2H, d, J 8.5 Hz, Ar C-H, isomer A or B), 6.84 (2H, d, J 8.5 Hz, Ar C-H, isomer A or B), 6.83 (2H, d, J 8.5 Hz, Ar C-H, isomer A or B), 5.81 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.80 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.65 (2H, br, CHONO₂, isomers A and B), 5.55 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.50 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.27 (1H, m, CHOH, isomer A or B), 5.23 (1H, m, CHOH, isomer A or B), 4.34 (1H, d, J 15.1 Hz, CH_aH_bN, isomer A or B), 4.32 (1H, d, J 15.1 Hz, CH_aH_bN, isomer A or B), 4.21 (1H, d, J 15.1 Hz, CH_aH_bN, isomer A or B), 4.18 (1H, d, J 15.1 Hz, CH_aH_bN, isomer A or B), 3.79 (3H, s, OCH₃, isomer A or B), 3.78 (3H, s, OCH₃, isomer A or B), 1.95-1.86 (2H, m, CHOHCH_aH_b, isomers A and B), 1.73 (6H, s, CH₃, isomers A and B), 1.72 (6H, s, CH₃, isomers A and B), 1.70-1.63 (2H, m, CHOHCH_aH_b, isomers A and B), 1.28 (3H, s, CH₃, isomer A or B), 1.25 (6H, s, CH₃, isomers A and B), 1.20 (3H, s, CH₃, isomer A or B), 1.19 (3H, s, CH₃, isomer A or B), 1.07 (3H, s, CH₃, isomer A or B), 1.02 (3H, s, CH₃, isomer A or B), 1.01 (3H, s, CH₃, isomer A or B); δ_{C} (125.8 MHz, CDCl₃) 173.9 and 173.8 (C=O, isomers A and B), 159.1 (Ar quat., isomers A and B), 147.5 and 147.4 (olef. quat., isomers A and B), 138.5 and 138.3 (N-C-CH=CH, isomers A and B), 129.5 (Ar C-H, isomers A and B), 129.4 (Ar quat., isomers A and B), 126.8 (N-C-CH=CH, isomers A and B), 120.2 (olef. quat., isomers A and B), 114.2 (Ar C-H, isomers A and B), 78.7 and 78.6 (CHONO₂, isomers A and B), 76.5 (CHOH, isomers A and B), 66.0 (N-C-CH₃, isomers A and B), 57.9 (C[CH₃]₂ lactam, isomers A and B), 55.2 (OCH₃, isomers A and B), 42.6 (CH₂N, isomers A and B), 37.1 (CH₂C[CH₃]₂, isomers A and B), 35.7 and 35.6 (CH₂CHOH, isomers A and B), 29.8, 29.7, 27.2, 20.7, 19.4, 19.3, 19.2 and 18.6 (6 x CH₃, some coincident signals, isomers A and B); m/z (FAB) 459 (MH)⁺, 457 (M-H)⁺, 396, 307, 154, 121; [Found: (M-H)⁺, 457.2353, C₂₅H₃₄N₂O₆ requires (M-H)⁺, 457.2339], and a 1:1 mixture of

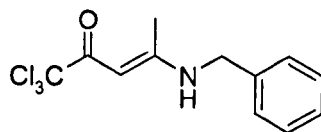
(3*S**,4*S**) 4-[2-(3-hydroxy-2,6,6-trimethyl-4-nitrooxycyclohex-1-enyl)-vinyl]-1-(4-methoxybenzyl)-3,3,4-trimethylazetid-2-one (**161**) (4.0 mg, 9%) as a pale yellow oil, R_f (1:1 petrol:ethyl acetate) 0.33; ν_{\max} (film)/ cm^{-1} 3369 (br, OH), 2965, 2932, 1725 (C=O), 1624 (ONO₂), 1514, 1464, 1404, 1301, 1278, 1247, 1178, 1035, 919, 868, 732; δ_H (400 MHz, CDCl₃) 7.20 (4H, d, J 8.5 Hz, Ar C-H, isomers A and B), 6.84 (4H, d, J 8.5 Hz, Ar C-H, isomers A and B), 5.84 (2H, d, J 16.3 Hz, N-C-CH=CH, isomers A and B), 5.51 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.48 (1H, d, J 16.3 Hz, N-C-CH=CH, isomer A or B), 5.13 (1H, m, CHONO₂, isomer A or B), 5.09 (1H, m, CHONO₂, isomer A or B), 4.39 (1H, d, J 15.3 Hz, CH_aH_bN, isomer A or B), 4.38 (1H, d, J 15.3 Hz, CH_aH_bN, isomer A or B), 4.23 (2H, br, CHOH, isomers A and B), 4.14 (1H, d, J 15.3 Hz, CH_aH_bN, isomer A or B), 4.12 (1H, d, J 15.3 Hz, CH_aH_bN, isomer A or B), 3.79 (6H, s, OCH₃, isomers A and B), 2.05-1.95 (2H, m, CH[ONO₂]CH_aH_b, isomers A and B), 1.78 (3H, s, CH₃, isomer A or B), 1.77 (3H, s, CH₃, isomer A or B), 1.70-1.55 (2H, m, CH[ONO₂]CH_aH_b, isomers A and B), 1.24 (12H, s, CH₃, isomers A and B), 1.19 (6H, s, CH₃, isomers A and B), 1.07 (3H, s, CH₃, isomer A or B), 1.02 (9H, s, CH₃, isomers A and B); δ_C (125.8 MHz, CDCl₃) 174.0 and 173.9 (C=O, isomers A and B), 159.0 (Ar quat., isomers A and B), 141.9 and 141.8 (olef. quat., isomers A and B), 137.3 and 137.2 (N-C-CH=CH, isomers A and B), 129.5 (Ar C-H, isomers A and B), 128.0 (N-C-CH=CH, isomers A and B), 127.8 (olef. quat., isomers A and B), 126.8 (Ar quat., isomers A and B), 114.1 (Ar C-H, isomers A and B), 79.9 (CHONO₂, isomers A and B), 68.5 and 68.4 (CHOH, isomers A and B), 66.0 (N-C-CH₃, isomers A and B), 57.8 and 57.7 (C[CH₃]₂ lactam, isomers A and B), 55.3 (OCH₃, isomers A and B), 42.6 (CH₂N, isomers A and B), 37.0 (CH₂C[CH₃]₂, isomers A and B), 35.3 (CH₂CH[ONO₂], isomers A and B), 29.8, 29.6, 27.2, 27.1, 20.5, 19.8, 19.5, 19.4 and 18.8 (6 x CH₃, some coincident signals, isomers A and B); m/z (FAB) 459 (MH)⁺, 307, 289, 154, 137; [Found: (MH)⁺, 459.2512, C₂₅H₃₄N₂O₆ requires (MH)⁺, 459.2495]. Data for (**160**) and (**161**) may be exchanged since regiochemistry could not be assigned conclusively.

N-Benzyl-2,2,2-trichloro-*N*-isopropenylacetamide (**167**)



Benzylamine (2.81 ml, 20.0 mmol) was added dropwise to a solution of mesityl oxide (2.29 ml, 20.0 mmol) in anhydrous DCM (20 ml) over 3Å molecular sieves under nitrogen. After 16 hours, the reaction mixture was filtered through a pad of MgSO₄, which was washed well with DCM. The combined filtrate was concentrated *in vacuo* to give a yellow oil (3.91 g), which was found to be a complex mixture by ¹H NMR. A portion of the yellow oil (749 mg) was dissolved in anhydrous DCM (20 ml), cooled to 0°C, and treated with trichloroacetyl chloride (446 μl, 4.00 mmol) followed by *N,N*-diethylaniline (636 μl, 4.00 mmol) under nitrogen. After 2 hours, the reaction mixture was washed with 1M HCl (10 ml) and brine (10 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a green residue. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *N*-benzyl-2,2,2-trichloro-*N*-isopropenylacetamide (**167**) as a pale yellow oil (250 mg, 22% from mesityl oxide), R_f (9:1 petrol:ethyl acetate) 0.33; ν_{max} (film)/cm⁻¹ 3032, 2928, 1673 (C=O), 1496, 1455, 1388, 1259, 1221, 1103, 911, 834, 811, 731, 898, 668, 614; δ_H (300 MHz, CDCl₃) 7.30-7.18 (5H, m, Ar C-H), 5.02 (1H, d, J 1.1 Hz, C=CH_aH_b), 4.86 (1H, br, C=CH_aH_b), 4.85-4.55 (2H, br, CH₂N), 1.92 (3H, br, CH₃); δ_C (75.5 MHz, CDCl₃) 160.4 (C=O), 142.0 (N-C=CH₂), 135.7 (Ar quat.), 128.5, 128.3 and 127.7 (Ar C-H), 118.0 (C=CH₂), 93.0 (CCl₃), 53.0 (CH₂N), 20.7 (CH₃); m/z (EI) 291 (M)⁺, 256, 220, 174, 146, 130, 91, 77, 65; [Found: (M)⁺, 291.0002, C₁₂H₁₂NO³⁵Cl₃ requires (M)⁺, 290.9984].

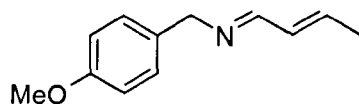
N-Benzylamino-1,1,1-trichloropent-3-en-2-one (168)



A stirred solution of *N*-benzyl-2,2,2-trichloro-*N*-isopropenylacetamide (**167**) (106 mg, 0.362 mmol), copper (I) chloride (10.8 mg, 0.109 mmol) and TPA (31.6 mg, 0.109 mmol) in anhydrous toluene (3.02 ml) were heated to reflux under nitrogen for 5 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The brown residue was purified by preparative thin layer chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *N*-benzylamino-1,1,1-trichloropent-3-en-2-one (**168**) as a pale yellow oil (6.0 mg, 6%), *R_f* (5:1 petrol:ethyl acetate) 0.29; ν_{\max} (film)/cm⁻¹ 3031, 2929, 1576, 1515, 1454, 1378, 1320, 1157, 1100, 1024, 815, 738, 698; δ_{H} (400 MHz, CDCl₃) 10.9 (1H, br, NH), 7.40-7.25 (5H, m, Ar C-H), 5.75 (1H, s, C=CH[CO]), 4.55 (2H, d, *J* 6.3 Hz, CH₂N), 2.14 (3H, s, CH₃); δ_{C} (125.8 MHz, CDCl₃) 180.6 (C=O), 168.9 (NH-C=CH), 136.1 (Ar quat.), 129.1, 128.2 and 127.2 (Ar C-H), 93.0 (CCl₃), 87.0 (CH=C-NH), 47.7 (CH₂N), 20.0 (CH₃); *m/z* (EI) 291 (M)⁺, 257, 208, 174, 144, 104, 91, 65; [Found: (M)⁺, 290.9984, C₁₂H₁₂NO³⁵Cl₃ requires (M)⁺, 290.9984].

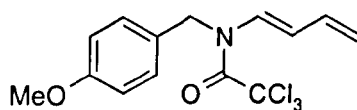
6.3 Experimental for Chapter 3

But-2-enylidene-(4-methoxybenzyl)-amine (175)



4-Methoxybenzylamine (5.23 ml, 40.0 mmol) was added dropwise to stirred *trans*-crotonaldehyde (3.31 ml, 40.0 mmol) at 0°C. After 15 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give *but-2-enylidene-(4-methoxybenzyl)-amine (175)* as a pale yellow oil (7.19 g, 95%, >80% purity) which was used without further purification, ν_{\max} (film)/cm⁻¹ 2998, 2909, 2832, 1655 (C=N), 1610, 1585, 1509, 1442, 1371, 1336, 1300, 1241, 1172, 1107, 1033, 967, 928, 815, 752; δ_{H} (400 MHz, CDCl₃) 7.89 (1H, d, J 8.5 Hz, $\underline{\text{C}}\underline{\text{H}}=\text{N}$), 7.17 (2H, d, J 8.6 Hz, Ar C- $\underline{\text{H}}$), 6.84 (2H, d, J 8.6 Hz, Ar C- $\underline{\text{H}}$), 6.31-6.13 (2H, m, $\underline{\text{C}}\underline{\text{H}}=\underline{\text{C}}\underline{\text{H}}\text{CH}_3$), 4.53 (2H, s, $\underline{\text{C}}\underline{\text{H}}_2\text{N}$), 3.74 (3H, s, OCH_3), 1.85 (3H, d, J 6.0 Hz, $\text{CH}=\text{CH}\underline{\text{C}}\underline{\text{H}}_3$); δ_{C} (100.6 MHz, CDCl₃) 163.1 ($\underline{\text{C}}\underline{\text{H}}=\text{N}$), 158.7 (Ar quat.), 140.7 (N=CH-CH= $\underline{\text{C}}\underline{\text{H}}$), 132.2 (N=CH- $\underline{\text{C}}\underline{\text{H}}=\text{CH}$), 131.6 (Ar quat.), 129.2 (Ar C- $\underline{\text{H}}$), 113.9 (Ar C- $\underline{\text{H}}$), 64.4 ($\underline{\text{C}}\underline{\text{H}}_2\text{N}$), 55.2 (OCH_3), 18.4 ($\text{CH}=\text{CH}\underline{\text{C}}\underline{\text{H}}_3$); *m/z* (EI) 189 (M)⁺, 174, 136, 121, 106, 91, 78; [Found: (M)⁺, 189.1138, C₁₂H₁₅NO requires (M)⁺, 189.1154].

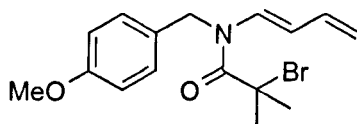
N-Buta-1,3-dienyl-2,2,2-trichloro-N-(4-methoxybenzyl)-acetamide (176a)



Trichloroacetyl chloride (446 μl , 4.00 mmol) followed by triethylamine (558 μl , 4.00 mmol), was added dropwise to a stirred solution of *but-2-enylidene-(4-methoxybenzyl)-amine (175)* (757 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100

ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give *N*-buta-1,3-dienyl-2,2,2-trichloro-*N*-(4-methoxybenzyl)-acetamide (**176a**) as a pale yellow oil (209 mg, 16%), R_f (9:1 petrol:ethyl acetate) 0.31; ν_{\max} (film)/cm⁻¹ 2935, 2837, 1684 (C=O), 1638, 1613, 1513, 1431, 1368, 1298, 1247, 1202, 1177, 1034, 997, 922, 811, 666; δ_{H} (400 MHz, CDCl₃) 7.40 (1H, d, J 13.6 Hz, N-CH=CH), 7.13 (2H, d, J 8.8 Hz, Ar C-H), 6.86 (2H, d, J 8.8 Hz, Ar C-H), 6.27 (1H, ddd, J 16.8, 10.7, 10.3 Hz, CH-CH=CH₂), 5.83 (1H, dd, J 13.6, 10.7 Hz, N-CH-CH=CH), 5.12 (1H, d, J 16.8 Hz, CH=CH_aH_b), 5.05 (1H, d, J 10.3 Hz, CH=CH_aH_b), 4.97 (2H, br s, CH₂N), 3.76 (3H, s, OCH₃); δ_{C} (100.6 MHz, CDCl₃) 159.1 and 159.0 (C=O and Ar quat.), 134.2 (CH-CH=CH₂), 130.9 (N-CH=CH), 127.8 (Ar C-H), 127.5 (Ar quat.), 117.1 (CH=CH₂), 116.9 (N-CH-CH=CH), 114.3 (Ar C-H), 92.5 (CCl₃), 55.3 (OCH₃), 50.6 (CH₂N); m/z (FAB) 307, 154, 136, 121.

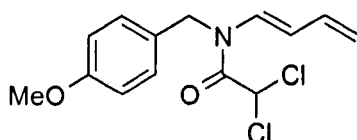
2-Bromo-*N*-buta-1,3-dienyl-*N*-(4-methoxybenzyl)-2-methyl-propionamide (176b)



2-Bromoisobutyryl bromide (494 μ l, 4.00 mmol) followed by triethylamine (558 μ l, 4.00 mmol) was added dropwise to a stirred solution of but-2-enylidene-(4-methoxybenzyl)-amine (**175**) (757 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give 2-bromo-*N*-buta-1,3-dienyl-*N*-(4-methoxybenzyl)-2-methyl-propionamide (**176b**) as a pale yellow oil (164 mg, 12%), R_f (9:1 petrol:ethyl acetate) 0.27; ν_{\max} (film)/cm⁻¹ 2932, 2836, 1660 (C=O), 1630, 1512, 1460, 1426, 1391, 1362, 1311, 1246, 1175, 1150, 1109, 1034, 998, 817, 647; δ_{H} (400 MHz, CDCl₃) 7.68 (1H, d, J 13.8 Hz, N-CH=CH), 7.09 (2H, d, J

8.5 Hz, Ar C-H), 6.84 (2H, d, J 8.5 Hz, Ar C-H), 6.31 (1H, ddd, J 17.0, 10.4, 10.4 Hz, CH-CH=CH₂), 5.72 (1H, dd, J 13.8, 10.4 Hz, N-CH-CH=CH), 5.06 (1H, d, J 17.0 Hz, CH=CH_aH_b), 4.97 (1H, d, J 10.4 Hz, CH=CH_aH_b), 4.91 (2H, br s, CH₂N), 3.76 (3H, s, OCH₃), 2.03 (6H, s, CBr[CH₃]₂); δ_C (100.6 MHz, CDCl₃) 169.1 (C=O), 158.7 (Ar quat.), 134.9 (CH-CH=CH₂), 132.8 (N-CH=CH), 128.7 (Ar quat.), 127.6 (Ar C-H), 115.2 (CH=CH₂), 114.2 and 114.1 (N-CH-CH=CH and Ar C-H), 56.7 (CBr[CH₃]₂), 55.2 (OCH₃), 48.9 (CH₂N), 32.6 (CBr[CH₃]₂); m/z (FAB) 338 (MH)⁺, 307, 289, 206, 154, 137, 121; [Found: (MH)⁺, 338.0759, C₁₆H₂₀NO₂⁷⁹Br requires (MH)⁺, 338.0756].

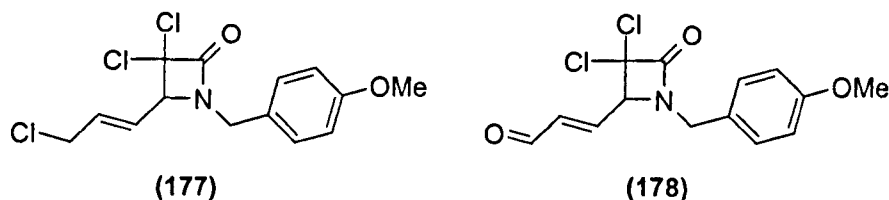
***N*-Buta-1,3-dienyl-2,2-dichloro-*N*-(4-methoxybenzyl)-acetamide (176c)**



Dichloroacetyl chloride (770 μl, 8.00 mmol) followed triethylamine (1.12 ml, 8.00 mmol) by was added dropwise to a stirred solution of but-2-enylidene-(4-methoxybenzyl)-amine (175) (1.51 g, 8.00 mmol) in anhydrous DCM (40 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give *N*-buta-1,3-dienyl-2,2-dichloro-*N*-(4-methoxybenzyl)-acetamide (176c) as a yellow oil (248 mg, 10%), R_f (9:1 petrol:ethyl acetate) 0.38; ν_{max} (film)/cm⁻¹ 3005, 2934, 2836, 1680 (C=O), 1639, 1612, 1513, 1431, 1386, 1356, 1293, 1247, 1176, 1114, 1033, 998, 918, 808, 684; δ_H (400 MHz, CDCl₃) 7.14 (2H, d, J 8.3 Hz, Ar C-H), 6.91 (1H, d, J 13.6 Hz, N-CH=CH), 6.86 (2H, d, J 8.3 Hz, Ar C-H), 6.42 (1H, s, CHCl₂), 6.28 (1H, ddd, J 17.0, 10.8, 10.0 Hz, CH=CH₂), 5.91 (1H, dd, J 13.6, 10.8 Hz, N-CH=CH), 5.16 (1H, d, J 17.0 Hz, CH=CH_aH_b), 5.09 (1H, d, J 10.0 Hz, CH=CH_aH_b), 4.84 (2H, s, CH₂N), 3.78 (3H, s, OCH₃); δ_C (100.6 MHz, CDCl₃) 162.5 (C=O), 159.0 (Ar quat.), 133.7 (CH=CH₂), 128.9 and 128.3 (N-CH=CH and Ar C-H), 127.7 (Ar quat.), 119.2 (N-CH=CH), 117.6

(CH=C \underline{H}_2), 114.2 (Ar C-H), 65.2 (C $\underline{H}Cl_2$), 55.3 (O $\underline{C}H_3$), 48.5 (C \underline{H}_2N); m/z (FAB) 248, 212, 176, 154, 121.

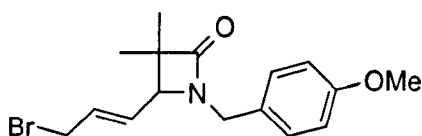
3,3-Dichloro-4-(3-chloropropenyl)-1-(4-methoxybenzyl)-azetidin-2-one (177) and 3-[3,3-dichloro-1-(4-methoxybenzyl)-4-oxoazetidin-2-yl]-propenal (178)



A stirred solution of *N*-buta-1,3-dienyl-2,2,2-trichloro-*N*-(4-methoxybenzyl)-acetamide (176a) (110 mg, 0.329 mmol), copper (I) chloride (9.8 mg, 98.6 μ mol) and TPA (28.6 mg, 98.6 μ mol) in anhydrous toluene (2.74 ml) was heated to reflux under nitrogen for 18 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give 3,3-dichloro-4-(3-chloropropenyl)-1-(4-methoxybenzyl)-azetidin-2-one (177) as a pale yellow gum (25.0 mg, 23%), R_f (3:1 petrol:ethyl acetate) 0.33; ν_{\max} (film)/cm⁻¹ 3005, 2932, 2838, 1784 (C=O), 1611, 1513, 1439, 1393, 1360, 1304, 1247, 1177, 1144, 1032, 971, 852, 678; δ_H (400 MHz, CDCl₃) 7.14 (2H, d, J 8.5 Hz, Ar C-H), 6.88 (2H, d, J 8.5 Hz, Ar C-H), 5.95 (1H, dt, J 15.2, 6.5 Hz, ClCH₂CH=CH), 5.62 (1H, ddt, J 15.2, 8.8, 1.2 Hz, ClCH₂CH=CH), 4.62 (1H, d, J 14.8 Hz, CH_aH_bN), 4.23 (1H, d, J 8.8 Hz, CCl₂CHN), 4.06 (1H, d, J 14.8 Hz, CH_aH_bN), 4.08-4.05 (2H, m, CH₂Cl), 3.81 (3H, s, OCH₃); δ_C (100.6 MHz, CDCl₃) 160.8 and 159.7 (C=O and Ar quat.), 135.8 (ClCH₂CH=CH), 130.0 (Ar C-H), 126.7 (ClCH₂CH=CH), 125.5 (Ar quat.), 114.5 (Ar C-H), 83.5 (CCl₂), 70.5 (CCl₂CHN), 55.3 (OCH₃), 44.7 (CH₂Cl), 43.0 (CH₂N); m/z (FAB) 334 (MH)⁺, 307, 289, 163, 154, 137; [Found: (M-H)⁺, 332.0004, C₁₄H₁₄NO₂³⁵Cl₃ requires (M-H)⁺, 332.0012], and 3-[3,3-dichloro-1-(4-methoxybenzyl)-4-oxoazetidin-2-yl]-propenal (178) as a pale yellow gum (12.0 mg, 12%), R_f (3:1 petrol:ethyl acetate) 0.17; ν_{\max} (film)/cm⁻¹ 2934, 2838, 1788 (C=O lactam), 1735, 1694 (C=O aldehyde), 1611,

1514, 1394, 1351, 1249, 1179, 1128, 1031, 978, 867; δ_{H} (400 MHz, CDCl_3) 9.55 (1H, d, J 7.4 Hz, HCO), 7.12 (2H, d, J 8.8 Hz, Ar C-H), 6.88 (2H, d, J 8.8 Hz, Ar C-H), 6.47 (1H, dd, J 15.8, 8.3 Hz, HCO-CH=CH), 6.24 (1H, dd, J 15.8, 7.4 Hz, HCO-CH=CH), 4.64 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.43 (1H, d, J 8.3 Hz, CCl_2CHN), 4.16 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.81 (3H, s, OCH_3); δ_{C} (100.6 MHz, CDCl_3) 191.5 (CHO), 160.3 and 160.0 (CON and Ar quat.), 145.6 (HCOCH=CH), 137.6 (HCOCH=CH), 130.0 (Ar C-H), 125.0 (Ar quat.), 114.6 (Ar C-H), 83.4 (CCl_2), 69.5 (CCl_2CHN), 55.4 (OCH_3), 45.3 (CH_2N); m/z (FAB) 314 (MH^+), 313 (M^+), 307, 289, 154, 136, 121; [Found: (M^+), 313.0269, $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{Cl}_2$ requires (M^+), 313.0272].

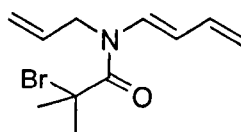
4-(3-Bromopropenyl)-1-(4-methoxybenzyl)-3,3-dimethylazetidin-2-one (182)



A stirred solution of 2-bromo-*N*-buta-1,3-dienyl-*N*-(4-methoxybenzyl)-2-methylpropionamide (**176b**) (136 mg, 0.402 mmol), copper (I) bromide (17.3 mg, 0.121 mmol) and TPA (35.0 mg, 0.121 mmol) in anhydrous toluene (3.35 ml) was heated to reflux under nitrogen for 1 hour. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 1:1 petrol:ethyl acetate) to give 4-(3-bromopropenyl)-1-(4-methoxybenzyl)-3,3-dimethylazetidin-2-one (**182**) as a colourless oil (82.0 mg, 60%), R_f (1:1 petrol:ethyl acetate) 0.49; ν_{max} (film)/ cm^{-1} 2961, 2927, 1740 (C=O), 1612, 1585, 1512, 1461, 1397, 1360, 1302, 1243, 1205, 1175, 1109, 1032, 970, 827, 627; δ_{H} (300 MHz, CDCl_3) 7.15 (2H, d, J 8.6 Hz, Ar C-H), 6.86 (2H, d, J 8.6 Hz, Ar C-H), 5.85 (1H, dt, J 15.3, 7.4 Hz, $\text{BrCH}_2\text{CH=CH}$), 5.59 (1H, dd, J 15.3, 8.4 Hz, $\text{BrCH}_2\text{CH=CH}$), 4.56 (1H, d, J 14.7 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.94 (1H, d, J 14.7 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.92 (2H, d, J 7.4 Hz, $\text{BrCH}_2\text{CH=CH}$), 3.80 (3H, s, OCH_3), 3.54 (1H, d, J 8.4 Hz, CMe_2CHN), 1.25 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$), 1.11 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_{C} (75.5 MHz, CDCl_3) 173.7 (C=O), 159.5 (Ar quat.), 132.3

(BrCH₂CH=CH), 131.3 (BrCH₂CH=CH), 130.2 (Ar C-H), 128.3 (Ar quat.), 114.5 (Ar C-H), 63.8 (CMe₂CHN), 55.8 (CMe₂), 55.7 (OCH₃), 44.2 (CH₂N), 31.6 (CH₂Br), 22.3 (C[CH₃][CH₃]), 18.1 (C[CH₃][CH₃]); m/z (FAB) 338 (MH)⁺, 258, 154, 121; [Found: (MH)⁺, 338.0749, C₁₆H₂₀NO₂⁷⁹Br requires (MH)⁺, 338.0756].

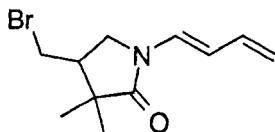
N-Allyl-2-bromo-*N*-buta-1,3-dienyl-2-methyl-propionamide (**185**)



Allylamine (3.00 ml, 40.0 mmol) was added dropwise to stirred *trans*-crotonaldehyde (3.31 ml, 40.0 mmol) at 0°C. After 30 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude yellow oil (3.72 g) which contained less than 40% *allyl-but-2-enylidene-amine* by ¹H NMR. 2-Bromoisobutyryl bromide (1.98 ml, 16.0 mmol) followed by triethylamine (2.23 ml, 16.0 mmol) was added dropwise to a stirred solution of this crude oil (1.75 g, 47% of total yield of crude) in anhydrous DCM (40 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give *N*-allyl-2-bromo-*N*-buta-1,3-dienyl-2-methyl-propionamide (**185**) as a yellow oil (198 mg, 4% from crotonaldehyde), R_f (9:1 petrol:ethyl acetate) 0.45; ν_{max} (film)/cm⁻¹ 3086, 2980, 2932, 1662 (C=O), 1631, 1603, 1459, 1426, 1391, 1362, 1310, 1257, 1220, 1153, 1109, 996, 928, 891, 780, 649; δ_H (400 MHz, CDCl₃) 7.63 (1H, d, J 13.8 Hz, N-CH=CH), 6.34 (1 H, ddd, J 16.8, 10.6, 10.6 Hz, CH₂=CH-CH=CH), 5.86-5.73 (2H, m, NCH₂CH=CH₂ and CH₂=CH-CH=CHN), 5.19 (1H, d, J 10.8 Hz, NCH₂CH=CH_aH_b), 5.15 (1H, d, J 16.8 Hz, CH_aH_b=CH-CH=CH), 5.12 (1H, d, J 17.1 Hz, NCH₂CH=CH_aH_b), 5.02 (1H, d, J 10.6 Hz, CH_aH_b=CH-CH=CH), 4.38 (2H, br, CH₂N), 2.01 (6H, s, CBr[CH₃]₂); δ_C (100.6 MHz, CDCl₃) 168.7 (C=O), 134.9 (CH₂=CH-CH=CH), 132.5 (CH₂=CH-CH=CHN), 132.0 (NCH₂CH=CH₂), 116.2

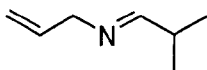
(NCH₂CH=CH₂), 115.1 (CH₂=CH-CH=CHN), 113.7 (CH₂=CH-CH=CHN), 56.6 (CBr[CH₃]₂), 48.2 (CH₂N), 32.6 (CBr[CH₃]₂); m/z (FAB) 258 (MH)⁺, 257 (M)⁺, 232, 194, 180, 154, 136, 121; [Found: (M)⁺ 257.0431, C₁₁H₁₆NO⁷⁹Br requires (M)⁺ 257.0415].

4-Bromomethyl-1-buta-1,3-dienyl-3,3-dimethylpyrrolidin-2-one (187)



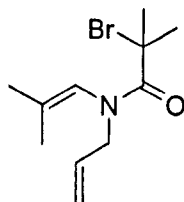
N-Allyl-2-bromo-*N*-buta-1,3-dienyl-2-methyl-propionamide (**185**) (75.0 mg, 0.291 mmol), copper (I) bromide (12.5 mg, 87.2 μmol) and TPA (25.3 mg, 87.2 μmol) in anhydrous acetonitrile (2.42 ml) were stirred at room temperature under nitrogen for 30 minutes. The reaction mixture was filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1 petrol:ethyl acetate) to give *4-bromomethyl-1-buta-1,3-dienyl-3,3-dimethylpyrrolidin-2-one* (**187**) as a white solid (68.4 mg, 91%), R_f(9:1 petrol:ethyl acetate) 0.22; m.pt. 77.0-78.0°C; ν_{max} (film)/cm⁻¹ 3084, 3032, 2965, 2925, 2868, 1700 (C=O), 1641, 1604, 1480, 1424, 1392, 1378, 1360, 1328, 1278, 1234, 1151, 1038, 996, 935, 888, 746, 680, 656; δ_H (400 MHz, CDCl₃) 7.07 (1H, d, J 14.3 Hz, CH₂=CH-CH=CHN), 6.35 (1H, ddd, J 16.8, 10.6, 10.6 Hz, CH₂=CH-CH=CHN), 5.71 (1H, dd, J 14.3, 10.6 Hz, CH₂=CH-CH=CHN), 5.16 (1H, d, J 16.8 Hz, CH_aH_b=CH), 5.01 (1H, d, J 10.6 Hz, CH_aH_b=CH), 3.77 (1H, dd, J 10.5, 7.8 Hz, NCH_aH_b), 3.55 (1H, dd, J 10.4, 4.8 Hz, CH_aH_bBr), 3.34 (1H, dd, J 10.4, 10.4 Hz, CH_aH_bBr), 3.20 (1H, dd, J 10.5, 8.5 Hz, NCH_aH_b), 2.53 (1H, dddd, J 10.4, 8.5, 7.8, 4.8 Hz, CHCH₂Br), 1.26 (3H, s, C[CH₃][CH₃]), 1.04 (3H, s, C[CH₃][CH₃]); δ_C (100.6 MHz, CDCl₃) 176.8 (C=O), 134.7 (CH₂=CH-CH=CHN), 126.4 (CH₂=CH-CH=CHN), 115.1 (CH₂=CH-CH=CHN), 113.3 (CH₂=CH-CH=CHN), 47.6 (CH₂N), 45.6 (CHCH₂Br), 44.6 (C[CH₃][CH₃]), 31.2 (CH₂Br), 24.2 (C[CH₃][CH₃]), 18.3 (C[CH₃][CH₃]); m/z (FAB) 258 (MH)⁺, 257 (M)⁺, 154, 136; [Found: (M)⁺ 257.0407, C₁₁H₁₆NO⁷⁹Br requires (M)⁺ 257.0415].

Allyl-isobutylidene-amine (189)



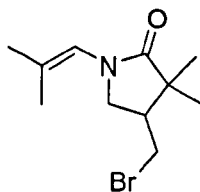
Allylamine (1.50 ml, 20.0 mmol) was added dropwise to stirred *iso*-butyraldehyde (1.82 ml, 20.0 mmol) at 0°C. After 15 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give *allyl-isobutylidene-amine (189)* as a pale yellow oil (2.07 g, 93%, >95% purity) which was used without further purification, ν_{\max} (film)/cm⁻¹ 2964, 2931, 2872, 2821, 1671 (C=N), 1642, 1464, 1438, 1365, 1316, 1289, 1104, 994, 916; δ_{H} (400 MHz, CDCl₃) 7.55 (1H, dt, J 4.8, 1.8 Hz, N=CH), 5.97 (1H, ddt, J 17.0, 10.3, 5.8 Hz, CH=CH₂), 5.14 (1H, dq, J 17.0, 1.8 Hz, CH=CH_aH_b), 5.09 (1H, dq, J 10.3, 1.8 Hz, CH=CH_aH_b), 3.99 (2H, ddd, J 5.8, 1.8, 1.8 Hz, CH₂N), 2.46 (1H, ds, J 4.8, 6.8 Hz, CH[CH₃]₂), 1.09 (6H, d, J 6.8 Hz, CH[CH₃]₂); δ_{C} (100.6 MHz, CDCl₃) 170.9 (CH=N), 136.1 (CH=CH₂), 115.5 (CH=CH₂), 63.2 (CH₂N), 34.1 (CH[CH₃]₂), 19.2 (CH[CH₃]₂); *m/z* (EI) 112 (MH)⁺, 111 (M)⁺, 110 (M-H)⁺, 96, 86, 83, 68, 56; [Found: (M-H)⁺ 110.0961, C₇H₁₃N requires (M-H)⁺ 110.0970].

N-Allyl-2-bromo-2-methyl-*N*-(2-methylpropenyl)-propionamide (**190**)



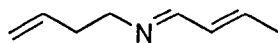
2-Bromoisobutyryl bromide (667 μ l, 5.40 mmol) followed by triethylamine (752 μ l, 5.40 mmol) was added dropwise to a stirred solution of allyl-isobutylidene-amine (**189**) (600 mg, 5.40 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 2 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give *N*-allyl-2-bromo-2-methyl-*N*-(2-methylpropenyl)-propionamide (**190**) as a pale yellow oil (1.05 g, 75%), *R*_f (9:1 petrol:ethyl acetate) 0.23; ν_{\max} (film)/cm⁻¹ 3079, 2974, 2929, 1637, 1463, 1389, 1365, 1342, 1276, 1180, 1107, 1053, 991, 918, 829, 778, 751, 635; δ_{H} (400 MHz, CDCl₃) 6.40 (1H, br s, N-CH=C), 5.83 (1H, ddt, *J* 17.3, 10.3, 5.6 Hz, CH=CH₂), 5.16 (1H, dq, *J* 17.3, 1.8 Hz, CH=CH_aH_b), 5.12 (1H, dq, *J* 10.3, 1.8 Hz, CH=CH_aH_b), 4.06 (2H, br d, *J* 5.6 Hz, CH₂N), 1.93 (6H, s, BrC[CH₃]₂), 1.76 (3H, d, *J* 1.5 Hz, CH=C[CH₃][CH₃]), 1.64 (3H, d, *J* 1.5 Hz, CH=C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 170.3 (C=O), 134.5 (CH=C[CH₃]₂), 132.6 (CH=CH₂), 125.8 (N-CH=C), 116.5 (CH=CH₂), 58.2 (BrC[CH₃]₂), 54.1 (CH₂N), 32.0 (BrC[CH₃]₂), 21.7 and 18.6 (CH=C[CH₃]₂); *m/z* (FAB) 262 (MH)⁺, 260 (MH)⁺, 180, 154, 136; [Found: (MH)⁺, 260.0636, C₁₁H₁₈NO⁷⁹Br requires (MH)⁺, 260.0650]; [Found: C, 50.43; H, 6.96; N, 5.25. C₁₁H₁₈NOBr requires C, 50.78; H, 6.97; N, 5.38].

4-Bromomethyl-3,3-dimethyl-1-(2-methylpropenyl)-pyrrolidin-2-one (191)



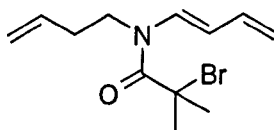
N-Allyl-2-bromo-2-methyl-*N*-(2-methylpropenyl)-propionamide (**190**) (400 mg, 1.54 mmol), copper (I) bromide (66.2 mg, 0.461 mmol) and TPA (134 mg, 0.461 mmol) in anhydrous toluene (12.8 ml) were heated to reflux under nitrogen for 15 minutes. The reaction mixture was filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give 4-bromomethyl-3,3-dimethyl-1-(2-methylpropenyl)-pyrrolidin-2-one (**191**) as a colourless oil (378 mg, 95%), *R*_f (3:1 petrol:ethyl acetate) 0.26; ν_{\max} (film)/cm⁻¹ 2967, 2929, 2871, 1697, 1408, 1361, 1279, 1239, 1165; δ_{H} (400 MHz, CDCl₃) 5.89 (1H, qq, *J* 1.5, 1.5 Hz, N-CH=C), 3.71 (1H, dd, *J* 10.0, 7.6 Hz, CH₂H_bN), 3.54 (1H, dd, *J* 10.0, 4.5 Hz, CH_aH_bBr), 3.34 (1H, dd, *J* 10.8, 10.0 Hz, CH_aH_bBr), 3.29 (1H, dd, *J* 10.0, 8.5 Hz, CH₂H_bN), 2.50 (1H, dddd, *J* 10.8, 8.5, 7.6, 4.5 Hz, CHCH₂Br), 1.75 (3H, d, *J* 1.2 Hz, CH=C[CH₃][CH₃]), 1.68 (3H, d, *J* 1.2 Hz, CH=C[CH₃][CH₃]), 1.24 (3H, s, C[CH₃][CH₃]), 1.04 (3H, s, C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 177.8 (C=O), 128.9 (CH=C[CH₃]₂), 119.1 (CH=C[CH₃]₂), 51.4 (CH₂N), 46.5 (CHCH₂Br), 43.7 (C[CH₃]₂), 31.4 (CH₂Br), 24.3 (C[CH₃][CH₃], lactam), 23.1 (CH=C[CH₃][CH₃]), 18.1 and 18.0 (C[CH₃][CH₃], lactam, and CH=C[CH₃][CH₃]); *m/z* (FAB) 262 (MH)⁺, 260 (MH)⁺, 180, 154, 136; [Found: (MH)⁺ 260.0661, C₁₁H₁₈NO⁷⁹Br requires (MH)⁺ 260.0650]; [Found: C, 50.66; H, 6.99; N, 5.16. C₁₁H₁₈NOBr requires C, 50.78; H, 6.97; N, 5.38].

But-3-enyl-but-2-enylidene-amine (193)



3-Buten-1-amine (824 μl , 9.00 mmol) was added dropwise to a solution of *trans*-crotonaldehyde (746 μl , 9.00 mmol) in diethyl ether (40 ml) at 0°C. After 30 minutes, MgSO_4 was added, the solution was filtered and the filtrate was concentrated *in vacuo* to give *but-3-enyl-but-2-enylidene-amine (193)* as a colourless oil (987 mg, <70% purity) which was used without further purification, ν_{max} (film)/ cm^{-1} 3075, 2970, 2920, 2832, 1657 (C=N), 1640, 1626, 1438, 1370, 1337, 1169, 1103, 976, 910; δ_{H} (400 MHz, CDCl_3) 7.74 (1H, d, J 8.0 Hz, $\text{CH}=\text{N}$), 6.16-6.10 (2H, m, $\text{CH}_3\text{CH}=\text{CH}$), 5.73 (1H, ddt, J 17.3, 10.3, 6.8 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.99 (1H, br d, J 17.3 Hz, $\text{CH}=\text{CH}_{\text{aHb}}$), 4.94 (1H, br d, J 10.3 Hz, $\text{CH}=\text{CH}_{\text{aHb}}$), 3.41 (2H, t, J 7.3 Hz, NCH_2), 2.30 (2H, dt, J 6.8, 7.3 Hz, NCH_2CH_2), 1.80 (3H, d, J 5.5 Hz, $\text{CH}=\text{CHCH}_3$); δ_{C} (100.6 MHz, CDCl_3) 162.9 ($\text{CH}=\text{N}$), 140.3 and 132.0 ($\text{CH}_2\text{CH}=\text{CH}$), 136.3 ($\text{CH}=\text{CH}_2$), 116.0 ($\text{CH}=\text{CH}_2$), 60.7 (N- CH_2), 35.2 (N CH_2CH_2), 18.3 ($\text{CH}_3\text{CH}=\text{CH}$); m/z (EI) 124 (MH)⁺, 108, 82.

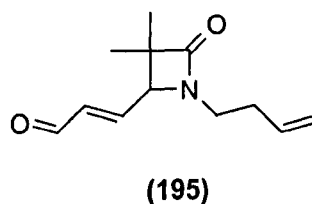
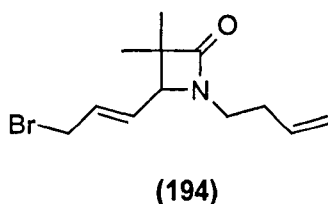
2-Bromo-N-buta-1,3-dienyl-N-but-3-enyl-2-methyl-propionamide (186)



2-Bromoisobutyryl bromide (351 μl , 2.84 mmol) followed by triethylamine (396 μl , 2.84 mmol) was added dropwise to a stirred solution of *but-3-enyl-but-2-enylidene-amine (193)* (350 mg, <70% purity) in anhydrous DCM (10 ml) at 0°C under nitrogen. After stirring at 0°C for 2 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 ; 9:1 petrol:ethyl acetate) to give 2-

bromo-N-buta-1,3-dienyl-N-but-3-enyl-2-methyl-propionamide (186) as an orange oil (113 mg, 15% from *trans*-crotonaldehyde), R_f (9:1 petrol:ethyl acetate) 0.56; ν_{\max} (film)/ cm^{-1} 3078, 2977, 2932, 1734, 1661, 1630, 1459, 1426, 1391, 1364, 1316, 1260, 1211, 1153, 1106, 996, 916, 804, 644; δ_{H} (400 MHz, CDCl_3) 7.59 (1H, d, J 14.0 Hz, $\text{N}-\text{CH}=\text{CH}$), 6.36 (1H, ddd, J 17.0, 10.0, 10.0 Hz, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}$), 5.85-5.71 (2H, m, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}$ and $\text{CH}_2\text{CH}=\text{CH}_2$), 5.21-5.02 (4H, m, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}$ and $\text{CH}_2\text{CH}=\text{CH}_2$), 3.78 (2H, t, J 7.5 Hz, NCH_2CH_2), 2.36 (2H, dt, J 7.5 Hz, NCH_2CH_2), 1.99 (6H, s, $\text{BrC}[\text{CH}_3]_2$); δ_{C} (100.6 MHz, CDCl_3) 167.0 ($\text{C}=\text{O}$), 34.1, 133.6 and 131.6 ($\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}$), 115.9 and 113.9 ($\text{CH}_2=\text{CH}-\text{CH}$ and $\text{CH}_2=\text{CHCH}_2$), 111.9 ($\text{CH}_2\text{CH}=\text{CH}_2$), 55.5 ($\text{BrC}[\text{CH}_3]_2$), 43.2 (CH_2N), 31.6 ($\text{CH}_2\text{CH}_2\text{N}$), 30.1 ($\text{BrC}[\text{CH}_3]_2$); m/z (FAB) 274 (MH^+), 272 (MH^+), 192, 176, 154, 136, 120; [Found: (MH^+) 272.0663, $\text{C}_{12}\text{H}_{18}\text{NO}^{79}\text{Br}$ requires (MH^+) 272.0650].

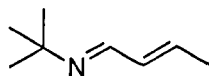
4-(3-Bromo-propenyl)-1-but-3-enyl-3,3-dimethyl-azetid-2-one (194) and 3-(1-but-3-enyl-3,3-dimethyl-4-oxo-azetid-2-yl)-propenal (195)



A stirred solution of 2-bromo-*N*-buta-1,3-dienyl-*N*-but-3-enyl-2-methyl-propionamide (**186**) (91.0 mg, 0.334 mmol), copper (I) bromide (14.4 mg, 0.100 mmol) and TPA (29.1 mg, 0.100 mmol) in anhydrous toluene (2.79 ml) was heated to reflux under nitrogen for 19 hours. The reaction mixture was filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (SiO_2 , 1:1 petrol:ethyl acetate) to give *4-(3-bromo-propenyl)-1-but-3-enyl-3,3-dimethyl-azetid-2-one (194)* as a yellow oil (18.0 mg, 20%), R_f (1:1 petrol:ethyl acetate) 0.59; ν_{\max} (film)/ cm^{-1} 2964, 2926, 1742, 1640, 1441, 1404, 1363, 1208, 1117, 972, 919; δ_{H} (400 MHz, CDCl_3) 5.98

(1H, dt, J 15.0, 7.5 Hz, BrCH₂CH=CH), 5.81-5.67 (2H, m, BrCH₂CH=CH and CH₂CH=CH₂), 5.12 (1H, br d, J 17.0 Hz, CH=CH_aH_b), 5.08 (1H, br d, J 9.8 Hz, CH=CH_aH_b), 3.98 (2H, dd, J 7.5, 1.0 Hz, BrCH₂CH=CH), 3.74 (1H, d, J 8.6 Hz, NCH=CH), 3.43 (1H, ddd, J 14.0, 7.3, 7.3 Hz, CH_aH_bN), 3.03 (1H, ddd, J 14.0, 6.8, 6.8 Hz, CH_aH_bN), 2.34-2.23 (2H, m, NCH₂CH₂), 1.30 (3H, s, C[CH₃][CH₃]), 1.10 (3H, s, C[CH₃][CH₃]); δ_C (125.8 MHz, CDCl₃) 174.0 (C=O), 135.4, 132.3 and 131.7 (CH=CH-CH-N and CH=CH₂), 117.6 (CH=CH₂), 64.7 (CH=CH-CH-N), 55.7 (C[CH₃]₂), 39.8 (CH₂N), 32.8 (CH₂CH=CH₂), 31.5 (CH₂Br), 22.8 and 18.1 (C[CH₃][CH₃]); m/z (FAB) 272 (MH)⁺, 274 (MH)⁺, 192, 176, 154, 137, 120; [Found: (MH)⁺, 272.0642, C₁₂H₁₈NO⁷⁹Br requires (MH)⁺, 272.0650], and *3-(1-but-3-enyl-3,3-dimethyl-4-oxoazetidin-2-yl)-propenal* (**195**) as a pale yellow gum (6.0 mg, 9%), R_f (1:1 petrol:ethyl acetate) 0.37; ν_{max} (film)/cm⁻¹ 2967, 2928, 1747 (C=O, lactam), 1689 (C=O, aldehyde), 1407, 1365, 1160, 1112, 986, 916; δ_H (400 MHz, CDCl₃) 9.63 (1H, d, J 7.5 Hz, COH), 6.73 (1H, dd, J 15.8, 7.6 Hz, N-CH-CH=CH), 6.30 (1H, ddd, J 15.8, 7.5, 1.0 Hz, N-CH-CH=CH), 5.75 (1H, ddt, J 17.1, 10.3, 6.8 Hz, CH=CH₂), 5.16-5.09 (2H, m, CH=CH₂), 4.01 (1H, dd, J 7.5, 0.8 Hz, CH=CH-CH-N), 3.54 (1H, ddd, J 14.1, 7.5, 7.5 Hz, CH_aH_bN), 3.05 (1H, ddd, J 14.1, 7.5, 6.5 Hz, CH_aH_bN), 2.38-2.22 (2H, m, NCH₂CH₂), 1.37 (3H, s, C[CH₃][CH₃]), 1.13 (3H, s, C[CH₃][CH₃]); δ_C (125.8 MHz, CDCl₃) 192.4 (C=O, aldehyde), 173.5 (C=O, lactam), 152.1 (N-CH-CH=CH), 135.4 and 135.1 (N-CH-CH=CH and CH=CH₂), 118.0 (CH=CH₂), 64.1 (N-CH-CH=CH), 57.3 (C[CH₃][CH₃]), 40.2 (CH₂N), 32.7 (CH₂CH=CH₂), 22.9 and 18.3 (C[CH₃][CH₃]); m/z (FAB) 208 (MH)⁺, 176, 154, 136, 120; [Found: (MH)⁺, 208.1337, C₁₂H₁₇NO₂ requires (MH)⁺, 208.1338].

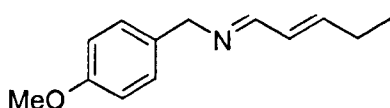
***But-2-enylidene-tert-butyl-amine* (196)**



Tert-butylamine (4.20 ml, 40.0 mmol) was added dropwise to stirred *trans*-crotonaldehyde (3.31 ml, 40.0 mmol) at 0°C. After 1 hour at room temperature, MgSO₄ was added. The mixture was filtered to give *but-2-enylidene-tert-butyl-amine* (**196**) as a

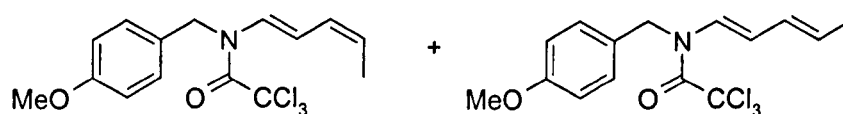
yellow oil (4.67 g, 93%, >85% purity) which was used without further purification, ν_{\max} (film)/ cm^{-1} 2966, 2871, 1655 (C=N), 1623, 1446, 1364, 1216, 1165, 978; δ_{H} (400 MHz, CDCl_3) 7.83 (1H, d, J 8.3 Hz, $\text{CH}=\text{N}$), 6.30-6.13 (2H, m, $\text{N}=\text{CH}-\text{CH}=\text{CH}$), 1.87 (3H, dd, J 6.3, 1.2 Hz, $\text{CH}=\text{CHCH}_3$), 1.20 (9H, s, $\text{C}[\text{CH}_3]_3$); δ_{C} (100.6 MHz, CDCl_3) 157.2 ($\text{CH}=\text{N}$), 139.5 and 132.9 ($\text{N}=\text{CH}-\text{CH}=\text{CH}$), 56.5 ($\text{C}[\text{CH}_3]_3$), 29.5 ($\text{C}[\text{CH}_3]_3$), 18.0 ($\text{CH}=\text{CHCH}_3$).

(4-Methoxybenzyl)-pent-2-enylidene-amine (199)



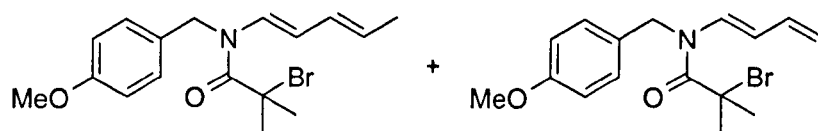
4-Methoxybenzylamine (2.61 ml, 20.0 mmol) was added dropwise to stirred *trans*-2-pentenal (1.96 ml, 20.0 mmol) at 0°C. After 30 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give *(4-methoxybenzyl)-pent-2-enylidene-amine (199)* as a pale yellow oil (3.87 g, 95%, >85% purity) which was used without further purification, ν_{\max} (film)/ cm^{-1} 2961, 2931, 2833, 1651 (C=N), 1610, 1584, 1509, 1458, 1337, 1300, 1242, 1172, 1107, 1033, 997, 969, 815; δ_{H} (400 MHz, CDCl_3) 7.91 (1H, d, J 8.0 Hz, $\text{N}=\text{CH}$), 7.17 (2H, d, J 8.8 Hz, Ar C-H), 6.84 (2H, d, J 8.8 Hz, Ar C-H), 6.27-6.22 (2H, m, $\text{N}=\text{CH}-\text{CH}=\text{CH}$), 4.53 (2H, s, CH_2N), 3.73 (3H, s, OCH_3), 2.24-2.16 (2H, m, CH_2CH_3), 1.04 (3H, t, J 7.5 Hz, CH_2CH_3); δ_{C} (100.6 MHz, CDCl_3) 163.3 ($\text{N}=\text{C}$), 158.7 (Ar quat.), 147.2 and 129.8 ($\text{N}=\text{CH}-\text{CH}=\text{CH}$), 131.6 (Ar quat.), 129.2 (Ar C-H), 113.9 (Ar C-H), 64.4 (CH_2N), 55.2 (OCH_3), 25.7 (CH_2CH_3), 13.1 (CH_2CH_3); m/z (FAB) 204 (MH^+), 176; [Found: (MH^+), 204.1377, $\text{C}_{13}\text{H}_{17}\text{NO}$ requires (MH^+), 204.1388].

1:1 Mixture of *Z*- and *E*-2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-penta-1,3-dienyl-acetamide (200a)



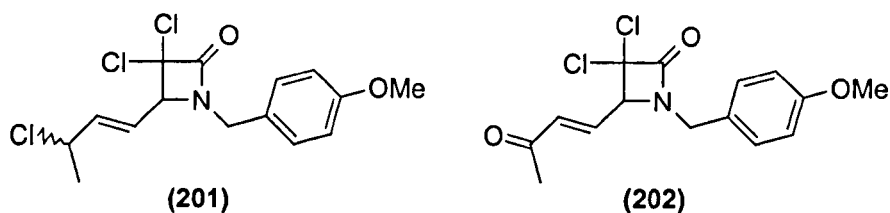
Trichloroacetyl chloride (446 μl , 4.00 mmol) followed by triethylamine (558 μl , 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-pent-2-enylideneamine (**199**) (813 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 ; 9:1 petrol:ethyl acetate) to give an inseparable 1:1 mixture of *Z*- and *E*-2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-penta-1,3-dienyl-acetamide (**200a**) as a yellow oil (365 mg, 26%), R_f (9:1 petrol:ethyl acetate) 0.32; ν_{max} (film)/ cm^{-1} 3005, 2934, 2837, 1680 (C=O), 1647, 1614, 1513, 1446, 1386, 1356, 1294, 1248, 1177, 1035, 975, 918, 808, 715, 664; δ_{H} (400 MHz, CDCl_3) 7.32 (1H, d, J 13.5 Hz, N-CH=CH, *Z*), 7.23 (1H, d, J 13.6 Hz, N-CH=CH, *E*), 7.17 (2H, d, J 8.6 Hz, Ar C-H, *Z* or *E*), 7.14 (2H, d, J 8.6 Hz, Ar C-H, *Z* or *E*), 6.88 (2H, d, J 8.6 Hz, Ar C-H, *Z* or *E*), 6.86 (2H, d, J 8.6 Hz, Ar C-H, *Z* or *E*), 6.11 (1H, dd, J 13.5, 12.5 Hz, N-CH=CH, *Z*), 6.04-5.91 (2H, m, N-CH=CH-CH=CH, *Z* and *E*), 5.81 (1H, dd, J 13.6, 12.7 Hz, N-CH=CH, *E*), 5.61 (1H, dq, J 14.6, 6.0 Hz, CH=CH-CH₃, *E*), 5.50 (1H, dq, J 10.5, 7.0 Hz, CH=CH-CH₃, *Z*), 5.00 (2H, br s, CH₂N, *Z* or *E*), 4.95 (2H, br s, CH₂N, *Z* or *E*), 3.78 (3H, s, OCH₃, *Z* or *E*), 3.77 (3H, s, OCH₃, *Z* or *E*), 1.73 (3H, d, J 6.0 Hz, CH=CH-CH₃, *E*), 1.63 (3H, d, J 7.0 Hz, CH=CH-CH₃, *Z*); δ_{C} (100.6 MHz, CDCl_3) 159.0 and 158.9 (C=O, *Z* and *E*), 130.0 (N-CH=CH, *Z*), 129.8 (CH=CH-CH₃, *E*), 128.4 (N-CH=CH and N-CH=CH-CH=CH, *E*), 128.0 and 127.9 (Ar C-H, *Z* and *E*), 126.5 (N-CH=CH-CH=CH, *Z*), 126.4 (CH=CH-CH₃, *Z*), 117.3 (N-CH=CH, *E*), 114.3 and 114.2 (Ar C-H, *Z* and *E*), 112.8 (N-CH=CH, *Z*), 93.2 (CCl₃, *Z* and *E*), 55.3 (OCH₃, *Z* and *E*), 50.9 (CH₂N, *Z* and *E*), 18.7 (C=CH-CH₃, *E*), 14.1 (C=CH-CH₃, *Z*), 4 x Ar quat. absent/broad; m/z (FAB) 347 (M)⁺; [Found: (M)⁺, 347.0258, C₁₅H₁₆NO₂³⁵Cl₃ requires (M)⁺, 347.0247].

2:1 Mixture of *E*- and *Z*-2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-penta-1,3-dienyl-propionamide (200b)



2-Bromoisobutyryl bromide (494 μl , 4.00 mmol) followed triethylamine (558 μl , 4.00 mmol) by was added dropwise to a stirred solution of (4-methoxybenzyl)-pent-2-enylidene-amine (**199**) (813 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 ; 9:1 petrol:ethyl acetate) to give a 2:1 mixture of *E*- and *Z*-2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-penta-1,3-dienyl-propionamide (**200b**) as a pale brown oil (577 mg, 41%), R_f (9:1 petrol:ethyl acetate) 0.27; ν_{max} (film)/ cm^{-1} 2933, 2837, 1664 (C=O), 1611, 1513, 1460, 1358, 1299, 1248, 1177, 1111, 1032, 826; δ_{H} (400 MHz, CDCl_3) 7.61 (0.5 H, d, J 13.1 Hz, N- $\text{CH}=\text{CH}$, *Z*), 7.53 (1H, d, J 13.8 Hz, N $\text{CH}=\text{CH}$, *E*), 7.12 (1H, d, J 8.8 Hz, Ar C- H , *Z*), 7.09 (2H, d, J 8.8 Hz, Ar C- H , *E*), 6.86 (1H, d, J 8.8 Hz, Ar C- H , *Z*), 6.84 (2H, d, J 8.8 Hz, Ar C- H , *E*), 6.06-5.93 (2H, m, N- $\text{CH}=\text{CH}-\text{CH}=\text{CH}$, *E*, and N $\text{CH}=\text{CH}-\text{CH}=\text{CH}$, *Z*), 5.70 (1H, dd, J 13.8, 10.5 Hz, N $\text{CH}=\text{CH}$, *E*), 5.55 (1H, dq, J 13.6, 6.8 Hz, $\text{CH}_3\text{CH}=\text{CH}$, *E*), 5.42 (0.5H, dq, J 9.5, 6.5 Hz, $\text{CH}_3\text{CH}=\text{CH}$, *Z*), 4.94 (1H, br s, CH_2N , *Z*), 4.89 (2H, br s, CH_2N , *E*), 3.77 (1.5 H, s, OCH_3 , *Z*), 3.76 (3H, s, OCH_3 , *E*), 2.04 (3H, s, $\text{CBr}[\text{CH}_3]_2$, *Z*), 2.03 (6H, s, $\text{CBr}[\text{CH}_3]_2$, *E*), 1.72 (3H, dd, J 6.8, 1.5 Hz, $\text{CH}=\text{CHCH}_3$, *E*), 1.62 (1.5 H, br d, J 6.5 Hz, $\text{CH}=\text{CHCH}_3$, *Z*); δ_{C} (100.6 MHz, CDCl_3) 169.1 and 169.0 (C=O, *E* and *Z*), 158.7 and 158.6 (Ar C- H , *E* and *Z*), 132.5 (N- $\text{CH}=\text{CH}$, *Z*), 130.2 (N- $\text{CH}=\text{CH}$, *E*), 129.1 (N $\text{CH}=\text{CH}-\text{CH}=\text{CH}$, *E*), 129.0 (Ar quat., *E* and *Z*), 127.8 (Ar C- H , *E* and *Z*, and $\text{CH}_3\text{CH}=\text{CH}$, *E*), 127.1 (N $\text{CH}=\text{CH}-\text{CH}=\text{CH}$, *Z*), 124.7 ($\text{CH}_3\text{CH}=\text{CH}$, *Z*), 114.5 (N- $\text{CH}=\text{CH}$, *E*), 114.1 (Ar C- H , *E* and *Z*), 109.5 (N $\text{CH}=\text{CH}$, *Z*), 56.9 ($\text{CBr}[\text{CH}_3]_2$, *E*), 56.8 ($\text{CBr}[\text{CH}_3]_2$, *Z*), 55.2 (OCH_3 , *E* and *Z*), 49.1 (CH_2N , *E* and *Z*), 32.6 ($\text{CBr}[\text{CH}_3]_2$, *E* and *Z*), 18.2 ($\text{CH}=\text{CHCH}_3$, *E*), 13.4 ($\text{CH}=\text{CHCH}_3$, *Z*); m/z (FAB) 307, 206, 154, 136, 121.

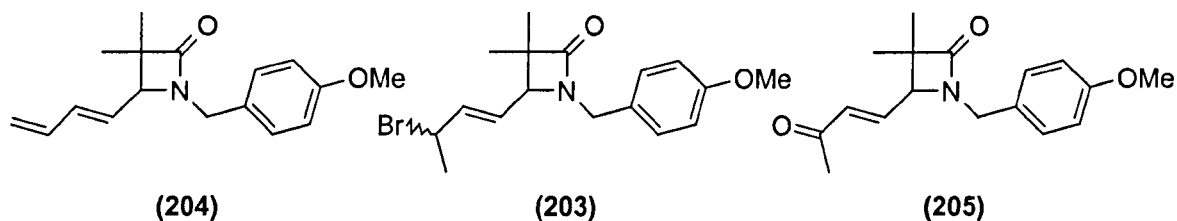
1:1 Mixture of 3,3-dichloro-4-(3-chloro-but-1-enyl)-1-(4-methoxybenzyl)-azetidin-2-one (201) and 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-oxo-but-1-enyl)-azetidin-2-one (202)



A stirred solution of a 1:1 mixture of *Z*- and *E*-2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-penta-1,3-dienyl-acetamide (**200a**) (117 mg, 0.336 mmol), copper (I) chloride (10.0 mg, 0.101 mmol) and TPA (29.2 mg, 0.101 mmol) in anhydrous toluene (2.80 ml) was heated to reflux under nitrogen for 16 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give diastereoisomer A of 3,3-dichloro-4-(3-chloro-but-1-enyl)-1-(4-methoxybenzyl)-azetidin-2-one (**201**) as a pale yellow gum (16.0 mg, 14%), *R_f* (3:1 petrol:ethyl acetate) 0.43; ν_{\max} (film)/cm⁻¹ 2930, 2839, 1788 (C=O), 1612, 1514, 1441, 1393, 1303, 1249, 1178, 1033, 971, 844; δ_{H} (400 MHz, CDCl₃) 7.15 (2H, d, *J* 8.6 Hz, Ar C-H), 6.89 (2H, d, *J* 8.6 Hz, Ar C-H), 5.89 (1H, dd, *J* 15.3, 7.8 Hz, CH₃-CHCl-CH=CH), 5.52 (1H, ddd, *J* 15.3, 9.0, 1.0 Hz, CH₂CHCl-CH=CH), 4.60 (1H, d, *J* 14.8 Hz, CH_aH_bN), 4.53 (1H, dq, *J* 7.8, 6.5 Hz, CH₃CHCl), 4.19 (1H, d, *J* 9.0 Hz, CCl₂CHN), 4.07 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.81 (3H, s, OCH₃), 1.60 (3H, d, *J* 6.5 Hz, CHClCH₃); δ_{C} (100.6 MHz, CDCl₃) 160.6 (C=O), 159.7 (Ar quat.), 141.8 (CH₃CHClCH=CH), 130.1 (Ar C-H), 125.5 (Ar quat.), 123.9 (CH₃CHClCH=CH), 114.5 (Ar C-H), 70.7 (CCl₂CHN), 55.8 (CH₃CHCl), 55.3 (OCH₃), 44.7 (CH₂N), 24.9 (CH₃CHCl), CCl₂ not visible; *m/z* (FAB) 348 (MH)⁺, 307, 289, 163, 154, 137, 121; [Found: (M)⁺, 347.0255, C₁₅H₁₆NO₂³⁵Cl₃ requires (M)⁺, 347.0247], diastereoisomer B of 3,3-dichloro-4-(3-chloro-but-1-enyl)-1-(4-methoxybenzyl)-azetidin-2-one (**201**) as a pale yellow gum (16.0 mg, 14%), *R_f* (3:1 petrol:ethyl acetate) 0.39; ν_{\max} (film)/cm⁻¹ 2930, 2838, 1783 (C=O), 1710, 1611, 1513, 1441, 1394, 1304, 1247, 1177, 1150, 1110, 1032,

972, 829, 685; δ_{H} (400 MHz, CDCl_3) 7.13 (2H, d, J 8.6 Hz, Ar C-H), 6.88 (2H, d, J 8.6 Hz, Ar C-H), 5.92 (1H, dd, J 15.6, 7.0 Hz, $\text{CH}_3\text{-CHCl-CH=CH}$), 5.52 (1H, ddd, J 15.6, 8.5, 1.2 Hz, $\text{CH}_2\text{CHCl-CH=CH}$), 4.58 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.51 (1H, dq, J 7.0, 6.5 Hz, CH_3CHCl), 4.22 (1H, d, J 8.5 Hz, CCl_2CHN), 4.10 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.81 (3H, s, OCH_3), 1.57 (3H, d, J 6.5 Hz, CHClCH_3); δ_{C} (100.6 MHz, CDCl_3) 160.7 (C=O), 159.7 (Ar quat.), 141.4 ($\text{CH}_3\text{CHClCH=CH}$), 130.0 (Ar C-H), 125.6 (Ar quat.), 123.6 ($\text{CH}_3\text{CHClCH=CH}$), 114.5 (Ar C-H), 83.5 (CCl_2), 70.6 (CCl_2CHN), 55.3 and 55.2 (CH_3CHCl and OCH_3), 44.7 (CH_2N), 24.3 (CH_3CHCl); m/z (FAB) 348 (MH)⁺, 307, 289, 163, 154, 136, 121; [Found: (M-H)⁺, 346.0188, $\text{C}_{15}\text{H}_{16}\text{NO}_2^{35}\text{Cl}_3$ requires (M-H)⁺, 346.0168], and *3,3-dichloro-1-(4-methoxybenzyl)-4-(3-oxo-but-1-enyl)-azetidin-2-one* (**202**) as a pale yellow gum (21.0 mg, 19%), R_f (3:1 petrol:ethyl acetate) 0.18; ν_{max} (film)/ cm^{-1} 2932, 2839, 1784 (C=O), 1681, 1611, 1585, 1513, 1438, 1393, 1359, 1304, 1248, 1177, 1110, 1031, 979, 869, 827, 685; δ_{H} (400 MHz, CDCl_3) 7.13 (2H, d, J 8.6 Hz, Ar C-H), 6.88 (2H, d, J 8.6 Hz, Ar C-H), 6.37 (1H, dd, J 16.0, 8.3 Hz, $\text{CH}_3\text{COCH=CH}$), 6.19 (1H, d, J 16.0 Hz, $\text{CH}_3\text{COCH=CH}$), 4.60 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.33 (1H, d, J 8.3 Hz, CCl_2CHN), 4.17 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.80 (3H, s, OCH_3), 2.23 (3H, s, COCH_3); δ_{C} (100.6 MHz, CDCl_3) 196.7 (C=O , ketone), 160.0 (C=O , lactam), 159.9 (Ar quat.), 137.1 ($\text{CH}_3\text{COCH=CH}$), 136.7 ($\text{CH}_3\text{COCH=CH}$), 130.0 (Ar C-H), 125.3 (Ar quat.), 114.6 (Ar C-H), 83.0 (CCl_2), 70.1 (CCl_2CHN), 55.4 (OCH_3), 45.2 (CH_2N), 27.3 (CH_3CO); m/z (FAB) 328 (MH)⁺, 307, 289, 163, 154, 137, 121; [Found: (MH)⁺, 328.0491, $\text{C}_{15}\text{H}_{15}\text{NO}_3^{35}\text{Cl}_2$ requires (MH)⁺, 328.0507].

4-Buta-1,3-dienyl-1-(4-methoxybenzyl)-3,3-dimethyl-azetid-2-one (204), 1:1 mixture of 4-(3-bromo-but-1-enyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetid-2-one (203) and 1-(4-methoxybenzyl)-3,3-dimethyl-(3-oxo-but-1-enyl)-azetid-2-one (205)

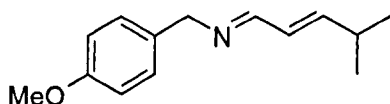


A stirred solution of a 2:1 mixture of *E*- and *Z*-2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-penta-1,3-dienyl-propionamide (**200b**) (320 mg, 0.908 mmol), copper (I) bromide (39.1 mg, 0.273 mmol) and TPA (79.1 mg, 0.273 mmol) in anhydrous toluene (7.57 ml) was heated to reflux under nitrogen for 19 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate then 1:1 petrol:ethyl acetate) to give 4-butadienyl-1-(4-methoxybenzyl)-3,3-dimethyl-azetid-2-one (**204**) as a pale yellow oil (45.0 mg, 18%), *R*_f (3:1 petrol:ethyl acetate) 0.20; ν_{\max} (film)/cm⁻¹ 2961, 2928, 2837, 1741 (C=O), 1612, 1586, 1512, 1461, 1397, 1348, 1302, 1244, 1175, 1129, 1110, 1032, 1009, 954, 906, 827, 765, 630; δ_{H} (400 MHz, CDCl₃) 7.14 (2H, d, *J* 8.8 Hz, Ar C-H), 6.85 (2H, d, *J* 8.8 Hz, Ar C-H), 6.33 (1H, ddd, *J* 17.0, 10.3, 10.3 Hz, CH₂=CH), 6.16 (1H, dd, *J* 15.2, 10.3 Hz, CH₂=CH-CH=CH), 5.52 (1H, dd, *J* 15.2, 8.6 Hz, CH₂=CH-CH=CH), 5.22 (1H, dd, *J* 17.0, 1.5 Hz, CH_aH_b=CH), 5.14 (1H, dd, *J* 10.3, 1.5 Hz, CH_aH_b=CH), 4.59 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.89 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.80 (3H, s, OCH₃), 3.56 (1H, d, *J* 8.6 Hz, CMe₂CHN), 1.25 (3H, s, C[CH₃][CH₃]), 1.11 (3H, s, C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 173.6 (C=O), 159.0 (Ar quat.), 135.9 and 135.8 (CH₂=CH-CH=CH), 127.7 (Ar C-H), 129.0 (CH₂=CH-CH=CH), 128.2 (Ar quat.), 118.5 (CH₂=CH), 114.1 (Ar C-H), 64.4 (CMe₂CHN), 55.4 (CMe₂), 55.3 (OCH₃), 43.6 (CH₂N), 21.9 (C[CH₃][CH₃]), 18.0 (C[CH₃][CH₃]); *m/z* (FAB) 543 (2MH)⁺, 272 (MH)⁺, 154, 136, 121; [Found: (MH)⁺ 272.1652, C₁₇H₂₁NO₂ requires (MH)⁺ 272.1651], a 1:1 mixture of 4-(3-bromo-but-1-enyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetid-2-one (**203**) as a pale

yellow oil (95.0 mg, 30%), R_f (3:1 petrol:ethyl acetate) 0.15; ν_{\max} (film)/ cm^{-1} 2961, 2924, 2837, 1742 (C=O), 1639, 1611, 1586, 1512, 1460, 1397, 1302, 1244, 1175, 1131, 1032, 970, 825, 760, 626; δ_H (400 MHz, CDCl_3) 7.16 (2H, d, J 8.6 Hz, Ar C-H, isomer A or B), 7.14 (2H, d, J 8.6 Hz, Ar C-H, isomer A or B), 6.87 (2H, d, J 8.6 Hz, Ar C-H, isomer A or B), 6.86 (2H, d, J 8.6 Hz, Ar C-H, isomer A or B), 5.91-5.82 (2H, m, $\text{CH}_3\text{CHBrCH}=\text{CH}$, isomers A and B), 5.52-5.43 (2H, m (2 x dd), $\text{CH}_3\text{CHBrCH}=\text{CH}$, isomers A and B), 4.64 (2H, dq, J 15.3, 8.5 Hz, CH_3CHBr , isomers A and B), 4.52 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 4.51 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 4.00 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 3.97 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 3.80 (6H, s, OCH_3 , isomers A and B), 3.53 (1H, d, J 8.0 Hz, CMe_2CHN , isomer A or B), 3.51 (1H, d, J 8.3 Hz, CMe_2CHN , isomer A or B), 1.74 (3H, d, J 6.8 Hz, CH_3CHBr , isomer A or B), 1.73 (3H, d, J 6.8 Hz, CH_3CHBr , isomer A or B), 1.26 (3H, s, CH_3 , isomer A or B), 1.25 (3H, s, CH_3 , isomer A or B), 1.11 (3H, s, CH_3 , isomer A or B) and 1.10 (3H, s, CH_3 , isomer A or B); δ_C (100.6 MHz, CDCl_3) 173.3 and 173.2 (C=O, isomers A and B), 159.1 (Ar quat., isomers A and B), 138.4 and 138.1 ($\text{CH}_3\text{CHBrCH}=\text{CH}$, isomers A and B), 129.9 (Ar C-H, isomers A and B), 127.9 (Ar quat., isomers A and B), 126.9 ($\text{CH}_3\text{CHBrCH}=\text{CH}$, isomers A and B), 114.1 (Ar C-H, isomers A and B), 63.5 (CMe_2CHN , isomers A and B), 55.3 (OCH_3 , isomers A and B), 55.2 (CMe_2 , isomers A and B), 47.6 and 47.4 (CH_3CHBr , isomers A and B), 43.8 (CH_2N , isomers A and B), 25.7 and 25.5 (CH_3CHBr , isomers A and B), 21.9 ($\text{C}[\text{CH}_3][\text{CH}_3]$, isomers A and B), 17.4 ($\text{C}[\text{CH}_3][\text{CH}_3]$, isomers A and B); m/z (FAB) 352 (MH^+), 307, 289, 272, 242, 176, 162, 154, 136, 121; [Found: (MH^+) 352.0896, $\text{C}_{17}\text{H}_{22}\text{NO}_2^{79}\text{Br}$ requires (MH^+) 352.0912]; [Found: C, 58.36; H, 6.34; N, 3.77. $\text{C}_{17}\text{H}_{22}\text{NO}_2\text{Br}$ requires C, 57.96; H, 6.29; N, 3.98], and *1-(4-methoxybenzyl)-3,3-dimethyl-(3-oxo-but-1-enyl)-azetidin-2-one* (**205**) as a pale yellow oil (20.9 mg, 8%), R_f (1:1 petrol:ethyl acetate) 0.23; ν_{\max} (film)/ cm^{-1} 2962, 2928, 2838, 1744 (C=O, lactam), 1675 (C=O, ketone), 1612, 1585, 1513, 1462, 1399, 1358, 1302, 1247, 1176, 1111, 1031, 985, 839, 761; δ_H (400 MHz, CDCl_3) 7.13 (2H, d, J 8.8 Hz, Ar C-H), 6.85 (2H, d, J 8.8 Hz, Ar C-H), 6.47 (1H, dd, J 16.0, 7.8 Hz, $\text{CH}_3\text{COCH}=\text{CH}$), 6.11 (1H, d, J 16.0 Hz, $\text{CHCOCH}=\text{CH}$), 4.54 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.05 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.80 (3H, s, OCH_3), 3.68 (1H, d, J 7.8 Hz, CMe_2CHN), 2.19 (3H, s, CH_3CO), 1.30 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$), 1.13 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_C (100.6 MHz, CDCl_3) 197.2 (C=O, ketone), 173.0 (C=O, lactam), 159.3

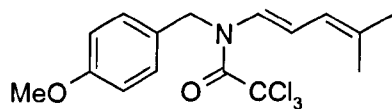
(Ar quat.), 142.2 (CH₃COCH=CH), 133.6 (CH₃COCH=CH), 129.9 (Ar C-H), 127.6 (Ar quat.), 114.2 (Ar C-H), 63.2 (CMe₂CHN), 56.5 (CMe₂), 55.3 (OCH₃), 44.3 (CH₂N), 27.2 (CH₃CO), 22.0 (C[CH₃][CH₃]), 17.9 (C[CH₃][CH₃]); m/z (FAB) 288 (MH)⁺, 154, 137, 121; [Found: (MH)⁺ 288.1594, C₁₇H₂₁NO₃ requires (MH)⁺ 288.1600].

(4-Methoxybenzyl)-(4-methyl-pent-2-enylidene)-amine (209)



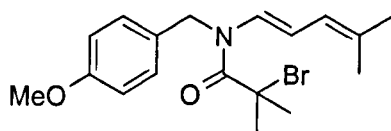
4-Methoxybenzylamine (2.61 ml, 20.0 mmol) was added dropwise to stirred 4-methyl-2-pentenal (2.34 ml, 20.0 mmol) at 0°C. After 30 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give (4-methoxybenzyl)-(4-methyl-pent-2-enylidene)-amine (209) as a pale yellow oil (4.07 g, 94%, >90% purity) which was used without further purification, ν_{\max} (film)/cm⁻¹ 2958, 2868, 2833, 1650 (C=N), 1610, 1585, 1510, 1461, 1366, 1334, 1300, 1243, 1172, 1107, 1034, 995, 971, 815, 753; δ_{H} (400 MHz, CDCl₃) 7.88 (1H, dt, J 8.5, 1.3 Hz, N=CH), 7.16 (2H, d, J 8.8 Hz, Ar C-H), 6.82 (2H, d, J 8.8 Hz, Ar C-H), 6.23 (1H, ddd, J 15.7, 8.5, 1.0 Hz, N=CH-CH=CH), 6.13 (1H, dd, J 15.7, 6.0 Hz, N=CH-CH=CH), 4.52 (2H, s, CH₂N), 3.69 (3H, s, OCH₃), 2.41 (1H, sd, J 6.8, 6.0 Hz, CHMe₂), 1.02 (6H, d, J 6.8 Hz, CH[CH₃]₂); δ_{C} (100.6 MHz, CDCl₃) 163.3 (N=CH), 158.7 (Ar quat.), 152.2 (N=CH-CH=CH), 131.5 (Ar quat.), 129.1 (Ar C-H), 127.9 (N=CH-CH=CH), 113.9 (Ar C-H), 64.4 (CH₂N), 55.1 (OCH₃), 31.1 (CH[CH₃]₂), 21.7 (CH[CH₃]₂); m/z (FAB) 218 (MH)⁺, 152, 121.

2,2,2-Trichloro-N-(4-methoxybenzyl)-N-(4-methyl-penta-1,3-dienyl)-acetamide (210a)



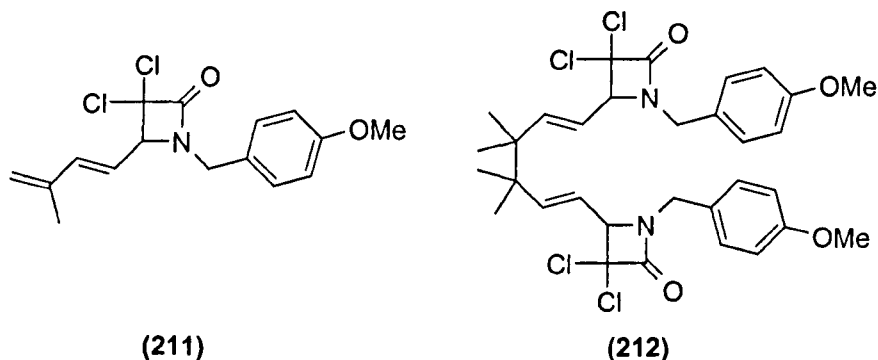
Trichloroacetyl chloride (446 μl , 4.00 mmol) followed by triethylamine (558 μl , 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-(4-methyl-pent-2-enylidene)-amine (**209**) (869 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 ; 9:1 petrol:ethyl acetate) to give 2,2,2-trichloro-N-(4-methoxybenzyl)-N-(4-methyl-penta-1,3-dienyl)-acetamide (**210a**) as a pale yellow gum (813 mg, 56%), R_f (9:1 petrol:ethyl acetate) 0.47; ν_{max} (film)/ cm^{-1} 2962, 2911, 2837, 1680 (C=O), 1614, 1514, 1445, 1393, 1345, 1301, 1248, 1205, 1178, 1036, 925, 835, 807, 690, 664; δ_{H} (400 MHz, d^8 -toluene) 7.28 (1H, d, J 13.6 Hz, NCH=CH), 7.06 (2H, d, J 8.3 Hz, Ar C-H), 6.69 (2H, d, J 8.3 Hz, Ar C-H), 5.99 (1H, br t, J 11.3 Hz, NCH=CH), 5.72 (1H, d, J 10.8 Hz, $\text{Me}_2\text{C}=\text{CH}$), 4.80 (2H, br s, CH_2N), 3.35 (3H, s, OCH_3), 1.61 (3H, s, $[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$), 1.48 (3H, s, $[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$); δ_{C} (100.6 MHz, d^8 -toluene) 159.4 (C=O), 158.9 (Ar quat.), 137.5 (olef. quat.), 135.0 (Ar quat.), 128.6 and 128.5 (NCH=CH and Ar C-H), 122.7 ($\text{Me}_2\text{C}=\text{CH}$), 114.5 and 114.2 (Ar C-H and NCH=CH), 94.0 (CCl_3), 54.7 (OCH_3), 50.9 (CH_2N), 25.9 and 20.3 ($[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$); m/z (FAB) 363 (MH^+), 329, 307, 154, 121.

2-Bromo-N-(4-methoxybenzyl)-2-methyl-N-(4-methyl-penta-1,3-dienyl)-propionamide (210b)



2-Bromoisobutyryl bromide (494 μ l, 4.00 mmol) followed by triethylamine (558 μ l, 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-(4-methyl-pent-2-enylidene)-amine (**209**) (869 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give 2-bromo-N-(4-methoxybenzyl)-2-methyl-N-(4-methyl-penta-1,3-dienyl)-propionamide (**210b**) as a pale yellow oil (846 mg, 58%), R_f (9:1 petrol:ethyl acetate) 0.37; ν_{\max} (film)/cm⁻¹ 2965, 2929, 2837, 1651 (C=O), 1612, 1513, 1456, 1395, 1372, 1340, 1310, 1248, 1173, 1145, 1109, 1036, 997, 946, 814; δ_{H} (400 MHz, CDCl₃) 7.50 (1H, d, J 13.5 Hz, N-CH=CH), 7.11 (2H, d, J 8.8 Hz, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 5.90 (1H, dd, J 13.5, 11.0 Hz, NCH=CH), 5.78 (1H, br d, N-CH=CH-CH), 4.92 (2H, br s, CH₂N), 3.73 (3H, s, OCH₃), 2.03 (6H, s, CBr[CH₃]₂), 1.74 (3H, s, C=C[CH₃][CH₃]), 1.60 (3H, s, C=C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 168.9 (C=O), 158.7 (Ar quat.), 133.8 (olef. quat.), 130.0 (N-CH=CH), 129.2 (Ar quat.), 127.8 (Ar C-H), 122.5 (N-CH=CH-CH), 114.1 (Ar C-H), 111.5 (N-CH=CH), 57.0 (CBrMe₂), 55.2 (OCH₃), 49.2 (CH₂N), 32.7 (CBr[CH₃]₂), 26.0 and 17.9 (C=C[CH₃][CH₃]); m/z (FAB) 206, 121.

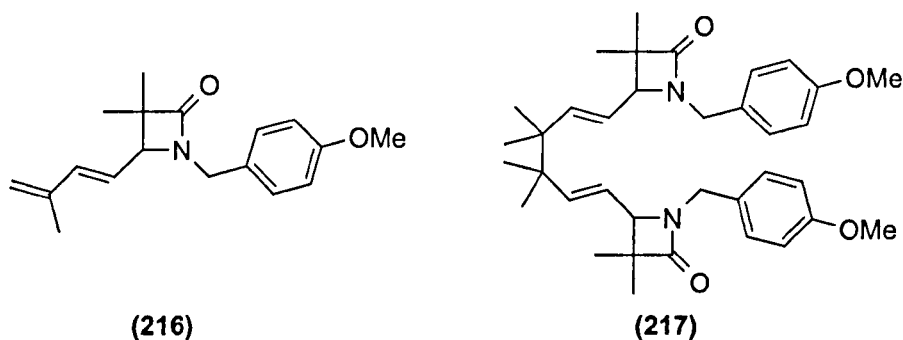
3,3-Dichloro-1-(4-methoxybenzyl)-4-(3-methyl-buta-1,3-dienyl)-azetid-2-one (211)
and 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-methyl-but-1-enyl)-azetid-2-one dimer (212)



A stirred solution of 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-(4-methyl-penta-1,3-dienyl)-acetamide (**210a**) (475 mg, 1.31 mmol), copper (I) chloride (38.9 mg, 0.393 mmol) and TPA (114 mg, 0.393 mmol) in anhydrous toluene (10.9 ml) was heated to reflux under nitrogen for 17 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1 petrol:ethyl acetate then 2:1 petrol:ethyl acetate) to give 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-methyl-buta-1,3-dienyl)-azetid-2-one (**211**) as a pale yellow oil (176 mg, 41%), *R_f* (9:1 petrol:ethyl acetate) 0.22; ν_{\max} (film)/cm⁻¹ 3082, 2927, 2838, 1780 (C=O), 1644, 1610, 1586, 1512, 1436, 1392, 1351, 1303, 1245, 1176, 1150, 1109, 1032, 970, 902, 866, 834, 805, 755, 680, 635; δ_{H} (400 MHz, CDCl₃) 7.14 (2H, d, *J* 8.8 Hz, Ar C-H), 6.87 (2H, d, *J* 8.8 Hz, Ar C-H), 6.37 (1H, d, *J* 15.6 Hz, CH₂=CMe-CH=CH), 5.38 (1H, dd, *J* 15.6, 8.8 Hz, CH₂=CMe-CH=CH), 5.13 (1H, br s, CH_aH_b=CMe), 5.08 (1H, br s, CH_aH_b=CMe), 4.56 (1H, d, *J* 14.8 Hz, CH_aH_bN), 4.30 (1H, d, *J* 8.8 Hz, CCl₂CHN), 4.09 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.79 (3H, s, OCH₃), 1.82 (3H, s, CH₂=C[CH₃]); δ_{C} (100.6 MHz, CDCl₃) 160.8 (C=O), 159.9 (Ar quat.), 141.7 (CH₂=CMe-CH=CH), 140.5 (olef. quat.), 129.9 (Ar C-H), 126.0 (Ar quat.), 121.2 (CH₂=CMe-CH=CH), 120.1 (CH₂=CMe), 114.4 (Ar C-H), 84.5 (CCl₂), 71.9 (CCl₂CHN), 55.3 (OCH₃), 44.5 (CH₂N), 18.0 (CH₂=C[CH₃]); *m/z* (FAB) 326 (MH)⁺, 289, 163, 154, 136, 121; [Found: (MH)⁺, 326.0696, C₁₆H₁₇NO₂³⁵Cl₂ requires (MH)⁺, 326.0715], and a 1:1 mixture 3,3-dichloro-1-

(4-methoxybenzyl)-4-(3-methyl-but-1-enyl)-azetidin-2-one dimer (**212**) as a pale yellow oil (59.0 mg, 14%), R_f (2:1 petrol:ethyl acetate) 0.41; ν_{\max} (film)/ cm^{-1} 2969, 2837, 1783 (C=O), 1704, 1659, 1611, 1586, 1513, 1461, 1394, 1355, 1303, 1247, 1176, 1111, 1032, 983, 918, 832, 732, 684, 645; δ_H (400 MHz, CDCl_3) 7.10 (8H, d, J 8.8 Hz, Ar C-H, isomers A and B), 6.86 (8H, d, J 8.8 Hz, Ar C-H, isomers A and B), 5.84 (2H, d, J 15.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer A), 5.82 (2H, d, J 15.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer B), 5.18 (2H, dd, J 15.8, 8.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer A or B), 5.17 (2H, dd, J 15.8, 8.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer A or B), 4.57 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 4.55 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 4.20 (4H, d, J 8.8 Hz, CCl_2CHN , isomers A and B), 4.06 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 4.05 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 3.80 (12H, s, OCH_3 , isomers A and B), 0.96 (6H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{C}[\text{CH}_3][\text{CH}_3]$), isomer A or B), 0.95 (6H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{C}[\text{CH}_3][\text{CH}_3]$), isomer A or B), 0.91 (12H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{C}[\text{CH}_3][\text{CH}_3]$), isomer A and B); δ_C (100.6 MHz, CDCl_3) 160.9 ($\text{C}=\text{O}$, isomers A and B), 159.6 (Ar quat., isomers A and B), 148.0 ($\text{CH}=\text{CH}-\text{CHN}$, isomers A and B), 129.7 (Ar C-H, isomer A and B), 125.8 (Ar quat., isomers A and B), 121.3 ($\text{CH}=\text{CH}-\text{CHN}$, isomers A and B), 114.4 (Ar C-H, isomers A and B), 84.1 (CCl_2 , isomers A and B), 72.2 (CCl_2CHN , isomers A and B), 55.3 (OCH_3 , isomers A and B), 44.5 (CH_2N , isomers A and B), 41.5 ($\text{C}[\text{CH}_3][\text{CH}_3]\text{C}[\text{CH}_3][\text{CH}_3]$), isomers A and B), 22.7, 22.4, 22.2 and 21.6 $\text{C}[\text{CH}_3][\text{CH}_3]\text{C}[\text{CH}_3][\text{CH}_3]$), isomers A and B); m/z (FAB) 653 (MH^+), 617, 391, 327, 292, 256, 162, 154; [Found: (MH^+), 655.1460, $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_4^{35}\text{Cl}_3^{37}\text{Cl}$ requires (MH^+), 655.1478].

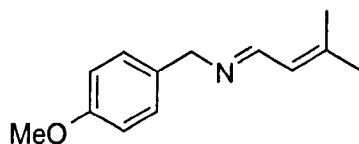
1-(4-Methoxybenzyl)-3,3-dimethyl-4-(3-methyl-but-1,3-dienyl)-azetidin-2-one (216)
and 1-(4-methoxybenzyl)-3,3-dimethyl-4-(3-methyl-but-1-enyl)-azetidin-2-one dimer (217)



A stirred solution of 2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-(4-methyl-penta-1,3-dienyl)-propionamide (**210b**) (516 mg, 1.41 mmol), copper (I) bromide (60.6 mg, 0.423 mmol) and TPA (123 mg, 0.423 mmol) in anhydrous toluene (11.7 ml) was heated to reflux under nitrogen for 19 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate then 1:1 petrol:ethyl acetate) to give *1-(4-methoxybenzyl)-3,3-dimethyl-4-(3-methyl-but-1,3-dienyl)-azetidin-2-one* (**216**) as a pale yellow oil (127 mg, 32%), *R_f* (3:1 petrol:ethyl acetate) 0.27; ν_{\max} (film)/cm⁻¹ 2962, 2929, 2838, 1730 (C=O), 1675, 1611, 1585, 1512, 1461, 1401, 1357, 1302, 1245, 1175, 1109, 1031, 977, 836, 762, 735, 632; δ_{H} (400 MHz, CDCl₃) 7.14 (2H, d, *J* 8.8 Hz, Ar C-H), 6.85 (2H, d, *J* 8.8 Hz, Ar C-H), 6.23 (1H, d, *J* 15.8 Hz, CH₂=CMe-CH=CH), 5.41 (1H, dd, 15.8, 8.7 Hz, CH₂=CMe-CH=CH), 5.01 (1H, br s, CH_aH_b=CMe), 4.97 (1H, br s, CH_aH_b=CMe), 4.52 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.98 (1H, d, *J* 14.8 Hz, CH_aH_bN), 3.78 (3H, s, OCH₃), 3.61 (1H, d, *J* 8.7 Hz, CMe₂CHN), 1.79 (3H, s, CH₂=C[CH₃]), 1.26 (3H, s, C[CH₃][CH₃]), 1.11 (3H, s, C[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 173.5 (C=O), 159.0 (Ar quat.), 141.0 (olef. quat.), 137.8 (CH₂=CMe-CH=CH), 129.7 (Ar C-H), 128.3 (Ar quat.), 125.0 (CH₂=CMe-CH=CH), 117.6 (CH₂=CMe), 114.0 (Ar C-H), 64.8 (CMe₂CHN), 55.3 (CMe₂), 55.2 (OCH₃), 43.6 (CH₂N), 21.9 (C[CH₃][CH₃]), 18.3 (CH₂=C[CH₃]), 17.5 (C[CH₃][CH₃]); *m/z* (FAB) 286 (MH)⁺, 218, 180, 154, 136, 121; [Found: (MH)⁺, 286.1810, C₁₈H₂₃NO₂ requires (MH)⁺, 286.1807], and a 1:1 mixture of *1-(4-*

methoxybenzyl)-3,3-dimethyl-4-(3-methyl-but-1-enyl)-azetid-2-one dimer (217) as a pale yellow oil (58.0 mg, 14%), R_f (1:1 petrol:ethyl acetate) 0.24; ν_{\max} (film)/ cm^{-1} 2962, 2926, 2838, 1741 (C=O), 1660, 1612, 1586, 1512, 1462, 1399, 1359, 1302, 1244, 1175, 1135, 1106, 1032, 983, 827, 762, 633; δ_H (400 MHz, CDCl_3) 7.03 (8H, d, J 8.3 Hz, Ar C-H, isomers A and B), 6.76 (8H, d, J 8.3 Hz, Ar C-H, isomers A and B), 5.58 (2H, d, J 15.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer A), 5.57 (2H, d, J 15.8 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomer B), 5.09 (4H, dd, J 15.8, 8.5 Hz, $\text{CH}=\text{CH}-\text{CHN}$, isomers A and B), 4.45 (4H, d, J 14.8 Hz, $\text{CH}_2\text{H}_b\text{N}$, isomers A and B), 3.86 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 3.83 (2H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$, isomer A or B), 3.71 (12H, s, OCH_3 , isomers A and B), 3.44 (2H, d, J 8.5 Hz, CMe_2CHN , isomer A or B), 3.43 (2H, d, J 8.5 Hz, CMe_2CHN , isomer A or B), 1.18 (6H, s, 2 x CH_3), 1.17 (6H, s, 2 x CH_3), 1.02 (6H, s, 2 x CH_3), 1.01 (6H, s, 2 x CH_3), 0.84 (12H, s, 4 x CH_3), 0.80 (6H, s, 2 x CH_3), 0.79 (6H, s, 2 x CH_3); δ_C (100.6 MHz, CDCl_3) 172.6 (C=O, isomers A and B), 158.0 (Ar quat., isomers A and B), 142.9 and 142.8 ($\text{CH}=\text{CH}-\text{CHN}$, isomers A and B), 128.6 (Ar C-H, isomers A and B), 127.2 (Ar quat., isomers A and B), 122.6 ($\text{CH}=\text{CH}-\text{CHN}$, isomers A and B), 113.0 (Ar C-H, isomers A and B), 64.2 (CMe_2CHN , isomers A and B), 54.2 (OCH_3 , isomers A and B), 53.7 (CMe_2 , isomers A and B), 42.5 (CH_2N , isomers A and B), 40.0 (CMe_2 , isomers A and B), 21.0 (4 x CH_3), 20.9 (4 x CH_3), 20.0 (4 x CH_3), 15.8 (4 x CH_3); m/z (FAB) 573 (MH)⁺, 286, 154, 121; [Found: (MH)⁺, 573.3681, $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_4$ requires (MH)⁺, 573.3692].

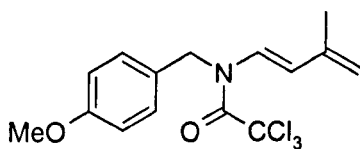
(4-Methoxybenzyl)-(3-methyl-but-2-enylidene)-amine (219)



4-Methoxybenzylamine (2.61 ml, 20.0 mmol) was added dropwise to stirred 3-methyl-2-butenal (1.93 ml, 20.0 mmol) at 0°C. After 30 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give *(4-methoxybenzyl)-(3-methyl-but-2-enylidene)-amine (219)* as a pale yellow oil (3.90 g, 96%, >95% purity) which was used without further purification, ν_{\max} (film)/ cm^{-1} 2995,

2907, 2862, 2833, 1649 (C=N), 1609, 1584, 1509, 1441, 1376, 1340, 1300, 1243, 1173, 1108, 1033, 813, 754; δ_{H} (400 MHz, CDCl_3) 8.24 (1H, dt, J 9.3, 1.2 Hz, $\text{CH}=\text{N}$), 7.17 (2H, d, J 8.8 Hz, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 6.04 (1H, br d, J 9.3 Hz, $\text{N}=\text{CH}-\text{CH}=\text{C}$), 4.55 (2H, s, CH_2N), 3.71 (3H, s, OCH_3), 1.89 (3H, s, $[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$), 1.84 (3H, s, $[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$); δ_{C} (100.6 MHz, CDCl_3) 159.8 ($\text{CH}=\text{N}$), 158.6 (Ar quat.), 146.7 (olef. quat.), 131.8 (Ar quat.), 129.1 (Ar C-H), 125.5 ($\text{N}=\text{CH}-\text{CH}=\text{C}$), 113.9 (Ar C-H), 64.8 (CH_2N), 55.1 (OCH_3), 26.5 and 18.5 ($[\text{CH}_3][\text{CH}_3]\text{C}=\text{CH}$); m/z (FAB) 204 (MH^+), 178, 154, 136, 121; [Found: (MH^+), 204.1391, $\text{C}_{13}\text{H}_{17}\text{NO}$ requires (MH^+), 204.1388].

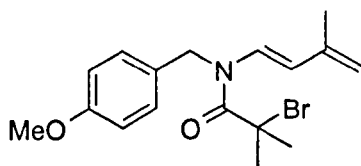
2,2,2-Trichloro-N-(4-methoxybenzyl)-N-(3-methyl-but-1,3-dienyl)-acetamide (220a)



Trichloroacetyl chloride (446 μl , 4.00 mmol) followed by triethylamine (558 μl , 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-(3-methyl-but-2-enylidene)-amine (**219**) (813 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 ; 9:1 petrol:ethyl acetate) to give 2,2,2-trichloro-N-(4-methoxybenzyl)-N-(3-methyl-but-1,3-dienyl)-acetamide (**220a**) as a cream solid (1.32 g, 95%), R_f (9:1 petrol:ethyl acetate) 0.42; m.pt. $65.2-65.7^\circ\text{C}$; ν_{max} (film)/ cm^{-1} 2939, 2836, 1682 (C=O), 1636, 1612, 1585, 1513, 1440, 1383, 1355, 1299, 1245, 1200, 1176, 1113, 1034, 927, 886, 810, 755, 713, 694, 664; δ_{H} (400 MHz, CDCl_3) 7.40 (1H, d, J 14.0 Hz, $\text{N}-\text{CH}=\text{CH}$), 7.14 (2H, d, J 8.8 Hz, Ar C-H), 6.84 (2H, d, J 8.8 Hz, Ar C-H), 5.94 (1H, d, J 14.0 Hz, $\text{N}-\text{CH}=\text{CH}$), 4.97 (2H, br s, CH_2N), 4.92 (1H, br s, $\text{CH}_a\text{H}_b=\text{C}$), 4.88 (1H, br s, $\text{CH}_a\text{H}_b=\text{C}$), 3.74 (3H, s, OCH_3), 1.85 (3H, s, $\text{CH}_2=\text{C}[\text{CH}_3]$); δ_{C}

(100.6 MHz, CDCl₃) 159.1 (C=O), 159.0 (Ar quat.), 139.8 (olef. quat.), 128.3 and 127.9 (N-CH=CH and Ar C-H), 127.9 (Ar quat.), 118.4 (N-CH=CH), 116.8 (C=CH₂), 114.3 (Ar C-H), 93.0 (CCl₃), 55.2 (OCH₃), 50.4 (CH₂N), 18.6 (CH₂=C[CH₃]); m/z (FAB) 350 (MH)⁺, 348 (MH)⁺, 329, 307, 289, 282, 154, 136, 121; [Found: (MH)⁺, 348.0337, C₁₅H₁₆NO₂³⁵Cl₃ requires (MH)⁺, 348.0325].

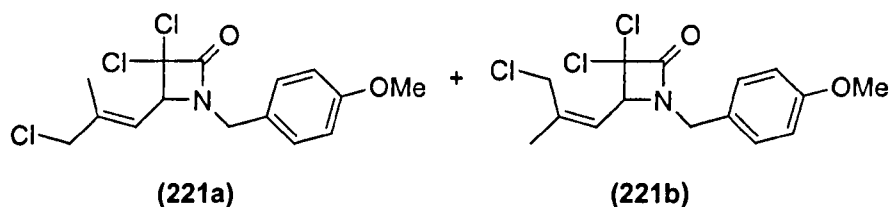
2-Bromo-N-(4-methoxybenzyl)-2-methyl-N-(3-methyl-buta-1,3-dienyl-propionamide
(220b)



2-Bromoisobutyryl bromide (494 μl, 4.00 mmol) followed by triethylamine (558 μl, 4.00 mmol) was added dropwise to a stirred solution of (4-methoxy-benzyl)-(3-methyl-but-2-enylidene)-amine (**219**) (813 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give *2-bromo-N-(4-methoxybenzyl)-2-methyl-N-(3-methyl-buta-1,3-dienyl-propionamide* (**220b**) as an orange oil (733 mg, 52%), R_f(9:1 petrol:ethyl acetate) 0.41; ν_{max} (film)/cm⁻¹ 2935, 2836, 1659 (C=O), 1628, 1512, 1456, 1392, 1381, 1299, 1246, 1175, 1160, 1108, 1033, 1001, 946, 878, 816, 778, 644, 610; δ_H (400 MHz, CDCl₃) 7.70 (1H, d, J 14.3 Hz, N-CH=CH), 7.10 (2H, d, J 8.8 Hz, Ar C-H), 6.83 (2H, d, J 8.8 Hz, Ar C-H), 5.83 (1H, d, J 14.3 Hz, N-CH=CH), 4.91 (2H, br s, CH₂N), 4.85 (1H, br s, CH_aH_b=C), 4.83 (1H, br s, CH_aH_b=C), 3.72 (3H, s, OCH₃), 2.04 (6H, s, CBr[CH₃]₂), 1.89 (3H, s, CH₂C=C[CH₃]); δ_C (100.6 MHz, CDCl₃) 169.2 (C=O), 158.7 (Ar quat.), 140.4 (olef. quat.), 130.1 (N-CH=CH), 128.9 (Ar quat.), 127.6 (Ar C-H), 115.8 (N-CH=CH), 115.1 (C=CH₂), 114.2 (Ar C-H), 56.9 (CBr[CH₃]₂), 55.2 (OCH₃), 48.6 (CH₂N), 32.6 (CBr[CH₃]₂), 19.2

(CH₂=C[CH₃]); m/z (FAB) 354 (MH)⁺, 352 (MH)⁺, 324, 307, 286, 234, 206, 190, 154, 136, 121; [Found: (MH)⁺, 352.0897, C₁₇H₂₂NO₂⁷⁹Br requires (MH)⁺, 352.0912].

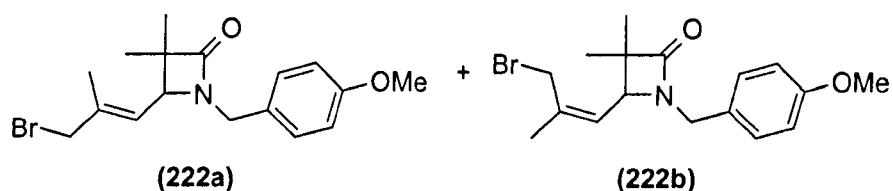
2:1 Mixture of *E*-3,3-Dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (221a) and *Z*-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (221b)



A stirred solution of 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-(3-methyl-buta-1,3-dienyl)-acetamide (**220a**) (850 mg, 2.44 mmol), copper (I) chloride (72.4 mg, 0.731 mmol) and TPA (212 mg, 0.731 mmol) in anhydrous toluene (20.3 ml) was heated to reflux under nitrogen for 15 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate then 2:1 petrol:ethyl acetate) to give an inseparable mixture of 2:1 mixture of *E*-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**221a**) and *Z*-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**221b**) as a pale yellow oil (133 mg, 16%), R_f (2:1 petrol:ethyl acetate) 0.79; ν_{max} (film)/cm⁻¹ 2934, 2838, 1781 (C=O), 1710, 1611, 1586, 1512, 1440, 1392, 1352, 1303, 1246, 1176, 1111, 1032, 923 870, 825, 755, 683, 642; δ_H (400 MHz, CDCl₃) 7.13 (3H, d, J 8.5 Hz, Ar C-H, *E* and *Z*), 6.89 (3H, d, J 8.5 Hz, Ar C-H, *E* and *Z*), 5.40 (1H, br d, J 9.0 Hz, ClCH₂C[CH₃]=CH, *E*), 5.22 (0.5H, br d, J 9.5 Hz, ClCH₂C[CH₃]=CH, *Z*), 4.63 (1H, d, J 14.8 Hz, CH_aH_bN, *E*), 4.60 (0.5H, d, J 14.8 Hz, CH_aH_bN, *Z*), 4.52 (0.5H, d, J 9.6 Hz, CCl₂CHN, *Z*), 4.48 (1H, d, J 9.0 Hz, CCl₂CHN, *E*), 4.06-3.95 (4.5H, m, CH_aH_bN, *E*, CH_aH_bN, *Z*, ClCH₂, *E* and ClCH₂, *Z*), 3.80 (4.5H, s, OCH₃, *E* and *Z*), 1.95 (1.5H, d, J 1.5 Hz, CH₃C[CH₂Cl]=CH, *Z*), 1.70 (3H, d, J 1.5 Hz, CH₃C[CH₂Cl]=CH, *E*); δ_C (100.6 MHz, CDCl₃) 160.7 (C=O, *E* and *Z*), 159.7 (Ar quat., *E*

and Z), 143.0 (olef. quat., Z), 142.8 (olef. quat., E), 129.9 (Ar C-H, E and Z), 125.8 (Ar quat., Z), 125.6 (Ar quat., E), 122.5 (CH₃C[CH₂Cl]=CH, Z), 121.7 (CH₃C[CH₂Cl]=CH, E), 114.5 (Ar C-H, E and Z), 82.7 (CCl₂, Z), 82.6 (CCl₂, E), 66.7 (CCl₂CHN, E), 66.4 (CCl₂CHN, Z), 55.3 (OCH₃, E and Z), 49.9 (CH₂Cl, E and Z), 44.5 (CH₂N, E and Z), 22.3 (CH₃C[CH₂Cl]=CH, Z), 15.0 (CH₃C[CH₂Cl]=CH, E); m/z (FAB) 348 (MH)⁺, 307, 289, 163, 154, 136, 121; [Found: (MH)⁺, 348.0322, C₁₅H₁₆NO₂³⁵Cl₃ requires (MH)⁺, 348.0325].

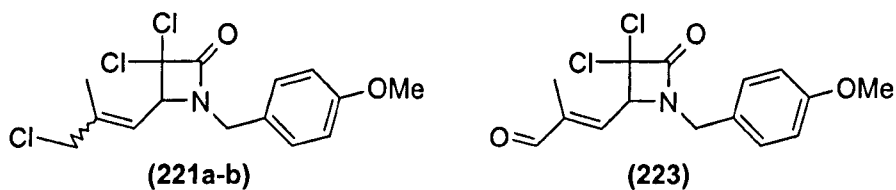
2:1 Mixture of E-4-(3-bromo-2-methyl-propenyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetidin-2-one (222a) and Z-4-(3-bromo-2-methyl-propenyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetidin-2-one (222b)



A stirred solution of 2-bromo-*N*-(4-methoxybenzyl)-2-methyl-*N*-(3-methyl-buta-1,3-dienyl)-propionamide (**220b**) (286 mg, 0.812 mmol), copper (I) bromide (34.9 mg, 0.244 mmol) and TPA (70.7 mg, 0.244 mmol) in anhydrous toluene (6.77 ml) was heated to reflux under nitrogen for 2 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 1:1 petrol:ethyl acetate) to give an inseparable 2:1 mixture of *E*-4-(3-bromo-2-methyl-propenyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetidin-2-one (**222a**) and *Z*-4-(3-bromo-2-methyl-propenyl)-1-(4-methoxybenzyl)-3,3-dimethyl-azetidin-2-one (**222b**) as a pale yellow oil (163 mg, 57%), R_f (1:1 petrol:ethyl acetate) 0.50; ν_{max} (film)/cm⁻¹ 2962, 2924, 2836, 1746 (C=O), 1612, 1513, 1440, 1400, 1304, 1246, 1177, 1111, 1033; δ_H (400 MHz, CDCl₃) 7.13 (3H, d, J 8.5 Hz, Ar C-H, E and Z), 6.86 (3H, d, J 8.5 Hz, Ar C-H, E and Z), 5.46 (1H, d, J 8.3 Hz, BrCH₂C[CH₃]=CH, E), 5.24 (0.5H, dd, J 9.8, 1.5 Hz, BrCH₂C[CH₃]=CH, Z), 4.54 (1.5H, d, J 14.8 Hz, CH_aH_bN, E and Z), 3.92 (1.5H, d, J 14.8

Hz, $\text{CH}_2\text{H}_b\text{N}$, *E* and *Z*), 3.91 (3H, s, BrCH_2 , *E* and *Z*), 3.79 (4.5H, s, OCH_3 , *E* and *Z*), 3.77 (1H, d, J 9.3 Hz, CMe_2CHN , *E*), 3.74 (0.5H, d, J 9.3 Hz, CMe_2CHN , *Z*), 1.88 (1.5H, d, J 1.5 Hz, $\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *Z*), 1.66 (3H, d, J 1.5 Hz, $\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *E*), 1.30 (1.5H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *Z*), 1.28 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *E*), 1.11 (1.5H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *Z*), 1.10 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *E*); δ_c (100.6 MHz, CDCl_3) 173.2 ($\text{C}=\text{O}$, *E* and *Z*), 159.1 (Ar quat., *E* and *Z*), 138.6 (olef. quat., *E* and *Z*), 129.7 (Ar $\text{C}-\text{H}$, *E* and *Z*), 128.0 and 127.9 (Ar quat., *E* and *Z*), 126.8 ($\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *Z*), 126.2 ($\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *E*), 114.1 (Ar $\text{C}-\text{H}$, *E* and *Z*), 59.9 (CMe_2CHN , *E*), 59.7 (CMe_2CHN , *Z*), 55.3 (CMe_2 , *E* and *Z*), 55.2 (OCH_3 , *E* and *Z*), 43.7 (CH_2N , *E* and *Z*), 39.5 (CH_2Br , *E* and *Z*), 22.4, 22.2 and 22.1 ($\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *E*, and $\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *E* and *Z*), 18.0 and 17.9 ($\text{C}[\text{CH}_3][\text{CH}_3]\text{CHN}$, *E* and *Z*), 15.2 ($\text{CH}_3\text{C}[\text{CH}_2\text{Br}]=\text{CH}$, *E*); m/z (FAB) 352 (MH^+), 272, 244, 188, 162, 154, 121; [Found: (MH^+), 352.0903, $\text{C}_{17}\text{H}_{22}\text{NO}_2^{79}\text{Br}$ requires (MH^+), 352.0912]; [Found: C, 58.29; H, 6.32; N, 3.93. $\text{C}_{17}\text{H}_{22}\text{NO}_2\text{Br}$ requires C, 57.96; H, 6.29; N, 3.98].

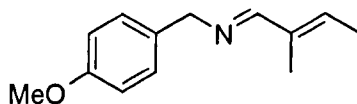
2:1 Mixture of *E*- (221a) and *Z*-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (221b) and *E*-3-[3,3-dichloro-1-(4-methoxybenzyl)-4-oxo-azetidin-2-yl]-2-methyl-propenal (223)



A stirred solution of 2,2,2-trichloro-*N*-(4-methoxybenzyl)-*N*-(3-methyl-buta-1,3-dienyl)-acetamide (**220a**) (339 mg, 0.972 mmol), copper (I) chloride (96.2 mg, 0.972 mmol) and TPA (282 mg, 0.972 mmol) in anhydrous toluene (8.10 ml) was heated to reflux under nitrogen for 15 hours. The reaction mixture was cooled and filtered through a small plug of silica, which was washed well with ethyl acetate. The combined filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 5:1 petrol:ethyl acetate then 2:1 petrol:ethyl acetate) to give an inseparable 2:1 mixture of

E-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**221a**) and *Z*-3,3-dichloro-4-(3-chloro-2-methyl-propenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**221b**) as a pale yellow oil (36.0 mg, 11%), and *E*-3-[3,3-dichloro-1-(4-methoxybenzyl)-4-oxo-azetidin-2-yl]-2-methyl-propenal (**223**) as a yellow oil (24.0 mg, 8%), R_f (3:1 petrol:ethyl acetate) 0.37; ν_{\max} (film)/ cm^{-1} 2927, 2842, 1788 (C=O lactam), 1694, 1611, 1514, 1440, 1391, 1306, 1249, 1179, 1145, 1032, 830; δ_H (400 MHz, CDCl_3) 9.42 (1H, s, CHO), 7.13 (2H, d, J 8.8 Hz, Ar C-H), 6.88 (2H, d, J 8.8 Hz, Ar C-H), 6.10 (1H, dq, J 8.8, 1.2 Hz, C=CHCHN), 4.71 (1H, d, J 8.8 Hz, C=CHCHN), 4.64 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.17 (1H, d, J 14.8 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.80 (3H, s, OCH_3), 1.72 (3H, s, C[CH_3]=CH); δ_C (100.6 MHz, CDCl_3) 193.0 ($\text{C}=\text{O}$ aldehyde), 160.5 ($\text{C}=\text{O}$ lactam), 159.9 (Ar quat.), 145.6 (C[CH_3]=CH), 141.6 (C[CH_3]=CH), 129.9 (Ar C-H), 125.2 (Ar quat.), 114.6 (Ar C-H), 83.1 (CCl_2), 66.7 (CCl_2CHN), 55.4 (OCH_3), 45.1 (CH_2N), 10.0 (C[CH_3]=CH); m/z (FAB) 328 (MH^+), 327 (M^+), 307, 289, 163, 154, 137; [Found: (M^+) 327.0414, $\text{C}_{15}\text{H}_{15}\text{NO}_3^{35}\text{Cl}_2$ requires (M^+) 327.0429].

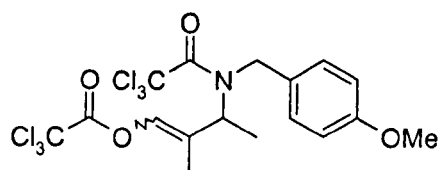
(4-Methoxybenzyl)-(2-methyl-but-2-enylidene)-amine (225)



4-Methoxybenzylamine (2.61 ml, 20.0 mmol) was added dropwise to stirred *trans*-2-methyl-2-butenal (1.94 ml, 20.0 mmol) at 0°C. After 30 minutes, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give (4-methoxybenzyl)-(2-methyl-but-2-enylidene)-amine (**225**) as a pale yellow oil (3.97 g, 98%, >95% purity) which was used without further purification, ν_{\max} (film)/ cm^{-1} 2997, 2913, 2832, 1648 (C=N), 1626, 1610, 1585, 1509, 1441, 1373, 1335, 1300, 1242, 1173, 1104, 1034, 818, 752; δ_H (400 MHz, CDCl_3) 7.84 (1H, s, $\text{CH}=\text{N}$), 7.16 (2H, d, J 8.5 Hz, Ar C-H), 6.81 (2H, d, J 8.5 Hz, Ar C-H), 5.91 (1H, q, J 7.0 Hz, $\text{MeCH}=\text{CMe}$), 4.56 (2H, s, CH_2N), 3.69 (3H, s, OCH_3), 1.86 (3H, s, $\text{MeCH}=\text{C}[\text{CH}_3]$), 1.79 (3H, d, J 7.0 Hz, $\text{CH}_3\text{CH}=\text{CMe}$); δ_C (100.6 MHz, CDCl_3) 166.1 ($\text{CH}=\text{N}$), 158.6 (Ar quat.), 137.0 (olef.

quat.), 136.4 (MeCH=CMe), 132.0 (Ar quat.), 129.0 (Ar C-H), 113.8 (Ar C-H), 64.0 (CH₂N), 55.1 (OCH₃), 14.5 ([CH₃]CH=CMe), 11.4 (MeCH=C[CH₃]); m/z (FAB) 204 (MH)⁺, 154, 136, 121; [Found: (MH)⁺, 204.1386, C₁₃H₁₇NO requires (MH)⁺, 204.1388].

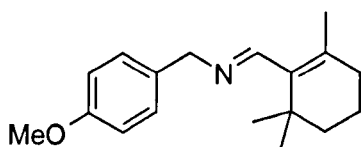
2:1 Mixture of trichloro-acetic acid 3-[(4-methoxybenzyl)-(2,2,2-trichloro-acetyl)-amino]-2-methyl-but-1-enyl ester (227)



Trichloroacetyl chloride (446 μ l, 4.00 mmol) followed by triethylamine (558 μ l, 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-(2-methyl-but-2-enylidene)-amine (**225**) (813 mg, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give a 2:1 mixture of *trichloro-acetic acid 3-[(4-methoxybenzyl)-(2,2,2-trichloro-acetyl)-amino]-2-methyl-but-1-enyl ester (227)* as a pale yellow oil (226 mg, 11%), R_f (9:1 petrol:ethyl acetate) 0.37; ν_{\max} (film)/cm⁻¹ 2991, 2936, 2837, 1764 (C=O, ester), 1686 (C=O, amide), 1663, 1612, 1585, 1512, 1440, 1383, 1305, 1242, 1176, 1112, 1070, 1034, 972, 923, 859, 812, 757, 671; δ_{H} (400 MHz, CDCl₃) 7.21 (1H, d, J 8.8 Hz, Ar C-H, isomer B), 7.20 (2H, d, J 8.5 Hz, Ar C-H, isomer A), 6.84 (1H, d, J 8.8 Hz, Ar C-H, isomer B), 6.83 (2H, d, J 8.5 Hz, Ar C-H, isomer A), 6.46 (1H, br s, C=CH-O, isomer A), 6.38 (0.5H, br s, C=CH-O, isomer B), 5.41 (1H, q, J 6.5 Hz, NCHCH₃, isomers A and B), 4.82-4.50 (3.5H, m, CH₂N, isomers A and B, and NCHCH₃, isomer B), 3.78 (4.5H, s, OCH₃, isomers A and B), 1.68 (1.5H, d, J 1.2 Hz, CH₃C=CHO isomer B), 1.60 (3H, d, J 1.2 Hz, CH₃C=CHO, isomer A), 1.57 (1.5H, d, J 6.5 Hz, CH₃CHN, isomer B), 1.46 (3H, d, J 6.5 Hz, CH₃CHN, isomer A); δ_{C} (100.6 MHz, CDCl₃) 160.7, 160.2 and 159.5 (C=O

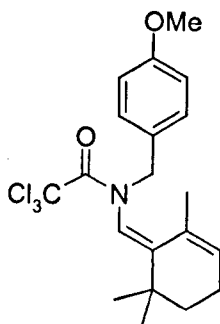
amide, $\underline{\text{C}}=\text{O}$ ester and Ar quat., isomers A and B), 141.0 and 138.0 (olef. quat., isomers A and B), 130.3 (Ar $\underline{\text{C}}\text{-H}$, isomers A and B), 127.4 (Ar quat., isomers A and B), 126.8 ($\text{C}=\underline{\text{C}}\text{HO}$, isomer A), 125.6 ($\text{C}=\underline{\text{C}}\text{HO}$, isomer B), 114.1 (Ar $\underline{\text{C}}\text{-H}$, isomers A and B), 93.1 and 90.4 ($\text{NCO}\underline{\text{C}}\text{Cl}_3$ and $\text{OCO}\underline{\text{C}}\text{Cl}_3$, isomers A and B), 77.7 ($\text{N}\text{-}\underline{\text{C}}\text{H}$, isomer A), 59.4 ($\text{N}\text{-}\underline{\text{C}}\text{H}$, isomer B), 55.2 ($\text{O}\underline{\text{C}}\text{H}_3$, isomers A and B), 55.0 ($\underline{\text{C}}\text{H}_2\text{N}$, isomers A and B), 23.3 ($\underline{\text{C}}\text{H}_3\text{CHN}$, isomer B), 18.3 ($\underline{\text{C}}\text{H}_3\text{CHN}$, isomer A), 13.0 ($\underline{\text{C}}\text{H}_3\text{C}=\text{CHO}$, isomer A), 12.8 ($\underline{\text{C}}\text{H}_3\text{C}=\text{CHO}$, isomer B); m/z (FAB) 512 (MH)⁺, 391, 365, 348, 307, 289, 256, 220, 154, 121; [Found: (MH)⁺, 511.9319, $\text{C}_{17}\text{H}_{17}\text{NO}_4^{35}\text{Cl}_5^{37}\text{Cl}$ requires (MH)⁺, 511.9338].

(4-Methoxybenzyl)-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-amine (231)



4-Methoxybenzylamine (2.61 ml, 20.0 mmol) was added dropwise to stirred β -cyclocitral (3.04 g, 20.0 mmol) and the mixture was heated to 50°C. After 2 hours, the mixture was dissolved in diethyl ether (100 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give *(4-methoxybenzyl)-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-amine (231)* as a pale yellow oil (5.21 g, 96%, >90% purity) which was used without further purification, ν_{max} (film)/ cm^{-1} 2927, 2864, 1625 ($\text{C}=\text{N}$), 1584, 1510, 1457, 1373, 1300, 1244, 1172, 1108, 1035, 814, 754; δ_{H} (400 MHz, CDCl_3) 8.27 (1H, s, $\underline{\text{C}}\text{H}=\text{N}$), 7.19 (2H, d, J 8.6 Hz, Ar $\underline{\text{C}}\text{-H}$), 6.83 (2H, d, J 8.6 Hz, Ar $\underline{\text{C}}\text{-H}$), 4.59 (2H, s, $\underline{\text{C}}\text{H}_2\text{N}$), 3.71 (3H, s, $\text{O}\underline{\text{C}}\text{H}_3$), 2.03 (2H, t, J 6.3 Hz, $\underline{\text{C}}\text{H}_2$), 1.79 (3H, s, $\text{C}=\underline{\text{C}}[\underline{\text{C}}\text{H}_3]\text{CH}_2$), 1.64-1.56 (2H, m, $\underline{\text{C}}\text{H}_2$), 1.47-1.42 (2H, m, $\underline{\text{C}}\text{H}_2$), 1.20 (6H, s, $\text{C}[\underline{\text{C}}\text{H}_3]_2$); δ_{C} (100.6 MHz, CDCl_3) 161.8 ($\underline{\text{C}}\text{H}=\text{N}$), 158.5 (Ar quat.), 138.7 and 138.7 (olef. quat.), 132.4 (Ar quat.), 128.9 (Ar $\underline{\text{C}}\text{-H}$), 113.8 (Ar $\underline{\text{C}}\text{-H}$), 65.6 ($\underline{\text{C}}\text{H}_2\text{N}$), 64.4 ($\text{C}[\underline{\text{C}}\text{H}_3][\underline{\text{C}}\text{H}_3]$), 55.1 ($\text{O}\underline{\text{C}}\text{H}_3$), 40.5 ($\underline{\text{C}}\text{H}_2$), 34.0 ($\underline{\text{C}}\text{H}_2$), 28.6 ($\text{C}[\underline{\text{C}}\text{H}_3]_2$), 20.4 ($\text{C}=\underline{\text{C}}[\underline{\text{C}}\text{H}_3]\text{CH}_2$), 19.0 ($\underline{\text{C}}\text{H}_2$); m/z (FAB) 272 (MH)⁺, 150, 121; [Found: (MH)⁺, 272.2019, $\text{C}_{18}\text{H}_{25}\text{NO}$ requires (MH)⁺, 272.2014].

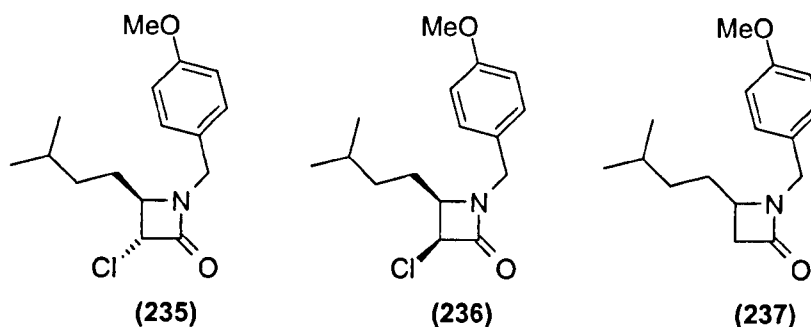
2,2,2-Trichloro-N-(4-methoxybenzyl)-N-(2,6,6-trimethyl-cyclohex-2-enylidene)methyl)-acetamide (232)



Trichloroacetyl chloride (446 μ l, 4.00 mmol) followed by triethylamine (558 μ l, 4.00 mmol) was added dropwise to a stirred solution of (4-methoxybenzyl)-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-amine (**231**) (1.09 g, 4.00 mmol) in anhydrous DCM (20 ml) at 0°C under nitrogen. After stirring at 0°C for 3 hours, the reaction mixture was partitioned between DCM (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂; 9:1 petrol:ethyl acetate) to give 2,2,2-trichloro-N-(4-methoxybenzyl)-N-(2,6,6-trimethyl-cyclohex-2-enylidene)methyl)-acetamide (**232**) as a colourless oil (1.26 g, 76%), R_f (9:1 petrol:ethyl acetate) 0.40; ν_{\max} (film)/cm⁻¹ 3010, 2953, 2922, 2837, 1680 (C=O), 1612, 1510, 1460, 1437, 1377, 1314, 1301, 1247, 1172, 1154, 1107, 1084, 1031, 926, 857, 811, 803, 780, 758, 686, 661; δ_{H} (400 MHz, CDCl₃) 7.19 (2H, d, J 8.5 Hz, Ar C-H), 6.83 (2H, d, J 8.5 Hz, Ar C-H), 6.27 (1H, s, N-CH=C), 5.74 (1H, br s, C=CHCH₂), 5.70-5.00 (1H, br, CH_aH_bN), 4.40-3.60 (1H, br, CH_aH_bN), 3.78 (3H, s, OCH₃), 2.25-2.15 (2H, m, C=CHCH₂), 1.99 (3H, s, CH=C[CH₃]), 1.48 (2H, t, J 6.3 Hz, C=CHCH₂CH₂), 1.03 (6H, s, C[CH₃]₂); δ_{C} (100.6 MHz, CDCl₃) 159.3 (C=O), 159.2 (Ar quat.), 143.1 (olef. quat.), 131.9 (C=CHCH₂), 129.9 (Ar C-H), 129.3 (olef. quat.), 128.3 (Ar quat.), 120.5 (N-CH=C), 113.8 (Ar C-H), 93.0 (CCl₃), 55.9 (C[CH₃]₂), 55.2 (OCH₃), 40.5 (CH₂N), 36.6 (CH₂CH₂CH=C), 27.8 (C[CH₃]₂), 23.8 (CH₂CH₂CH=C), 21.2 (CH=C[CH₃]); m/z (FAB) 416 (MH)⁺, 346, 121; [Found: (M-H)⁺, 414.0784, C₂₀H₂₄NO₂³⁵Cl₃ requires (M-H)⁺, 414.0794].

414.0794], and 3,3-dichloro-1-(4-methoxybenzyl)-4-(2,6,6-trimethyl-cyclohexa-1,3-dienyl)-azetidin-2-one (**234**) as a pale yellow oil (53.0 mg, 13%), R_f (5:1 petrol:ethyl acetate) 0.45; ν_{\max} (film)/ cm^{-1} 3037, 2925, 2856, 1785 (C=O), 1612, 1513, 1462, 1362, 1304, 1249, 1176, 1150, 1111, 1033, 871, 822, 658; δ_H (400 MHz, CDCl_3) 7.15 (2H, d, J 8.5 Hz, Ar C-H), 6.88 (2H, d, J 8.5 Hz, Ar C-H), 5.83 (1H, ddd, J 9.5, 5.5, 3.0 Hz, $\text{CH}_2\text{CH}=\text{CH}$), 5.75 (1H, dd, J 9.5, 3.0 Hz, $\text{CH}_2\text{CH}=\text{CH}$), 4.90 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.36 (1H, s, CCl_2CHN), 3.81 (3H, s, OCH_3), 3.65 (1H, d, J 14.6 Hz, $\text{CH}_a\text{H}_b\text{N}$), 2.20 (1H, dt, J 17.2, 3.0 Hz, $\text{CH}_a\text{H}_b\text{CH}=\text{CH}$), 1.93 (1H, dd, J 17.2, 5.5 Hz, $\text{CH}_a\text{H}_b\text{CH}=\text{CH}$), 1.86 (3H, s, $\text{C}=\text{C}[\text{CH}_3]$), 1.00 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$), 0.71 (3H, s, $\text{C}[\text{CH}_3][\text{CH}_3]$); δ_C (125.8 MHz, CDCl_3) 161.3 (C=O), 159.7 (Ar quat.), 132.5 (olef. quat.), 130.6 and 130.4 (Ar C-H and $\text{CH}_2\text{CH}=\text{CH}$), 128.5 (olef. quat.), 126.8 ($\text{CH}_2\text{CH}=\text{CH}$), 125.4 (Ar quat.), 114.5 (Ar C-H), 85.1 (CCl_2), 69.3 (CCl_2CHN), 55.3 (OCH_3), 45.0 (CH_2N), 39.2 ($\text{CH}_2\text{CH}=\text{CH}$), 33.7 (CMe_2), 27.0 and 24.8 ($\text{C}[\text{CH}_3][\text{CH}_3]$), 18.7 ($\text{C}=\text{C}[\text{CH}_3]$); m/z (FAB) 380 (MH)⁺, 344, 307, 289, 154, 121; [Found: (M-H)⁺, 378.1024, $\text{C}_{20}\text{H}_{23}\text{NO}_2^{35}\text{Cl}_2$ requires (M-H)⁺, 378.1028].

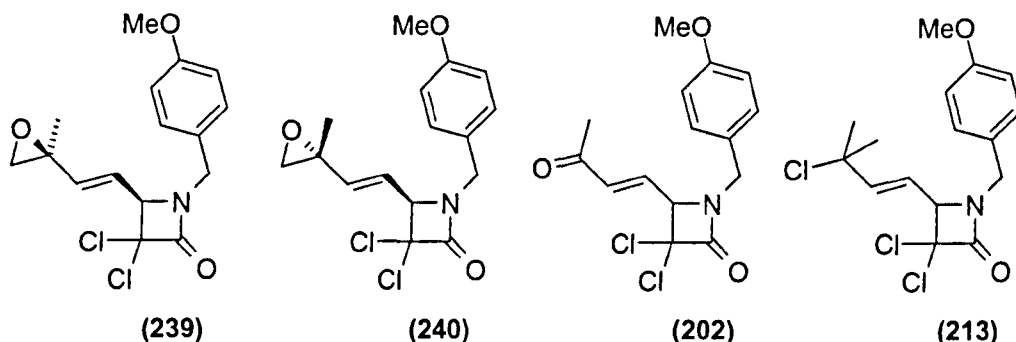
(3R*,4R*) 3-chloro-1-(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one (235),
(3S*,4R*) 3-chloro-1-(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one (236) and 1-
(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one (237)



A suspension of 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-methyl-buta-1,3-dienyl)-azetidin-2-one (**211**) (140 mg, 0.429 mmol), sodium acetate (106 mg, 1.29 mmol) and 10 wt% palladium on carbon (cat.) in ethanol (20 ml) and ethyl acetate (50 ml) was stirred at room temperature under hydrogen for 4 days. The reaction mixture, which contained undissolved starting material, was filtered through a pad of celite which was washed well with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by preparative thin layer chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give **(3R*,4R*) 3-chloro-1-(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one (235)** as a pale yellow oil (33.0 mg, 26%), R_f (3:1 petrol:ethyl acetate) 0.46; ν_{\max} (film)/cm⁻¹ 2953, 2868, 1760, 1612, 1585, 1513, 1462, 1400, 1303, 1246, 1176, 1112, 1034, 921, 830, 755, 655; δ_{H} (400 MHz, CDCl₃) 7.17 (2H, d, J 8.8 Hz, Ar C-H), 6.88 (2H, d, J 8.8 Hz, Ar C-H), 4.85 (1H, d, J 4.8 Hz, CHCl), 4.59 (1H, d, J 15.1 Hz, CH_aH_bN), 4.09 (1H, d, J 15.1 Hz, CH_aH_bN), 3.81 (3H, s, OCH₃), 3.63-3.58 (1H, m, CHN), 1.70-1.59 (2H, m, CH₂CHN), 1.50 (1H, qq, J 6.5, 6.5 Hz, CH[CH₃]₂), 1.28-1.17 (1H, m, CH_aH_bCH₂CHN), 1.13-1.04 (1H, m, CH_aH_bCH₂CHN), 0.86 (3H, d, J 6.5 Hz, CH[CH₃][CH₃]), 0.84 (3H, d, J 6.5 Hz, CH[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 164.0 (C=O), 159.4 (Ar quat.), 129.5 (Ar C-H), 127.1 (Ar quat.), 114.3 (Ar C-H), 59.6 (CHCl), 57.1 (CHN), 55.3 (OCH₃), 44.5 (CH₂N), 34.7 (CH₂CH₂CHN), 28.1 (CH[CH₃]₂), 26.9 (CH₂CHN), 22.4 and 22.3 (CH[CH₃][CH₃]); m/z (FAB) 298 (MH)⁺, 296 (MH)⁺, 260, 188, 163, 136, 121; [Found: (MH)⁺ 296.1422, C₁₆H₂₂NO₂³⁵Cl requires (MH)⁺, 296.1417], **(3S*,4R*) 3-chloro-1-(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one (236)** as a pale yellow oil (15.0 mg, 12%), R_f (3:1

petrol:ethyl acetate) 0.54; ν_{\max} (film)/ cm^{-1} 2954, 2868, 1762, 1612, 1586, 1513, 1462, 1398, 1303, 1246, 1175, 1108, 1034, 921, 830, 757, 619; δ_{H} (400 MHz, CDCl_3) 7.18 (2H, d, J 8.5 Hz, Ar C-H), 6.89 (2H, d, J 8.5 Hz, Ar C-H), 4.63 (1H, d, J 15.1 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.34 (1H, d, J 1.8 Hz, CHCl), 4.07 (1H, d, J 15.1 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.81 (3H, s, OCH_3), 3.45 (1H, ddd, J 8.8, 4.3, 1.8 Hz, CHN), 1.76-1.66 (1H, m, $\text{CH}_a\text{H}_b\text{CHN}$), 1.49 (1H, qq, J 6.5, 6.5 Hz, $\text{CH}[\text{CH}_3]_2$), 1.43-1.34 (1H, m, $\text{CH}_a\text{H}_b\text{CHN}$), 1.21-1.12 (2H, m, $\text{CH}_2\text{CH}_2\text{CHN}$), 0.85 (3H, d, J 6.5 Hz, $\text{CH}[\text{CH}_3][\text{CH}_3]$), 0.84 (3H, d, J 6.5 Hz, $\text{CH}[\text{CH}_3][\text{CH}_3]$); δ_{C} (100.6 MHz, CDCl_3) 163.4 ($\text{C}=\text{O}$), 159.4 (Ar quat.), 129.5 (Ar C-H), 126.9 (Ar quat.), 114.3 (Ar C-H), 63.4 (CHN), 59.6 (CHCl), 55.3 (OCH_3), 44.4 (CH_2N), 33.9 (CH_2CHN), 29.2 ($\text{CH}_2\text{CH}_2\text{CHN}$), 27.8 ($\text{CH}[\text{CH}_3]_2$), 22.4 and 22.3 ($\text{CH}[\text{CH}_3][\text{CH}_3]$); m/z (FAB) 298 (MH)⁺, 296 (MH)⁺, 188, 154, 136, 121; [Found: (MH)⁺ 296.1408, $\text{C}_{16}\text{H}_{22}\text{NO}_2^{35}\text{Cl}$ requires (MH)⁺, 296.1417], and *1-(4-methoxybenzyl)-4-(3-methyl-butyl)-azetidin-2-one* (**237**) as a pale yellow oil (8.0 mg, 7%), R_f (3:1 petrol:ethyl acetate) 0.25 ν_{\max} (film)/ cm^{-1} 2954, 2869, 1744, 1663, 1612, 1513, 1463, 1398, 1247, 1178, 1035; δ_{H} (400 MHz, CDCl_3) 7.18 (2H, d, J 8.6 Hz, Ar C-H), 6.87 (2H, d, J 8.6 Hz, Ar C-H), 4.55 (1H, d, J 15.0 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.05 (1H, d, J 15.0 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.80 (3H, s, OCH_3), 3.44-3.38 (1H, m, CHN), 2.97 (1H, dd, J 14.5, 5.0 Hz, $\text{CH}_a\text{H}_b\text{CO}$), 2.54 (1H, dd, J 14.5, 2.0 Hz, $\text{CH}_a\text{H}_b\text{CO}$), 1.73-1.59 (1H, m, $\text{CH}_a\text{H}_b\text{CHN}$), 1.46 (1H, qq, J 6.8, 6.8 Hz, $\text{CH}[\text{CH}_3]_2$), 1.39-1.28 (1H, m, $\text{CH}_a\text{H}_b\text{CHN}$), 1.19-1.05 (2H, m, $\text{CH}_2\text{CH}_2\text{CHN}$), 0.83 (6H, d, J 6.8 Hz, $\text{CH}[\text{CH}_3][\text{CH}_3]$); δ_{C} (100.6 MHz, CDCl_3) 167.2 ($\text{C}=\text{O}$), 159.1 (Ar quat.), 129.5 (Ar C-H), 128.3 (Ar quat.), 114.1 (Ar C-H), 55.3 (OCH_3), 51.4 (CHN), 44.1 (CH_2N), 42.2 (CH_2CO), 34.3 ($\text{CH}_2\text{CH}_2\text{CHN}$), 30.6 (CH_2CHN), 27.9 ($\text{CH}[\text{CH}_3]_2$), 22.5 and 22.4 ($\text{CH}[\text{CH}_3][\text{CH}_3]$); m/z (FAB) 262 (MH)⁺, 218, 190, 136, 121, 112; [Found: (MH)⁺ 262.1802, $\text{C}_{16}\text{H}_{23}\text{NO}_2$ requires (MH)⁺, 262.1807].

3,3-Dichloro-1-(4-methoxybenzyl)-4-[2-(2-methyl-oxiranyl)-vinyl]-azetidin-2-one, isomers (239) and (240), 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-oxo-but-1-enyl)-azetidin-2-one (202) and 3,3-dichloro-4-(3-chloro-3-methyl-but-1-enyl)-1-(4-methoxybenzyl)-azetidin-2-one (213)

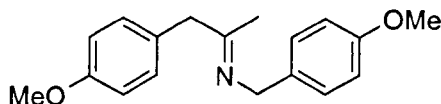


Meta-chloroperoxybenzoic acid (111 mg, 77%, ~0.497 mmol) was added in small portions to a stirred mixture of 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-methyl-buta-1,3-dienyl)-azetidin-2-one (**211**) (162 mg, 0.497 mmol), DCM (5 ml) and 0.5M aqueous NaHCO₃ solution (1.5 ml) at room temperature. After 2 hours, the reaction mixture was partitioned between DCM (50 ml) and 1M NaOH (50 ml), the layers were separated and the aqueous layer was extracted with DCM (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give stereochemically unassigned isomers (**239**) and (**240**) of 3,3-dichloro-1-(4-methoxybenzyl)-4-[2-(2-methyl-oxiranyl)-vinyl]-azetidin-2-one as colourless oils (33.7 mg, 20%, each isomer); isomer A, R_f (3:1 petrol:ethyl acetate) 0.32; ν_{\max} (film)/cm⁻¹ 2924, 2852, 1787, 1612, 1513, 1461, 1394, 1249, 1179, 1033, 974, 849, 686; δ_{H} (400 MHz, CDCl₃) 7.14 (2H, d, J 8.8 Hz, Ar C-H), 6.88 (2H, d, J 8.8 Hz, Ar C-H), 5.61 (1H, d, J 15.6 Hz, CH=CHCHN), 5.55 (1H, dd, J 15.6, 8.0 Hz, CH=CHCHN), 4.54 (1H, d, J 15.0 Hz, CH_aH_bN), 4.24 (1H, d, J 8.0 Hz, CHN), 4.12 (1H, d, J 15.0 Hz, CH_aH_bN), 3.81 (3H, s, OCH₃), 2.85 (1H, d, J 5.0 Hz, CH_aH_bO), 2.70 (1H, d, J 5.0 Hz, CH_aH_bO), 1.42 (3H, s, CH₃); δ_{C} (100.6 MHz, CDCl₃) 160.7 (C=O), 159.7 (Ar quat.), 142.0 (CH=CHCHN), 130.0 (Ar C-H), 125.8 (Ar quat.), 125.2 (CH=CHCHN), 114.5 (Ar C-H), 84.2 (CCl₂), 71.3 (CHN), 55.7 (OCH₃), 54.9 (CH₂O), 52.8 (CH₃-C-O), 44.7 (CH₂N), 18.7 (CH₃); m/z

(FAB) 344 (MH)⁺, 342 (MH)⁺, 329, 307, 289, 176, 154, 136; isomer B, R_f (3:1 petrol:ethyl acetate) 0.31; ν_{\max} (film)/cm⁻¹ 2925, 2850, 1787, 1612, 1514, 1461, 1394, 1302, 1249, 1179, 1032, 973, 844, 685; δ_{H} (400 MHz, CDCl₃) 7.13 (2H, d, J 8.5 Hz, Ar C-H), 6.88 (2H, d, J 8.5 Hz, Ar C-H), 5.65 (1H, d, J 15.6 Hz, CH=CHCHN), 5.59 (1H, dd, J 15.6, 7.8 Hz, CH=CHCHN), 4.62 (1H, d, J 14.8 Hz, CH_aH_bN), 4.22 (1H, d, J 7.8 Hz, CHN), 4.06 (1H, d, J 14.8 Hz, CH_aH_bN), 3.81 (3H, s, OCH₃), 2.85 (1H, d, J 5.3 Hz, CH_aH_bO), 2.71 (1H, d, J 5.3 Hz, CH_aH_bO), 1.44 (3H, s, CH₃); δ_{C} (100.6 MHz, CDCl₃) 160.6 (C=O), 159.7 (Ar quat.), 141.4 (CH=CHCHN), 130.0 (Ar C-H), 125.7 (Ar quat.), 124.7 (CH=CHCHN), 114.4 (Ar C-H), 84.3 (CCl₂), 70.9 (CHN), 56.0 (OCH₃), 54.9 (CH₂O), 52.7 (CH₃-C-O), 43.7 (CH₂N), 18.8 (CH₃); m/z (FAB) 344 (MH)⁺, 342 (MH)⁺, 307, 289, 154, 136, 121, 3,3-dichloro-1-(4-methoxybenzyl)-4-(3-oxo-but-1-enyl)-azetidin-2-one (**202**) as a pale yellow oil (23.0 mg, 14%), and 3,3-dichloro-4-(3-chloro-3-methyl-but-1-enyl)-1-(4-methoxybenzyl)-azetidin-2-one (**213**) as a pale yellow oil (21.0 mg, 12%), R_f (5:1 petrol:ethyl acetate) 0.38; ν_{\max} (film)/cm⁻¹ 2926, 2844, 1786, 1611, 1514, 1460, 1393, 1363, 1303, 1248, 1177, 1111, 1033, 972, 835, 686; δ_{H} (400 MHz, CDCl₃) 7.15 (2H, d, J 8.8 Hz, Ar C-H), 6.88 (2H, d, J 8.8 Hz, Ar C-H), 6.01 (1H, d, J 15.6 Hz, CH=CHCHN), 5.45 (1H, dd, J 15.6, 8.8 Hz, CH=CHCHN), 4.54 (1H, d, J 14.8 Hz, CH_aH_bN), 4.22 (1H, d, J 8.8 Hz, CHN), 4.14 (1H, d, J 14.8 Hz, CH_aH_bN), 3.81 (3H, s, OCH₃), 1.66 (3H, s, ClC[CH₃][CH₃]), 1.65 (3H, s, ClC[CH₃][CH₃]); δ_{C} (100.6 MHz, CDCl₃) 160.6 (C=O), 159.7 (Ar quat.), 146.3 (CH=CHCHN), 130.5 (Ar C-H), 126.1 (Ar quat.), 121.1 (CH=CHCHN), 114.9 (Ar C-H), 83.4 (CCl₂), 71.4 (CHN), 66.7 (C[CH₃]₂), 55.7 (OCH₃), 45.1 (CH₂N), 32.5 and 31.8 (C[CH₃][CH₃]); m/z (FAB) 364 (MH)⁺, 362 (MH)⁺, 326, 289, 163, 136, 121; [Found: (MH)⁺ 364.0454, C₁₆H₁₈NO₂³⁵Cl₂³⁷Cl requires (MH)⁺, 364.0452].

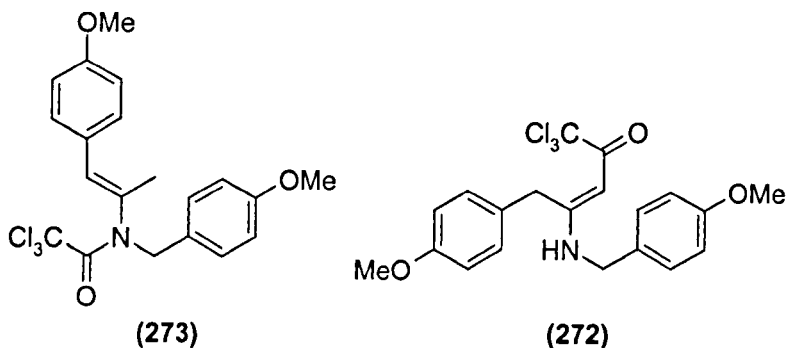
6.4 Experimental for Chapter 4

(4-Methoxybenzyl)-[2-(4-methoxyphenyl)-1-methyl-ethylene]-amine (271)



A stirred solution of 4-methoxyphenylacetone (9.23 ml, 60.0 mmol) and 4-methoxybenzylamine (7.79 ml, 60.0 mmol) in toluene (100 ml) was heated to reflux in a Dean-Stark apparatus for 27 hours. The reaction mixture was concentrated *in vacuo* to give *(4-methoxybenzyl)-[2-(4-methoxyphenyl)-1-methyl-ethylene]-amine (271)* as a brown oil (17.0 g, 100%, >80% purity), which was used without further purification, ν_{\max} (film)/ cm^{-1} 2932, 2833, 1709, 1651 (C=N), 1606, 1508, 1459, 1373, 1300, 1240, 1172, 1107, 1029, 814; δ_{H} (300 MHz, CDCl_3) 7.24 (2H, d, J 8.6 Hz, Ar C-H), 7.16 (2H, d, J 8.6 Hz, Ar C-H), 6.86 (2H, d, J 8.6 Hz, Ar C-H), 6.82 (2H, d, J 8.6 Hz, Ar C-H), 4.41 (2H, s, CH_2N), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.54 (2H, s, $\text{ArCH}_2\text{C}=\text{N}$), 1.77 (3H, s, $\text{N}=\text{C}-\text{CH}_3$); δ_{C} (75.5 MHz, CDCl_3) 170.1 ($\text{C}=\text{N}$), 158.8, 158.7, 133.8 and 130.1 (4 x Ar quat.), 131.5, 129.3, 114.6 and 114.4 (4 x Ar C-H), 55.6 (2 x OCH_3), 55.2 (CH_2N), 49.2 ($\text{ArCH}_2\text{C}=\text{N}$), 17.3 ($\text{N}=\text{C}-\text{CH}_3$); m/z (EI) 284 (MH)⁺, 256, 239, 203, 162, 135, 121, 78.

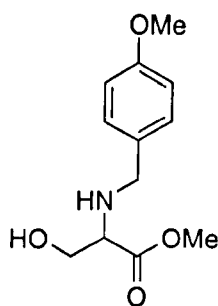
2,2-Dichloro-N-(4-methoxybenzyl)-N-[2-(4-methoxyphenyl)-1-methyl-vinyl]-acetamide (273) and 1,1,1-trichloro-4-(4-methoxybenzylamino)-5-(4-methoxyphenyl)-pent-3-en-2-one (272)



Trichloroacetyl chloride (6.70 ml, 60.0 mmol), followed by *N,N*-diethylaniline (9.55 ml, 60.0 mmol), were added dropwise over 10 minutes to a stirred solution of (4-methoxybenzyl)-[2-(4-methoxyphenyl)-1-methyl-ethylene]-amine (**271**) (17.0 g, 60.0 mmol) in anhydrous toluene (330 ml) at 0°C. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (100ml), 1M HCl (100 ml) and brine (100 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) to give 2,2-dichloro-*N*-(4-methoxybenzyl)-*N*-[2-(4-methoxyphenyl)-1-methyl-vinyl]-acetamide (**273**) as a yellow oil (4.96 g, 19%), R_f (3:1 petrol:ethyl acetate) 0.44; ν_{\max} (film)/cm⁻¹ 2934, 2835, 1669 (C=O), 1606, 1509, 1460, 1439, 1389, 1298, 1243, 1173, 1110, 1030, 903, 810, 784, 663; δ_{H} (300 MHz, CDCl₃) 7.31 (2H, d, J 8.7 Hz, Ar C-H), 7.06 (2H, d, J 8.7 Hz, Ar C-H), 6.86 (4H, d, J 8.7 Hz, Ar C-H), 6.15 (1H, br, C=C-H), 5.25-5.05 (1H, br, CH_aH_bN), 4.30-4.05 (1H, br, CH_aH_bN), 3.80 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 2.20-2.00 (3H, br, C=C-CH₃); δ_{C} (75.5 MHz, CDCl₃) 159.8 and 159.5 (Ar quat.), 134.2 (CH=C-N), 131.2 and 130.3 (Ar C-H), 128.4 and 127.9 (Ar quat.), 114.3 and 114.2 (Ar C-H), 93.8 (CCl₃), 55.7 (2 x OCH₃), 52.8 (CH₂N), 18.6 (C=C-CH₃), C=O and C=C-N signals not visible or coincident with Ar quat.; *m/z* (EI) 427 (M)⁺, 391, 355, 310, 284, 266, 231, 195, 135, 121, 91, 77; [Found: (M)⁺, 427.0505, C₂₀H₂₀NO₃³⁵Cl₃ requires (M)⁺, 427.0509], and 1,1,1-trichloro-4-(4-methoxybenzylamino)-5-(4-methoxyphenyl)-pent-3-en-2-one (**272**) as an orange oil (13.5 g, 53%), R_f (3:1 petrol:ethyl acetate) 0.26;

ν_{\max} (film)/ cm^{-1} 2933, 2834, 1721, 1607, 1569, 1506, 1458, 1368, 1300, 1243, 1172, 1106, 1029, 808, 738, 669, 637; δ_{H} (300 MHz, CDCl_3) 10.81 (1H, br t, NH), 7.14 (2H, d, J 8.7 Hz, Ar C-H), 7.09 (2H, d, J 8.7 Hz, Ar C-H), 6.88 (2H, d, J 8.7 Hz, Ar C-H), 6.84 (2H, d, J 8.7 Hz, Ar C-H), 5.76 (1H, s, C=CHCO), 4.36 (2H, d, J 5.9 Hz, CH_2N), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.67 (2H, s, $\text{ArCH}_2\text{C}=\text{C}$); δ_{C} (75.5 MHz, CDCl_3) 181.1 ($\text{C}=\text{O}$), 170.3 (NH-C=CH), 159.8 and 159.2 (Ar quat.), 130.0 and 129.1 (Ar C-H), 128.5 and 126.9 (Ar quat.), 114.9 and 114.8 (Ar C-H), 97.6 (CCl_3), 88.0 (C=CHCO), 55.7 (2 x OCH_3), 47.5 (CH_2N), 39.0 ($\text{ArCH}_2\text{C}=\text{C}$); m/z (EI) 427 (M)⁺, 393, 364, 310, 190, 121, 91, 77; [Found: (M)⁺, 427.0505, $\text{C}_{20}\text{H}_{20}\text{NO}_3^{35}\text{Cl}_3$ requires (M)⁺, 427.0509].

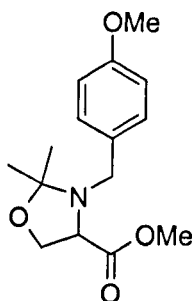
*3-Hydroxy-2-(4-methoxybenzylamino)-propionic acid methyl ester (280)*¹⁴⁹



Triethylamine (7.25 ml, 52.1 mmol), *p*-anisaldehyde (6.15 ml, 50.6 mmol), and anhydrous magnesium sulfate (5.00 g) were added to a stirred solution of D,L-serine methyl ester hydrochloride (7.87 g, 50.4 mmol) in anhydrous DCM (50 ml). After 24 hours, the mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was dissolved in anhydrous methanol (100 ml). The solution was cooled to 0°C and was then treated portionwise with sodium borohydride (1.90 g, 50.2 mmol). After 4 hours, water (50 ml) and ethyl acetate (50 ml) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 50 ml), and the combined organic extracts were washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give *3-hydroxy-2-(4-methoxybenzylamino)-propionic acid methyl ester (280)* as a colourless oil (11.7 g, 97%), R_f (ethyl acetate) 0.27; ν_{\max} (film)/ cm^{-1} 3324 (br, OH and NH), 2951, 2838, 1735 (C=O), 1612, 1585, 1513, 1460,

1300, 1246, 1177, 1141, 1034, 822; δ_{H} (300 MHz, CDCl_3) 7.24 (2H, d, J 8.6 Hz, Ar C-H), 6.86 (2H, d, J 8.6 Hz, Ar C-H), 3.80 (1H, d, J 12.9 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.81-3.75 (1H, m, $\text{CH}_a\text{H}_b\text{O}$), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.68 (1H, d, J 12.9 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.67-3.58 (1H, m, $\text{CH}_a\text{H}_b\text{O}$), 3.43 (1H, dd, J 6.0, 4.5 Hz, OCH_2CHN), 2.90-2.50 (2H, br, OH and NH); δ_{C} (75.5 MHz, CDCl_3) 173.7 ($\text{C}=\text{O}$), 159.3 and 131.5 (Ar quat.), 130.0 and 114.3 (Ar C-H), 62.8 (CH_2O), 62.0 (OCH_2CHN), 55.7 (OCH_3), 52.6 (OCH_3), 51.8 (CH_2N); m/z (EI) 238 (M-H)⁺, 208, 180, 136, 121, 109, 91, 78; [Found: (M-H)⁺ 238.1076, $\text{C}_{12}\text{H}_{17}\text{NO}_4$ requires (M-H)⁺ 238.1079].

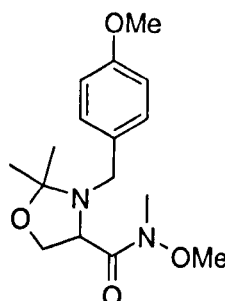
3-(4-Methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methyl ester (281)²⁰⁷



2,2-Dimethoxypropane (7.51 ml, 61.0 mmol) and *p*-toluenesulfonic acid monohydrate (154 mg, 0.812 mmol) were added to a solution of 3-hydroxy-2-(4-methoxybenzylamino)-propionic acid methyl ester (**280**) (4.87 g, 20.3 mmol) in anhydrous toluene (100 ml) and the solution was heated to reflux for 24 hours. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (SiO_2 , 3:1:0.2, petrol:ethyl acetate:triethylamine) to give 3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methyl ester (**281**) as a pale yellow oil (4.86 g, 86%), R_f (1:1 petrol:ethyl acetate) 0.49; ν_{max} (film)/ cm^{-1} 2977, 2947, 2889, 2836, 1735 ($\text{C}=\text{O}$), 1611, 1586, 1511, 1438, 1380, 1362, 1242, 1172, 1105, 1033, 937, 827; δ_{H} (300 MHz, CDCl_3) 7.26 (2H, d, J 8.6 Hz, Ar C-H), 6.82 (2H, d, J 8.6 Hz, Ar C-H), 4.10 (1H, dd, J 8.1, 8.1 Hz, $\text{CH}_a\text{H}_b\text{O}$), 3.95 (1H, dd, 8.1, 5.5 Hz, $\text{CH}_a\text{H}_b\text{O}$), 3.89 (1H, d, J 13.2 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.78 (3H, s, ArOCH_3), 3.63 (1H, d, J 13.2 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.61 (1H, dd, J 8.1, 5.5 Hz, OCH_2CHN), 3.44 (3H, s, $[\text{CO}]\text{OCH}_3$), 1.37 (3H, s, $\text{OC}[\text{CH}_3][\text{CH}_3]\text{N}$), 1.28 (3H,

s, OC[CH₃][CH₃N]; δ_C (75.5 MHz, CDCl₃) 173.4 (C=O), 159.1 and 131.3 (Ar quat.), 130.3 and 113.8 (Ar C-H), 96.6 (OC[CH₃]₂N), 67.0 (CH₂O), 64.2 (OCH₂CHN), 55.6 (ArOCH₃), 52.2 (CH₂N), 52.1 ([CO]OCH₃), 27.0 and 22.6 (OC[CH₃]₂N); m/z (EI) 279 (M)⁺, 264, 220, 162, 136, 121, 107, 91, 78, 65; [Found: (M)⁺ 279.1479, C₁₅H₂₁NO₄ requires (M)⁺ 279.1471].

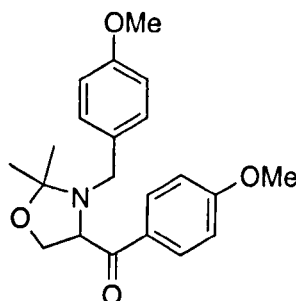
3-(4-Methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methoxy-methyl-amide (282)



Iso-Propylmagnesium chloride (49.6 ml, 9.92 mmol, 2.0 M solution in THF) was added dropwise to a solution of 3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methyl ester (**281**) (9.24 g, 3.31 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (4.84 g, 4.96 mmol) in anhydrous THF (160 ml) at -20°C under nitrogen. The reaction was allowed to warm to -10°C over 2 hours, and was quenched with saturated NH₄Cl solution (50 ml). Water (50 ml) was added, and the mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with brine (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 1:1:0.2, petrol:ethyl acetate:triethylamine) to give 3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methoxy-methyl-amide (**282**) as a pale yellow oil (8.42 g, 82%), R_f (1:1 petrol:ethyl acetate) 0.22; ν_{max} (film)/cm⁻¹ 2970, 2934, 1664 (C=O), 1611, 1585, 1510, 1459, 1379, 1300, 1241, 1173, 1111, 1032, 996, 962, 823, 621; δ_H (300 MHz, CDCl₃) 7.30 (2H, d, J 8.5 Hz, Ar C-H), 6.83 (2H, d, J 8.5 Hz, Ar C-H), 4.20-4.10 (1H, m, CH_aH_bO), 4.07-3.96 (1H, m, OCH₂CHN), 3.94-3.84 (2H, m, CH_aH_bN and CH_aH_bO), 3.78 (3H, s, ArOCH₃), 3.82-3.65 (1H, m, CH_aH_bN), 3.36 (3H, br s, OCH₃, amide), 3.03 (3H, br s, NCH₃, amide),

1.40 (3H, s, OC[CH₃][CH₃]N), 1.33 (3H, s, OC[CH₃][CH₃]N); δ_C (75.5 MHz, CDCl₃) 173.3 (C=O), 159.0 and 131.6 (Ar quat.), 130.2 and 113.7 (Ar C-H), 96.1 (OC[CH₃]₂N), 66.9 (CH₂O), 61.2 (OCH₃, amide), 60.7 (OCH₂CHN), 55.5 (ArOCH₃), 51.1 (CH₂N), 32.5 (NCH₃), 26.6 and 24.0 (OC[CH₃]₂N); m/z (EI) 308 (M)⁺, 277, 237, 220, 180, 162, 147, 136, 121, 91, 78; [Found: (M)⁺ 308.1733, C₁₆H₂₄N₂O₄ requires (M)⁺ 308.1736].

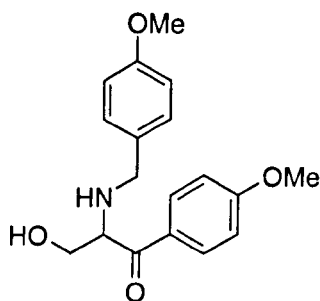
[3-(4-Methoxybenzyl)-2,2-dimethyl-oxazolidin-4-yl]-(4-methoxyphenyl)-methanone (283)



4-Methoxyphenylmagnesium bromide (54.2 ml, 27.1 mmol, 0.5 M solution in THF) was added dropwise to a stirred solution of 3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methoxy-methyl-amide (**282**) (4.18 g, 13.6 mmol) in anhydrous THF (150 ml) at -78°C under nitrogen. The reaction was allowed to warm to room temperature over 16 hours, and was quenched with a saturated solution of NH₄Cl (50 ml). Water (50 ml) and ethyl acetate (100 ml) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 100 ml), and the combined organic extracts were washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1:0.12, petrol:ethyl acetate:triethylamine) to give [3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidin-4-yl]-(4-methoxyphenyl)-methanone (**283**) as an orange crystalline solid (3.72 g, 77%), R_f (3:1 petrol:ethyl acetate) 0.28; m.p. 81.5-82.3 °C; ν_{max} (film)/cm⁻¹ 2933, 2835, 1665 (C=O), 1597, 1574, 1509, 1459, 1419, 1376, 1304, 1243, 1170, 1111, 1028, 914, 835, 757, 730; δ_H (300 MHz, CDCl₃) 7.89 (2H, d, J 9.0 Hz, Ar C-H), 6.99 (2H, d, J 8.6 Hz, Ar C-H), 6.80 (2H, d, J 9.0 Hz, Ar C-H), 6.57 (2H, d, J 8.6 Hz, Ar C-H), 4.29 (1H, dd, J 8.7, 8.7 Hz, CH_aH_bO), 4.08 (1H, dd, J 8.7, 5.9 Hz, OCH₂CHN), 4.00 (1H, dd, J 8.7, 5.9 Hz,

CH₄H_bO), 3.84 (3H, s, ArOCH₃), 3.82 (1H, d, J 12.8 Hz, CH_aH_bN), 3.70 (3H, s, OCH₃), 3.50 (1H, d, J 12.8 Hz, CH_aH_bN), 1.47 (3H, s, OC[CH₃][CH₃]N), 1.31 (3H, s, OC[CH₃][CH₃]N); δ_C (75.5 MHz, CDCl₃) 198.5 (C=O), 163.5 and 159.0 (Ar quat.), 131.6 and 130.9 (Ar C-H), 130.4 and 128.3 (Ar quat.), 113.6 and 113.4 (Ar C-H), 97.0 (OC[CH₃]₂N), 70.7 (OCH₂CHN), 67.1 (CH₂O), 55.8 (OCH₃), 55.5 (OCH₃), 53.2 (CH₂N), 27.0 and 20.5 (OC[CH₃]₂N); m/z (FAB, with TFA) 356 (MH)⁺, 316, 220, 154, 133, 121, 91, 81, 67; [Found: (MH)⁺ 356.1860, C₂₁H₂₅NO₄ requires (MH)⁺ 356.1862]; [Found: C, 70.71, 70.71; H, 7.00, 7.01; N, 4.07, 4.02. C₂₁H₂₅NO₄ requires C, 70.96; H, 7.09; N, 3.94].

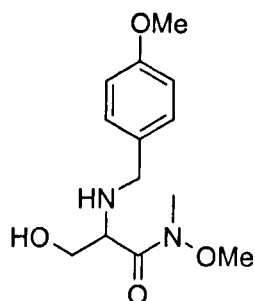
3-Hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)-propan-1-one (284)



A solution of [3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidin-4-yl]-(4-methoxyphenyl)-methanone (**283**) (3.00 g, 8.44 mmol) in 4:1 AcOH:H₂O (50 ml) was stirred at room temperature for 1 hour. The reaction was concentrated *in vacuo*, and the residue was partitioned between saturated NaHCO₃ solution (100 ml) and ethyl acetate (100 ml). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was recrystallised from ethyl acetate to give *3-hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)-propan-1-one (284)* as an off-white solid (2.42 g, 91%), R_f (ethyl acetate) 0.15; m.p. 106.9-107.2 °C; ν_{max} (film)/cm⁻¹ 3300-2500 (br, NH and OH), 1671 (C=O), 1598, 1573, 1510, 1460, 1418, 1388, 1301, 1243, 1173, 1137, 1107, 1023, 982, 957, 882, 855, 810, 752, 686, 635, 608; δ_H (300 MHz, CDCl₃) 7.91 (2H, d, J 8.9 Hz, Ar C-H), 7.24 (2H, d, J 8.5 Hz, Ar C-H), 6.95 (2H, d, J 8.9 Hz, Ar

C-H), 6.85 (2H, d, J 8.5 Hz, Ar C-H), 4.32 (1H, dd, J 7.9, 4.3 Hz, OCH₂CHN), 3.88 (3H, s, OCH₃), 3.87-3.76 (2H, m, CH_aH_bO and CH_aH_bN), 3.79 (3H, s, OCH₃), 3.60 (1H, d, J 12.6 Hz, CH_aH_bN), 3.36 (1H, dd, J 10.9, 7.9 Hz, CH_aH_bO), 2.90-2.58 (2H, br, OH and NH); δ_C (75.5 MHz, CDCl₃) 198.8 (C=O), 163.8, 158.6 and 131.5 (Ar quat.), 130.5 and 129.4 (Ar C-H), 128.1 (Ar quat.), 113.8 and 113.7 (Ar C-H), 63.3 (OCH₂CHN), 63.1 (CH₂O), 55.3 (OCH₃), 55.0 (OCH₃), 51.5 (CH₂N); m/z (FAB, with TFA) 316 (MH)⁺, 219, 180, 153, 136, 121; [Found: (MH)⁺ 316.1552, C₁₈H₂₁NO₄ requires (MH)⁺ 316.1549]; [Found: C, 68.38; H, 6.71; N, 4.45. C₁₈H₂₁NO₄ requires C, 68.55; H, 6.71; N, 4.44].

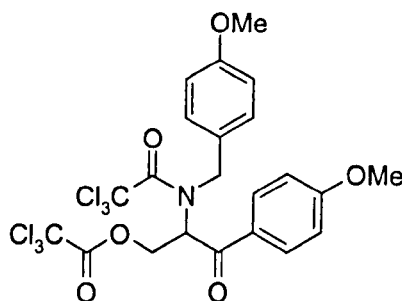
3-Hydroxy-N-methoxy-2-(4-methoxybenzylamino)-N-methyl-propionamide (285)



Purification of impure 3-(4-methoxybenzyl)-2,2-dimethyl-oxazolidine-4-carboxylic acid methoxy-methyl-amide (**282**) by flash column chromatography (SiO₂, 1:1 petrol:ethyl acetate) gave *3-hydroxy-N-methoxy-2-(4-methoxybenzylamino)-N-methyl-propionamide (285)* (yield dependent upon quantity of silica used and chromatography time) as a yellow oil, R_f (ethyl acetate) 0.13; ν_{max} (film)/cm⁻¹ 3335 (br, OH and NH), 2936, 2836, 1644, 1611, 1585, 1511, 1461, 1387, 1301, 1244, 1175, 1110, 1031, 988, 910, 812, 727; δ_H (300 MHz, CDCl₃) 7.25 (2H, d, J 8.5 Hz, Ar C-H), 6.86 (2H, d, J 8.5 Hz, Ar C-H), 3.80 (3H, s, ArOCH₃), 3.83-3.70 (3H, m, CH_aH_bN and OCH_aH_bCHN), 3.64 (3H, s, OCH₃, amide), 3.58 (1H, d, J 12.6 Hz, CH_aH_bN), 3.39 (1H, dd, J 9.4, 7.2 Hz, OCH_aH_bCHN), 3.21 (3H, s, NCH₃), 2.90-2.20 (2H, br, OH and NH); δ_C (75.5 MHz, CDCl₃) 173.1 (C=O), 158.6 and 131.3 (Ar quat.), 129.3 and 113.6 (Ar C-H), 62.3 (CH₂O), 61.3 (OCH₃, amide), 58.8 (OCH₂CHN), 55.0 (ArOCH₃), 51.3 (CH₂N), 31.9 (NCH₃); m/z (EI) 269 (MH)⁺, 267 (M-

H)⁺, 237, 206, 180, 147, 136, 121, 91, 78, 63; [Found: (M-H)⁺ 267.1362, C₁₃H₁₉N₂O₄ requires (M-H)⁺ 267.1345].

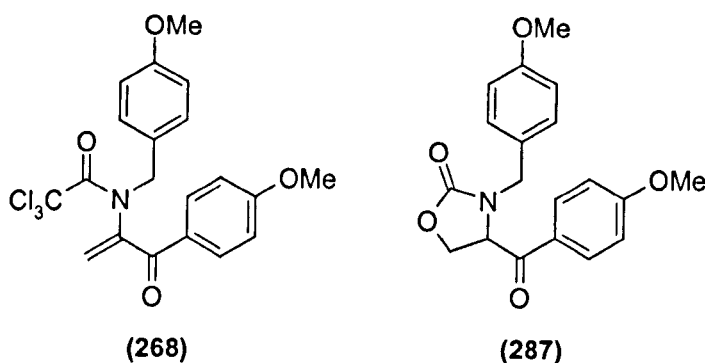
Trichloro-acetic acid 2-[(4-methoxybenzyl)-(2,2,2-trichloro-acetyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (286)



Trichloroacetyl chloride (674 μ l, 6.03 mmol) was added dropwise to a stirred solution of 3-hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)propan-1-one (**284**) (865 mg, 2.74 mmol) and triethylamine (840 μ l, 6.03 mmol) in anhydrous acetonitrile (87 ml) at 0°C under nitrogen. After 1 hour, the reaction was partitioned between water (50 ml) and ethyl acetate (50 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give *trichloro-acetic acid 2-[(4-methoxybenzyl)-(2,2,2-trichloro-acetyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (286)* as a white solid (1.37 g, 83%), R_f (3:1 petrol:ethyl acetate) 0.34; m.p. 120.0-121.0 °C; ν_{\max} (film)/cm⁻¹ 2934, 2840, 1769, 1674, 1600, 1574, 1513, 1460, 1418, 1302, 1250, 1174, 1116, 1029, 967, 908, 832, 733, 674; δ_{H} (300 MHz, CDCl₃) 7.70 (2H, d, J 8.3 Hz, Ar C-H), 7.24 (2H, d, J 8.7 Hz, Ar C-H), 6.91 (2H, d, J 8.3 Hz, Ar C-H), 6.83 (2H, d, J 8.7 Hz, Ar C-H), 5.72 (1H, br dd, J 5.9, 5.9 Hz, OCH₂CHN), 5.11 (1H, d, J 15.8 Hz, CH_aH_bN), 4.85-4.65 (2H, m, CH_aH_bN and OCH_aH_bCHN), 4.55-4.40 (1H, br m, OCH_aH_bCHN), 3.88 (3H, s, OCH₃), 3.80 (3H, s, OCH₃); δ_{C} (75.5 MHz, CDCl₃) 192.4 (C=O, ketone), 164.6, 161.7 and 160.3 (2 x C=O and 2 x Ar quat., 2 signals coincident), 130.8 and 130.4 (Ar C-H), 128.1 and 126.1 (Ar quat.), 114.6 and 114.5 (Ar C-H), 93.2 (2

x CCl_3 , signals coincident), 66.9 (CH_2O), 60.9 (OCH_2CHN), 56.0 and 55.7 (2 x OCH_3), 53.0 (CH_2N); m/z (FAB) 604 (MH)⁺, 460, 307, 289, 154, 136; [Found: C, 43.68, 43.71; H, 3.15, 3.14; N, 2.20, 2.15; Cl, 34.61, 34.79. $\text{C}_{22}\text{H}_{19}\text{NO}_6\text{Cl}_6$ requires: C, 43.60; H, 3.16; N, 2.31; Cl, 35.10].

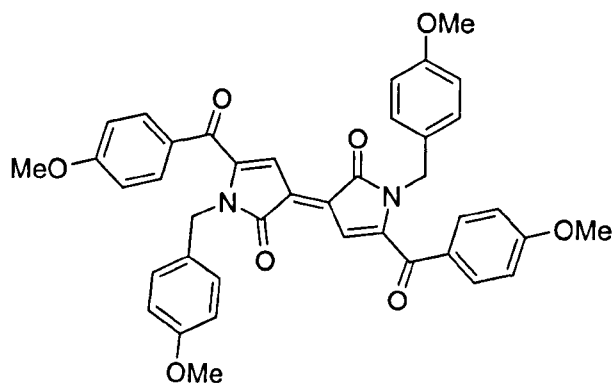
2,2,2-Trichloro-N-[1-(4-methoxybenzoyl)-vinyl]-N-(4-methoxybenzyl)-acetamide (268)
and 4-(4-methoxybenzoyl)-3-(4-methoxybenzyl)-oxazolidine-2-one (287)



Potassium *tert*-butoxide (239 mg, 2.23 mmol) was added in small portions to a solution of trichloro-acetic acid 2-[(4-methoxybenzyl)-(2,2,2-trichloro-acetyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (**286**) (1.29 g, 2.13 mmol) in anhydrous THF (50 ml) at room temperature under nitrogen. After 20 minutes, further potassium *tert*-butoxide (47.8 mg, 0.446 mmol) was added. After an additional 20 minutes, the reaction was partitioned between saturated NH_4Cl solution (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 1:1 petrol:ethyl acetate) to give 2,2,2-trichloro-N-[1-(4-methoxybenzoyl)-vinyl]-N-(4-methoxybenzyl)-acetamide (**268**) as a white solid (319 mg, 34%), R_f (1:1 petrol:ethyl acetate) 0.58; m.p. 122.0-123.0 °C; ν_{max} (film)/ cm^{-1} 2922, 2852, 1684, 1654, 1600, 1512, 1461, 1375, 1306, 1254, 1170, 1031, 973, 847, 814, 788; δ_{H} (300 MHz, CDCl_3) 7.83 (2H, d, J 8.9 Hz, Ar C-H), 7.30 (2H, d, J 8.7 Hz, Ar C-H), 6.94 (2H, d, J 8.9 Hz, Ar C-H), 6.86 (2H, d, J 8.7 Hz, Ar C-H), 5.90-5.80 (1H, br s, $\text{C}=\text{CH}_a\text{H}_b$), 5.61 (1H, s, $\text{C}=\text{CH}_a\text{H}_b$), 5.40-

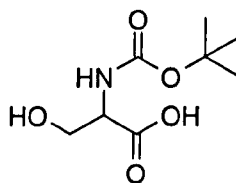
4.60 (<2H, almost flat, $\underline{\text{C}}\underline{\text{H}}_2\text{N}$), 3.87 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 3.80 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$); δ_{C} (125.8 MHz, CDCl_3) 190.3 ($\underline{\text{C}}=\text{O}$, ketone), 163.5, 160.4 and 159.4 ($\underline{\text{C}}=\text{O}$, amide and 2 x Ar quat.), 143.1 ($\text{N}-\underline{\text{C}}=\underline{\text{C}}\text{H}_2$), 132.3 and 130.2 (Ar $\underline{\text{C}}-\text{H}$), 128.7 and 127.9 (Ar quat.), 114.0 and 113.7 (Ar $\underline{\text{C}}-\text{H}$), 92.9 ($\underline{\text{C}}\text{Cl}_3$), 55.5 and 55.3 (2 x $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), $\underline{\text{C}}\underline{\text{H}}_2\text{N}$ and $\text{C}=\underline{\text{C}}\text{H}_2$ not visible/flat; m/z (FAB) 442 (MH)⁺, 307, 289, 219, 154, 136, 121; [Found: C, 54.49; H, 4.18; N, 2.99. $\text{C}_{20}\text{H}_{18}\text{NO}_4\text{Cl}_3$ requires C, 54.26; H, 4.10; N, 3.16], and 4-(4-methoxybenzoyl)-3-(4-methoxybenzyl)-oxazolidine-2-one (**287**) as a white solid (241 mg, 33%), R_f (1:1 petrol:ethyl acetate) 0.18; m.p. 93.8-94.0 °C; ν_{max} (film)/ cm^{-1} 2928, 2841, 1753, 1681, 1599, 1574, 1513, 1419, 1366, 1311, 1243, 1173, 1115, 1030, 845; δ_{H} (400 MHz, CDCl_3) 7.74 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}-\underline{\text{H}}$), 7.12 (2H, d, J 8.5 Hz, Ar $\underline{\text{C}}-\underline{\text{H}}$), 6.94 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}-\underline{\text{H}}$), 6.81 (2H, d, J 8.5 Hz, Ar $\underline{\text{C}}-\underline{\text{H}}$), 4.97 (1H, d, J 14.8 Hz, $\underline{\text{C}}\underline{\text{H}}_a\text{H}_b\text{N}$), 4.90 (1H, dd, J 10.0, 6.2 Hz, $\text{O}\underline{\text{C}}\underline{\text{H}}_2\underline{\text{C}}\underline{\text{H}}\text{N}$), 4.53 (1H, dd, J 10.0, 8.8 Hz, $\text{O}\underline{\text{C}}\underline{\text{H}}_a\text{H}_b\text{CHN}$), 4.12 (1H, dd, J 8.8 Hz, 6.2 Hz, $\text{O}\underline{\text{C}}\underline{\text{H}}_a\text{H}_b\text{CHN}$), 4.07 (1H, d, J 14.8 Hz, $\underline{\text{C}}\underline{\text{H}}_a\text{H}_b\text{N}$), 3.88 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 3.78 (3H, s, $\text{O}\underline{\text{C}}\underline{\text{H}}_3$); δ_{C} (100.6 MHz, CDCl_3) 192.5 ($\underline{\text{C}}=\text{O}$, ketone), 164.6 ($\underline{\text{C}}=\text{O}$, carbamate), 159.5 and 158.0 (Ar quat.), 130.6 and 130.1 (Ar $\underline{\text{C}}-\text{H}$), 127.3 and 126.8 (Ar quat.), 114.5 and 114.3 (Ar $\underline{\text{C}}-\text{H}$), 64.5 ($\underline{\text{C}}\underline{\text{H}}_2\text{O}$), 57.6 ($\text{O}\underline{\text{C}}\underline{\text{H}}_2\underline{\text{C}}\underline{\text{H}}\text{N}$), 55.7 and 55.3 (2 x $\text{O}\underline{\text{C}}\underline{\text{H}}_3$), 46.5 ($\underline{\text{C}}\underline{\text{H}}_2\text{N}$); m/z (FAB) 683 (2MH)⁺, 434, 342 (MH)⁺, 277, 234, 185, 135, 121; [Found: ($\text{M}-\text{H}$)⁺ 340.1195, $\text{C}_{19}\text{H}_{19}\text{NO}_5$ requires ($\text{M}-\text{H}$)⁺ 340.1185]; [Found: C, 66.73, 66.70; H, 5.58, 5.61; N, 4.04, 4.15. $\text{C}_{19}\text{H}_{19}\text{NO}_5$ requires C, 66.85; H, 5.61; N, 4.10].

5,5'-Bis-(4-methoxybenzoyl)-1,1'-bis-(4-methoxybenzyl)-1H, 1'H-[3,3']bipyrrolylidene-2,2'-dione (289)



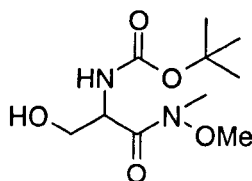
TPA (54.3 mg, 0.187 mmol) and copper (I) chloride (18.5 mg, 0.187 mmol) were added to a stirred solution of 2,2,2-trichloro-*N*-[1-(4-methoxybenzoyl)-vinyl]-*N*-(4-methoxybenzyl)-acetamide (**268**) (166 mg, 0.375 mmol) in anhydrous toluene (3.1 ml) under nitrogen. The reaction was heated to reflux for 5 hours, cooled and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give *5,5'-bis-(4-methoxybenzoyl)-1,1'-bis-(4-methoxybenzyl)-1H, 1'H-[3,3']bipyrrolylidene-2,2'-dione (289)* as a dark purple solid (44.0 mg, 34%), *R*_f (1:1 petrol:ethyl acetate) 0.47; m.p. 184.0-186.0 °C; λ_{max} (CHCl₃) 273 nm (ε = 29853), 375 nm (ε = 6931), 567 nm (ε = 11018); ν_{max} (film)/cm⁻¹ 2956, 2925, 2852, 1718, 1684, 1635, 1597, 1512, 1441, 1393, 1350, 1256, 1169, 1118, 1077, 1030, 907, 843, 772, 615; δ_H (400 MHz, CDCl₃) 7.78 (4H, d, *J* 8.8 Hz, Ar C-H), 7.12 (4H, d, *J* 8.8 Hz, Ar C-H), 7.08 (2H, s, C=CH-C=C), 6.93 (4H, d, *J* 8.8 Hz, Ar C-H), 6.72 (4H, d, *J* 8.8 Hz, Ar C-H), 4.99 (4H, s, CH₂N), 3.89 (6H, s, OCH₃), 3.71 (6H, s, OCH₃); δ_C (125.8 MHz, CDCl₃) 186.3, 169.1, 164.3, 158.9, 147.4, 132.8, 129.3, 129.2 (4 x Ar quat., 2 x C=O, 2 x olef. quat.), 132.3, 129.5, 114.0 and 113.9 (4 x Ar C-H), 111.5 (C=CH-C=C), 55.7 and 55.2 (2 x OCH₃), 43.5 (CH₂N); *m/z* (FAB) 671 (MH)⁺, 523, 460, 391, 341, 307, 289, 219, 154, 136, 121; [Found: (MH)⁺ 671.2388, C₄₀H₃₅N₂O₈ requires (MH)⁺ 671.2393].

2-tert-Butoxycarbonylamino-3-hydroxy-propionic acid (301)



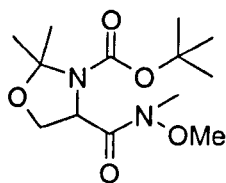
Di-*tert*-butyl dicarbonate (9.85 g, 45.1 mmol) in 1,4-dioxane (35 ml) was added to a stirred solution of DL-serine (3.95 g, 37.6 mmol) in 1M NaOH (75 ml) at 0°C. The reaction was warmed to room temperature and stirred for 3 days, maintaining the pH at 9 by the addition, when necessary, of 1M NaOH. The mixture was concentrated to about half volume under reduced pressure, cooled to 0°C and carefully treated with 1M H₂SO₄ (~38 ml) until pH 2-3 was achieved. The solution was saturated with solid NaCl, and extracted with ethyl acetate (6 x 50 ml). The combined organic extracts were concentrated *in vacuo* to give 2-*tert*-butoxycarbonylamino-3-hydroxy-propionic acid (**301**) as a thick colourless oil (6.05 g, 78%), R_f (ethyl acetate) 0.04; ν_{\max} (film)/cm⁻¹ 3332 (br, -OH, NH, CO₂H), 2977, 2934, 1701 (C=O, acid), 1682 (C=O, carbamate), 1511, 1456, 1393, 1367, 1280, 1248, 1155, 1056, 850, 778, 752; δ_{H} (300 MHz, D₆-DMSO) 6.71 (1H, d, J 8.1 Hz, NH), 3.96 (1H, ddd, J 8.1, 4.9, 4.9 Hz, CHNH), 3.62 (2H, d, J 4.9 Hz, CH₂OH), 1.38 (9H, s, C[CH₃]₃); δ_{C} (75.5 MHz, CDCl₃) 172.8 (C=O), 155.7 (C=O), 78.5 (OC[CH₃]₃), 61.8 (CH₂O), 56.5 (CHNH), 28.5 (OC[CH₃]₃); m/z (EI) 204 (M-H)⁺, 194, 160, 150, 132, 119, 104, 74, 57.

[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester
(302)²⁰⁸



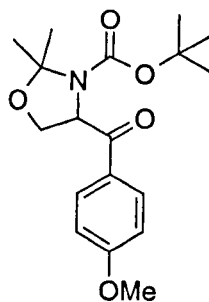
A solution of 2-*tert*-butoxycarbonylamino-3-hydroxy-propionic acid (301) (12.1 g, 59.1 mmol) in THF (53 ml) was treated with a solution of *N,O*-dimethyl hydroxylamine hydrochloride (6.42 g, 65.8 mmol) in water (53 ml). The pH was adjusted to 4.5 by the addition of 1M NaOH. While cooling in an ice bath, and maintaining the pH at 4.5 by the addition of 1M NaOH, a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (13.2 g, 68.9 mmol) in water (134 ml) was added slowly during 45 minutes. After stirring at room temperature for 3.5 hours, the solution was saturated with solid NaCl, and extracted with ethyl acetate (4 x 200ml) and with 9:1 ethyl acetate:methanol (3 x 100 ml). The combined organic extracts were concentrated *in vacuo*, and the residue was recrystallised from a mixture of 40-60°C petrol and ethyl acetate to give *[2-hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester* (302) as a white crystalline solid (11.5 g, 78%), R_f (ethyl acetate) 0.19; m.p. 116.1-116.3 °C; ν_{\max} (film)/cm⁻¹ 3406 (NH), 3254 (OH), 3061, 2980, 2929, 2879, 1687 (C=O, carbamate), 1648 (C=O, amide), 1544, 1472, 1426, 1389, 1368, 1341, 1281, 1254, 1161, 1088, 1057, 1023, 975, 915, 859, 830, 784, 759, 614; δ_H (300 MHz, D₆-DMSO) 6.77 (1H, d, J 8.3 Hz, NH), 4.82 (1H, t, J 6.2 Hz, OH), 4.60-4.40 (1H, br m, CHNH), 3.72 (3H, s, OCH₃), 3.60-3.41 (2H, m, CH₂O), 3.12 (3H, s, NCH₃), 1.37 (9H, s, C[CH₃]₃); δ_C (75.5 MHz, D₆-DMSO) 171.1 (C=O), 155.6 (C=O), 78.4 (OC[CH₃]₃), 61.4 (OCH₃), 61.3 (CH₂O), 54.8 (CHNH), 32.2 (NCH₃), 28.5 (OC[CH₃]₃); m/z (EI) 249 (MH)⁺, 193, 188, 175, 162, 149, 132, 117, 104, 86, 60; [Found: (MH)⁺, 249.1484, C₁₀H₂₀N₂O₅ requires (MH)⁺, 249.1450]; [Found: C, 48.37, 48.43; H, 8.09, 8.11; N, 11.23, 11.21. C₁₀H₂₀N₂O₅ requires C, 48.38; H, 8.12; N, 11.28].

4-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (303)²⁰⁸⁻²⁰⁹



2,2-Dimethoxypropane (5.90 ml, 48.0 mmol) and *p*-toluenesulfonic acid monohydrate (122 mg, 0.640 mmol) were added to a solution of [2-hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (**302**) (3.97 g, 16.0 mmol) in anhydrous toluene (80 ml) and the solution was heated to reflux for 3 hours. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (SiO₂, 1:1, petrol:ethyl acetate) to give a 1:1 mixture of rotational isomers of 4-(methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**303**) as a white crystalline solid (4.12 g, 89%), R_f (1:1 petrol:ethyl acetate) 0.33; m.p. 67.0-67.8 °C; ν_{\max} (film)/cm⁻¹ 2977, 2936, 1696 (C=O, carbamate), 1674 (C=O, amide), 1452, 1364, 1325, 1271, 1248, 1167, 1089, 1057, 992, 950, 871, 846, 766, 713, 632, 604; δ_{H} (300 MHz, CDCl₃) 4.73 (1H, dd, J 7.0, 2.6 Hz, CHN, isomer X), 4.66 (1H, dd, J 7.2, 3.4 Hz, CHN, isomer Y), 4.13 (1H, dd, J 9.0, 7.2 Hz, CH_aH_bO, isomer Y), 4.11 (1H, dd, J 9.0, 7.2 Hz, CH_aH_bO, isomer X), 3.90 (1H, dd, J 9.4, 2.6 Hz, CH_aH_bO, isomer X), 3.86 (1H, dd, J 9.0, 3.4 Hz, CH_aH_bO, isomer Y), 3.68 and 3.63 (3H, s, NOCH₃, isomers X and Y), 3.15 (6H, s, NCH₃, isomers X and Y), 1.64, 1.61, 1.50 and 1.45 (3H, s, C[CH₃]₂, 2 signals for each isomer), 1.43 and 1.35 (9H, s, C[CH₃]₃, isomers X and Y); δ_{C} (75.5 MHz, CDCl₃) 171.1 and 170.3 (C=O, isomers X and Y), 151.9 and 151.1 (C=O, isomers X and Y), 94.7 and 94.2 (O-C-N, isomers X and Y), 80.3 and 79.7 (OC[CH₃]₃, isomers X and Y), 65.9 and 65.6 (CH₂O, isomers X and Y), 61.0 (NOCH₃, isomers X and Y), 57.6 and 57.5 (CHN, isomers X and Y), 32.3 and 32.2 (NCH₃, isomers X and Y), 28.2 and 28.1 (OC[CH₃]₃, isomers X and Y), 25.4, 25.2, 24.4 and 24.3 (OC[CH₃]₂N, isomers X and Y); m/z (EI) 289 (MH)⁺, 273, 233, 215, 200, 189, 175, 173, 157, 144, 127, 100, 84, 57; [Found: (MH)⁺, 289.1750, C₁₃H₂₄N₂O₅ requires (MH)⁺, 289.1763]; [Found: C, 54.16, 54.08; H, 8.34, 8.34; N, 9.65, 9.62. C₁₃H₂₄N₂O₅ requires C, 54.15; H, 8.39; N, 9.72].

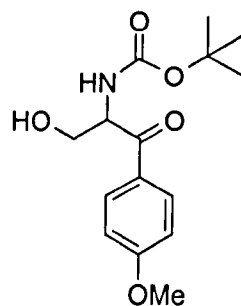
4-(4-Methoxybenzoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (304)



4-Methoxyphenylmagnesium bromide, 0.5 M solution in THF (73.5 ml, 36.8 mmol) was added dropwise to a stirred solution of 4-(methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**303**) (5.30 g, 18.4 mmol) in anhydrous THF (180 ml) at -78°C under nitrogen. The reaction was allowed to warm to room temperature over 16 hours, and was quenched with a saturated solution of NH_4Cl (50 ml). Water (50 ml) and ethyl acetate (100 ml) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 100 ml), and the combined organic extracts were washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 3:1, petrol:ethyl acetate) and then triturated with petrol to give a 1.4:1 mixture (major isomer=X, minor isomer=Y) of rotational isomers of 4-(4-methoxybenzoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**304**) as a white crystalline solid (2.76 g, 45%), R_f (1:1 petrol:ethyl acetate) 0.58; m.p. $123.8\text{--}124.1^{\circ}\text{C}$; ν_{max} (film)/ cm^{-1} 2973, 2936, 1700 (C=O), 1693 (C=O), 1600, 1577, 1511, 1459, 1425, 1382, 1359, 1233, 1165, 1090, 1041, 993, 934, 870, 845, 804, 764, 695, 632; δ_{H} (300 MHz, CDCl_3) 7.90 (2H, d, J 8.7 Hz, Ar C-H, isomer X), 7.90 (2H, d, J 8.7 Hz, Ar C-H, isomer Y), 6.96 (2H, d, J 8.7 Hz, Ar C-H, isomer X), 6.93 (2H, d, J 8.7 Hz, Ar C-H, isomer Y), 5.43 (1H, dd, J 7.4, 2.6 Hz, CHN, isomer Y), 5.33 (1H, dd, J 7.5, 3.8 Hz, CHN, isomer X), 4.30 (1H, dd, J 7.5, 7.5 Hz, CH_aH_bO, isomer X), 4.29 (1H, dd, J 7.4, 7.4 Hz, CH_aH_bO, isomer Y), 3.98-3.87 (1 H, m, CH_aH_bO, isomer X), 3.98-3.87 (1 H, m, CH_aH_bO, isomer Y), 3.87 (3H, s, OCH₃, isomer X), 3.86 (3H, s, OCH₃, isomer Y), 1.76 (3H, s, C[CH₃][CH₃], isomer X), 1.72 (3H, s, C[CH₃][CH₃], isomer Y), 1.60 (3H, s, C[CH₃][CH₃], isomer X), 1.56 (3H, s, C[CH₃][CH₃], isomer Y), 1.49 (9H, s, C[CH₃]₃, isomer Y), 1.27 (9H, s, C[CH₃]₃, isomer X)

X); δ_c (125.8 MHz, CDCl_3) 194.3 ($\text{C}=\text{O}$, ketone, isomer X), 193.6 ($\text{C}=\text{O}$, ketone, isomer Y), 163.8 ($\text{C}=\text{O}$, carbamate, isomer X), 163.7 ($\text{C}=\text{O}$, carbamate, isomer Y), 152.1 (Ar quat., isomer Y), 151.3 (Ar quat., isomer X), 130.7 (Ar $\text{C}-\text{H}$, isomer Y), 130.4 (Ar $\text{C}-\text{H}$, isomer X), 128.1 (Ar quat., isomer X), 127.9 (Ar quat., isomer Y), 114.1 (Ar $\text{C}-\text{H}$, isomer X), 114.0 (Ar $\text{C}-\text{H}$, isomer Y), 95.2 (O- $\text{C}-\text{N}$, isomer X), 94.6 (O- $\text{C}-\text{N}$, isomer Y), 80.6 ($\text{OC}[\text{CH}_3]_3$, isomer Y), 80.2 ($\text{OC}[\text{CH}_3]_3$, isomer X), 66.3 (CH_2O , isomer X), 65.9 (CH_2O , isomer Y), 61.5 (CHN , isomer Y), 61.3 (CHN , isomer X), 55.5 (OCH_3 , signals for X and Y coincident), 28.3 and 28.2 ($\text{OC}[\text{CH}_3]_3$, isomers X and Y), 25.8 and 25.4 ($\text{OC}[\text{CH}_3]_2\text{N}$, isomer Y), 24.8 and 24.7 ($\text{OC}[\text{CH}_3]_2\text{N}$, isomer X); m/z (FAB, with TFA) 336 (MH^+), 327, 260, 221, 204, 193, 165, 132, 105, 91; [Found: (MH^+), 336.1813, $\text{C}_{18}\text{H}_{26}\text{NO}_5$ requires (MH^+), 336.1811]; [Found: C, 64.27, 64.42; H, 7.47, 7.52; N, 4.18, 4.22. $\text{C}_{18}\text{H}_{25}\text{NO}_5$ requires C, 64.46; H, 7.51; N, 4.18].

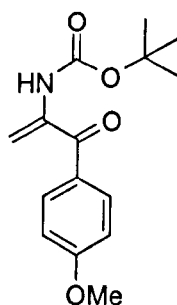
[1-Hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (305)



A suspension of 4-(4-methoxybenzoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**304**) (685 mg, 2.04 mmol) in 4:1 AcOH:H₂O (20 ml) was heated to 60°C for 48 hours. The resulting orange solution was concentrated in *vacuo*, and the residue was partitioned between saturated NaHCO₃ solution (50 ml) and ethyl acetate (50 ml). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 2:1, petrol:ethyl acetate) to give recovered starting material (69.0 mg, 10%) and *[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (305)* as a pale yellow solid

(453 mg, 75%), R_f (1:1 petrol:ethyl acetate) 0.20; m.p. 102.7-103.0 °C; ν_{\max} (film)/ cm^{-1} 3459 (NH), 3306 (OH), 2961, 2930, 1667 (br, C=O), 1602, 1579, 1533, 1454, 1422, 1386, 1364, 1297, 1237, 1158, 1086, 1061, 1022, 972, 840, 779, 755; δ_H (400 MHz, CDCl_3) 8.00 (2H, d, J 8.8 Hz, Ar C-H), 6.97 (2H, d, J 8.8 Hz, Ar C-H), 5.95-5.83 (1H, br d, NH), 5.35-5.25 (1H, br m, CHN), 4.06-3.95 (1H, m, $\text{CH}_a\text{H}_b\text{OH}$), 3.89 (3H, s, OCH_3), 3.90-3.79 (1H, m, $\text{CH}_a\text{H}_b\text{OH}$), 3.00-2.88 (1H, br, OH), 1.47 (9H, s, $\text{C}[\text{CH}_3]_3$); δ_C (100.6 MHz, CDCl_3) 195.3 ($\text{C}=\text{O}$, ketone), 164.3 ($\text{C}=\text{O}$, carbamate), 156.6 (Ar quat.), 131.2 (Ar C-H), 127.7 (Ar quat.), 114.1 (Ar C-H), 80.6 ($\text{OC}[\text{CH}_3]_3$), 65.3 (CH_2OH), 57.6 (CHN), 55.6 (OCH_3), 28.7 ($\text{OC}[\text{CH}_3]_3$); m/z (FAB, with TFA) 296 (MH)⁺, 289, 273, 219, 166, 154, 137, 120; [Found: (MH)⁺, 296.1512, $\text{C}_{15}\text{H}_{21}\text{NO}_5$ requires (MH)⁺, 296.1498]; [Found: C, 60.85, 61.00; H, 7.14, 7.16; N, 4.72, 4.72. $\text{C}_{15}\text{H}_{21}\text{NO}_5$ requires C, 61.00; H, 7.17; N, 4.74].

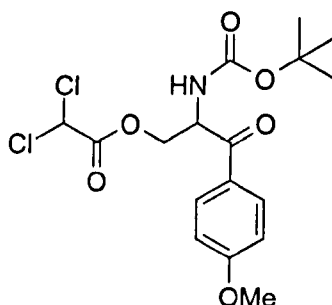
[1-(4-Methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (306)



Triethylamine (519 μl , 3.72 mmol), and then dichloroacetyl chloride (358 μl , 3.72 mmol), were added dropwise to a stirred solution of [1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (**305**) (1.00 g, 3.39 mmol) in anhydrous acetonitrile (25 ml) at 0°C under nitrogen. After 30 minutes, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (810 μl , 5.42 mmol) was added, and the reaction was heated to reflux for 3 hours. The solvent was removed under reduced pressure, and the dark brown residue was purified by flash column chromatography (SiO_2 , 5:1, petrol:ethyl acetate) to give [1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (**306**) as a pale yellow oil (901 mg, 96%), R_f (1:1 petrol:ethyl acetate) 0.67; ν_{\max}

(film)/cm⁻¹ 3403 (NH), 2977, 2934, 1724, 1645, 1600, 1504, 1420, 1392, 1368, 1329, 1257, 1157, 1078, 1030, 994, 958, 846, 792; δ_{H} (300 MHz, CDCl₃) 7.75 (2H, d, J 8.8 Hz, Ar C-H), 7.30 (1H, br, NH), 6.94 (2H, d, J 8.8 Hz, Ar C-H), 6.57 (1H, s, C=CH_aH_b), 5.39 (1H, d, J 1.0 Hz, C=CH_aH_b), 3.88 (3H, s, OCH₃), 1.51 (9H, s, C[CH₃]₃); δ_{C} (75.5 MHz, CDCl₃) 191.8 (C=O, ketone), 163.6 (C=O, carbamate), 153.3 (Ar quat.), 138.6 (NH-C=CH₂), 132.3 (Ar C-H), 129.0 (Ar quat.), 113.9 (Ar C-H), 110.5 (C=CH₂), 81.0 (OC[CH₃]₃), 55.9 (OCH₃), 28.7 (OC[CH₃]₃); m/z (FAB, with TFA) 278 (MH)⁺, 238, 222, 178, 154, 137, 120; [Found: (MH)⁺, 278.1397, C₁₅H₁₉NO₄ requires (MH)⁺, 278.1392].

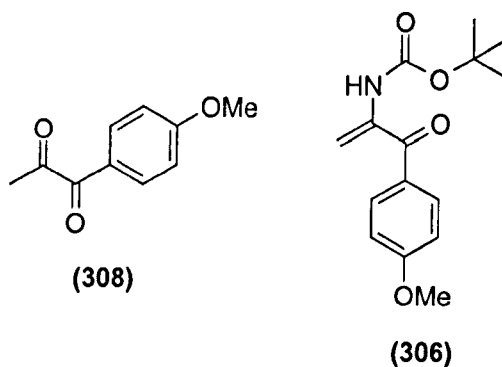
Dichloro-acetic acid 2-tert-butoxycarbonylamino-3-(4-methoxyphenyl)-3-oxo-propyl ester (307)



Dichloroacetyl chloride (17.9 μ l, 0.186 mmol) was added to a stirred solution of [1-hydroxymethyl-2-(4-methoxy-phenyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (**305**) (50.0 mg, 0.169 mmol) and triethylamine (26.0 μ l, 0.186 mmol) in anhydrous DCM (4 ml) at room temperature under nitrogen. After 1 hour, the reaction was partitioned between water (25 ml) and ethyl acetate (25 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with brine (25 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1, petrol:ethyl acetate) to give *dichloro-acetic acid 2-tert-butoxycarbonylamino-3-(4-methoxyphenyl)-3-oxo-propyl ester (307)* as a pale yellow solid (66.2 mg, 96%), R_f (1:1 petrol:ethyl acetate) 0.58; m.p. 132.8-133.3 °C; ν_{max} (film)/cm⁻¹ 3314 (NH), 2981, 2937, 1769, 1686, 1662, 1596, 1571, 1516, 1455, 1427, 1389, 1368, 1331, 1307, 1258, 1215, 1158, 1063, 1032, 992, 959, 856, 814, 782, 736, 677, 634, 605; δ_{H} (400 MHz, CDCl₃) 8.02 (2H, d, J 8.5 Hz,

Ar C-H), 6.99 (2H, d, J 8.5 Hz, Ar C-H), 5.91 (1H, s, CHCl₂), 5.71-5.65 (1H, br d, NH), 5.64-5.57 (1H, m, CHNH), 4.68 (1H, dd, J 11.2, 4.0 Hz, CH_aH_bO), 4.31 (1H, dd, J 11.2, 6.5 Hz, CH_aH_bO), 3.89 (3H, s, OCH₃), 1.46 (9H, s, C[CH₃]₃); δ_C (100.6 MHz, CDCl₃) 193.0 (C=O, ketone), 164.6 (C=O), 164.4 (C=O), 155.3 (Ar quat.), 131.2 (Ar C-H), 127.0 (Ar quat.), 114.3 (Ar C-H), 80.4 (OC[CH₃]₃), 67.8 (CH₂O), 64.0 (CHCl₂), 55.6 (OCH₃), 53.6 (CHNH), 28.3 (OC[CH₃]₃); m/z (CI) 406 (MH)⁺, 350, 332, 306, 288, 222, 204, 177, 170, 143, 107, 92, 77; [Found (FAB, with TFA): (M-H)⁺, 404.0652, C₁₇H₂₁NO₆³⁵Cl₂ requires (M-H)⁺, 404.0668].

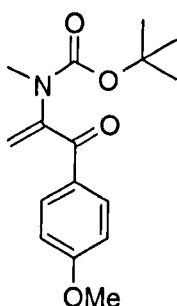
1-(4-Methoxyphenyl)-propane-1,2-dione (308) and [1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (306)



Triethylamine (195 μl, 1.40 mmol), and then dichloroacetyl chloride (134 μl, 1.40 mmol), were added dropwise to a stirred solution of [1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (305) (375 mg, 1.27 mmol) in anhydrous acetonitrile (10 ml) at 0°C under nitrogen. After 30 minutes, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (314 μl, 2.10 mmol) was added, and the reaction was heated to reflux for 2 hours. The solvent was removed under reduced pressure, and the dark brown residue was partitioned between DCM (50 ml) and 10% citric acid solution (50 ml). The aqueous layer was extracted with DCM (2 x 50 ml), and the combined organic extracts were washed with brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) to give *1-(4-methoxyphenyl)-propane-1,2-dione (308)* as a bright yellow solid (68.0 mg, 30%), R_f (1:1 petrol:ethyl acetate) 0.60; ν_{max} (film)/cm⁻¹ 1707,

1647, 1595, 1567, 1507, 1422, 1350, 1300, 1258, 1152, 1117, 1022, 899, 844, 815, 755, 694, 669; δ_{H} (400 MHz, CDCl_3) 7.95 (2H, d, J 8.8 Hz, Ar C-H), 6.91 (2H, d, J 8.8 Hz, Ar C-H), 3.83 (3H, s, OCH_3), 2.45 (3H, s, $[\text{CO}]\underline{\text{C}}\text{H}_3$); δ_{C} (100.6 MHz, CDCl_3) 201.6 ($\underline{\text{C}}=\text{O}$), 190.5 ($\underline{\text{C}}=\text{O}$), 165.0 (Ar quat.), 133.2 (Ar $\underline{\text{C}}\text{-H}$), 124.7 (Ar quat.), 114.6 (Ar $\underline{\text{C}}\text{-H}$), 55.9 (OCH_3), 26.8 ($[\text{CO}]\underline{\text{C}}\text{H}_3$); m/z (EI) 177 (M^+), 152, 135, 121, 107, 92, 77, 64, 57; [Found: (M^+), 178.0618, $\text{C}_{10}\text{H}_{10}\text{O}_3$ requires (M^+), 178.0630], and *[1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (306)* as a pale yellow oil (98.2 mg, 28%).

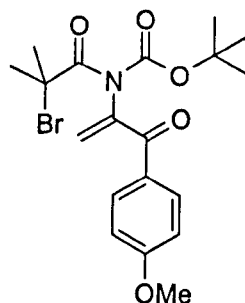
[1-(4-Methoxybenzoyl)-vinyl]-methyl-carbamic acid tert-butyl ester (310)



Sodium hydride (9.6 mg, 60% dispersion in mineral oil, 0.240 mmol) was added to a solution of *[1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (306)* (55.5 mg, 0.200 mmol) in anhydrous THF (1 ml) at 0°C under nitrogen to give a yellow solution/suspension. After 15 minutes, methyl iodide (14.9 μl , 0.240 mmol) was added and the reaction was allowed to warm to room temperature. After 2 hours, the reaction mixture was partitioned between saturated NH_4Cl solution (10 ml) and ethyl acetate (10 ml). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , 3:1, petrol:ethyl acetate) gave *[1-(4-methoxybenzoyl)-vinyl]-methyl-carbamic acid tert-butyl ester (310)* as a colourless oil (25.0 mg, 43%), R_f (1:1 petrol:ethyl acetate) 0.53; ν_{max} (film)/ cm^{-1} 2975, 2932, 1703, 1666, 1597, 1573, 1509, 1458, 1420, 1392, 1330, 1244, 1143, 1025, 973, 846, 771, 730; δ_{H} (300 MHz, CDCl_3) 7.86 (2H, d, J 8.8 Hz, Ar C-H), 6.91 (2H, d, J 8.8 Hz, Ar C-H), 5.17 (1H, s, $\text{C}=\underline{\text{C}}\text{H}_\text{a}\text{H}_\text{b}$),

5.10 (1H, s, C=CH_aH_b), 3.87 (3H, s, OCH₃), 3.25 (3H, s, NCH₃), 1.18 (9H, br s, C[CH₃]₃); δ_C (75.5 MHz, CDCl₃) 190.7 (C=O, ketone), 163.1 (C=O, carbamate), 152.9 (Ar quat.), 147.4 (N-C=CH₂), 131.6 (Ar C-H), 128.8 (Ar quat.), 113.2 (Ar C-H), 107.8 (C=C₂H₂), 81.9 (OC[CH₃]₃), 55.2 (OCH₃), 35.5 (NCH₃), 27.6 (OC[CH₃]₃); m/z (EI) 291 (M)⁺, 276, 235, 218, 207, 191, 162, 152, 135, 122, 107, 92, 77.

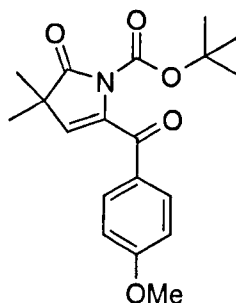
(2-Bromo-2-methyl-propionyl)-[1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (311)



Lithium di-*iso*-propylamide (133 ml, 0.240 mmol, 1.8 M solution in THF) was added to a solution of [1-(4-methoxybenzoyl)-vinyl]-carbamic acid *tert*-butyl ester (**306**) (55.5 mg, 0.200 mmol) in anhydrous THF (1 ml) at -78°C under nitrogen. After 10 minutes, 2-bromoisobutyryl bromide (29.7 μl, 0.240 mmol) was added and the reaction was allowed to warm to room temperature over 16 hours. The reaction mixture was partitioned between saturated NH₄Cl solution (10 ml) and ethyl acetate (10 ml). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 3:1, petrol:ethyl acetate) gave *(2-bromo-2-methyl-propionyl)-[1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (311)* as an off-white solid (53.7 mg, 63%), R_f (1:1 petrol:ethyl acetate) 0.63; m.p. 72.5-72.9 °C; ν_{max} (film)/cm⁻¹ 2978, 2933, 1737, 1661, 1598, 1572, 1509, 1460, 1369, 1296, 1249, 1164, 1104, 1028, 968, 911, 843, 778, 730; δ_H (400 MHz, CDCl₃) 7.88 (2H, d, J 8.8 Hz, Ar C-H), 6.93 (2H, d, J 8.8 Hz, Ar C-H), 5.84 (1H, d, J 1.5 Hz, C=CH_aH_b), 5.73 (1H, d, J 1.5 Hz, C=CH_aH_b), 3.86 (3H, s, OCH₃), 2.11 (6H, s, CBr[CH₃]₂), 1.40 (9H, s, C[CH₃]₃); δ_C (100.6 MHz, CDCl₃) 190.0 (C=O, ketone),

178.0 ($\underline{\text{C}}=\text{O}$, amide), 164.3 ($\underline{\text{C}}=\text{O}$, carbamate), 151.8 (Ar quat.), 144.2 (N- $\underline{\text{C}}=\text{CH}_2$), 132.5 (Ar $\underline{\text{C}}-\text{H}$), 129.6 (Ar quat.), 121.7 ($\text{C}=\underline{\text{C}}\text{H}_2$), 114.0 (Ar $\underline{\text{C}}-\text{H}$), 84.7 ($\text{OC}[\underline{\text{C}}\text{H}_3]_3$), 62.0 ($\underline{\text{C}}\text{Br}[\underline{\text{C}}\text{H}_3]_2$), 55.9 ($\text{O}\underline{\text{C}}\text{H}_3$), 32.9 ($\text{CBr}[\underline{\text{C}}\text{H}_3]_2$), 28.1 ($\text{OC}[\underline{\text{C}}\text{H}_3]_3$); m/z (EI) 424 (M)⁺, 369, 325, 289, 246, 204, 135, 107, 77; [Found: C, 53.46, 53.50; H, 5.64, 5.63; N, 3.23, 3.21; Br, 18.45, 18.31. $\text{C}_{19}\text{H}_{24}\text{NO}_5\text{Br}$ requires C, 53.53; H, 5.67; N, 3.29; Br, 18.74].

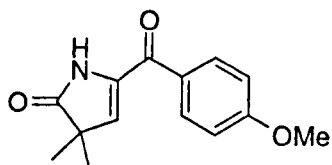
5-(4-Methoxybenzoyl)-3,3-dimethyl-2-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (312)



(2-Bromo-2-methyl-propionyl)-[1-(4-methoxybenzoyl)-vinyl]-carbamic acid *tert*-butyl ester (**311**) (30.0 mg, 0.0704 mmol), TPA (10.2 mg, 0.0352 mmol) and copper (I) bromide (5.0 mg, 0.0352 mmol) in anhydrous toluene (0.6 ml) were heated to reflux for 6.5 hours under nitrogen. The toluene was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2 , 3:1, petrol:ethyl acetate) to give *5-(4-methoxybenzoyl)-3,3-dimethyl-2-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (312)* as an off-white solid (14.1 mg, 58%), R_f (1:1 petrol:ethyl acetate) 0.46; m.p. 149.0-150.0 °C; ν_{max} (film)/ cm^{-1} 2676, 2934, 1790, 1730, 1660, 1600, 1575, 1510, 1462, 1366, 1289, 1256, 1165, 1063, 1027, 986, 848, 774; δ_{H} (300 MHz, CDCl_3) 7.92 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}-\text{H}$), 6.96 (2H, d, J 8.8 Hz, Ar $\underline{\text{C}}-\text{H}$), 5.73 (1H, s, $\text{C}=\underline{\text{C}}\text{H}-\text{C}[\underline{\text{C}}\text{H}_3]_2$), 3.88 (3H, s, $\text{O}\underline{\text{C}}\text{H}_3$), 1.36 (6H, s, $\text{C}[\underline{\text{C}}\text{H}_3]_2[\text{CO}]$), 1.32 (9H, s, $\text{C}[\underline{\text{C}}\text{H}_3]_3$); δ_{C} (100.6 MHz, CDCl_3) 185.3, 179.4, 164.2 (3 x $\underline{\text{C}}=\text{O}$), 147.4 (Ar quat.), 138.5 (N- $\underline{\text{C}}=\text{CH}$), 131.6 (Ar $\underline{\text{C}}-\text{H}$), 128.7 (Ar quat.), 123.8 (N- $\underline{\text{C}}=\underline{\text{C}}\text{H}$), 114.0 (Ar $\underline{\text{C}}-\text{H}$), 84.8 ($\text{OC}[\underline{\text{C}}\text{H}_3]_3$), 55.6 ($\text{O}\underline{\text{C}}\text{H}_3$), 47.4 ($\underline{\text{C}}[\underline{\text{C}}\text{H}_3]_2[\text{CO}]$), 27.5 ($\text{OC}[\underline{\text{C}}\text{H}_3]_3$), 23.6 ($\text{C}[\underline{\text{C}}\text{H}_3]_2[\text{CO}]$); m/z (EI) 345 (M)⁺, 272, 245, 230, 214, 202, 187, 174, 135, 128, 92, 84, 77; [Found: (M)⁺ 345.1567, $\text{C}_{19}\text{H}_{23}\text{NO}_5$ requires (M)⁺ 345.1576]; [Found: C, 66.00, 65.96; H, 6.72, 6.67; N, 4.02,

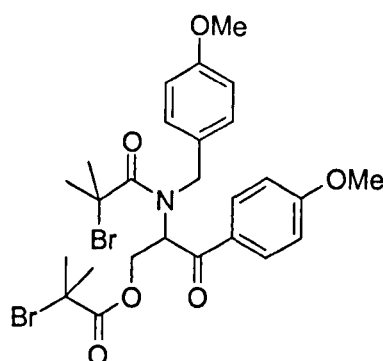
3.90. C₁₉H₂₃NO₅ requires C, 66.07; H, 6.71; N, 4.06], and recovered (2-bromo-2-methyl-propionyl)-[1-(4-methoxybenzoyl)-vinyl]-carbamic acid tert-butyl ester (**311**) (12.0 mg, 40%).

5-(4-Methoxybenzoyl)-3,3-dimethyl-1,3-dihydro-pyrrol-2-one (313)



A solution of 5-(4-methoxybenzoyl)-3,3-dimethyl-2-oxo-2,3-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (**312**) (35.0 mg, 0.101 mmol) in 9:1 TFA:H₂O (2 ml) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between saturated NaHCO₃ solution (10 ml) and ethyl acetate (10 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 3:1, ethyl acetate) gave 5-(4-methoxybenzoyl)-3,3-dimethyl-1,3-dihydro-pyrrol-2-one (**313**) as a pale brown solid (24.0 mg, 97%), R_f (ethyl acetate) 0.50; m.p. 153.7-154.2 °C; ν_{\max} (film)/cm⁻¹ 3300 (NH), 2969, 2931, 2361, 1715, 1639, 1599, 1510, 1462, 1416, 1384, 1310, 1256, 1170, 1028, 849; δ_{H} (300 MHz, CDCl₃) 7.92 (1H, br s, NH), 7.84 (2H, d, J 8.9 Hz, Ar C-H), 6.97 (2H, d, J 8.9 Hz, Ar C-H), 6.01 (1H, d, J 1.9 Hz, NH-C=CH), 3.88 (3H, s, OCH₃), 1.33 (6H, s, C[CH₃]₂[CO]); δ_{C} (75.5 MHz, CDCl₃) 184.5 (C=O, ketone), 182.0 (C=O, amide), 163.5 (Ar quat.), 137.5 (C=C-NH), 131.0 (Ar C-H), 128.6 (Ar quat.), 128.5 (CH=C-NH), 113.7 (Ar C-H), 55.3 (OCH₃), 48.6 (C[CH₃]₂[CO]), 22.6 (C[CH₃]₂[CO]); m/z (EI) 245 (M)⁺, 230, 202, 187, 174, 159, 135, 107, 92, 82, 77, 64; [Found: (M)⁺ 245.1055, C₁₄H₁₅NO₃ requires (M)⁺ 245.1052].

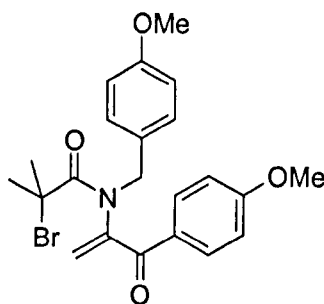
2-Bromo-2-methyl-propionic acid 2-[(2-bromo-2-methyl-propionyl)-(4-methoxybenzyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (314)



Triethylamine (180 μ l, 1.30 mmol) and 2-bromoisobutyryl bromide (160 μ l, 1.30 mmol) were added dropwise to a stirred solution of 3-hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)propan-1-one (**284**) (186 mg, 0.590 mmol) in anhydrous acetonitrile (18 ml) at 0°C under nitrogen. After 30 minutes, the reaction was partitioned between water (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give 2-bromo-2-methyl-propionic acid 2-[(2-bromo-2-methyl-propionyl)-(4-methoxybenzyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (**314**) as a white solid (267 mg, 74%), *R_f* (3:1 petrol:ethyl acetate) 0.36; m.p. 91.5-92.5 °C; ν_{max} (film)/cm⁻¹ 3003, 2933, 2837, 1735, 1674, 1634, 1599, 1511, 1461, 1390, 1370, 1303, 1247, 1157, 1106, 1028, 967, 917, 837, 644; δ_{H} (300 MHz, CDCl₃) 7.80-7.65 (2H, br d, Ar C-H), 7.23 (2H, d, J 8.5 Hz, Ar C-H), 6.90 (2H, br d, Ar C-H), 6.82 (2H, d, J 8.5 Hz, Ar C-H), 5.68 (1H, br m, OCH₂CHN), 5.16 (1H, d, J 15.6 Hz, CH_aH_bN), 4.77 (1H, d, J 15.6 Hz, CH_aH_bN), 4.59 (1H, m, CH_aH_bO), 4.28 (1H, m, CH_aH_bO), 3.85 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 2.00 (6H, br s, CBr[CH₃]₂), 1.88 (6H, br s, CBr[CH₃]₂); δ_{C} (125.8 MHz, CDCl₃) 193.4 (C=O, ketone), 171.1 (C=O, ester), 163.8 (C=O, amide), 159.4 (2 x Ar quat.), 130.5 (Ar C-H), 129.4 (Ar C-H), 128.6 (Ar quat.), 127.4 (Ar quat.), 114.0 (Ar C-H), 113.8 (Ar C-H), 64.0 (CH₂O), 59.7 (OCH₂CHN), 56.9 (2 x BrC[CH₃]₂), 55.5 (OCH₃), 55.3 (OCH₃), 51.8 (CH₂N), 33.4 (BrC[CH₃][CH₃]), 32.8 (BrC[CH₃][CH₃]), 30.8 (BrC[CH₃][CH₃]), 30.7

(BrC[CH₃][CH₃]); m/z (FAB, with TFA) 614 (MH)⁺, 551, 524, 369, 307, 289, 154, 136, 121; [Found: (MH)⁺ 614.0573, C₂₆H₃₁NO₆⁷⁹Br⁸¹Br requires (MH)⁺ 614.0576]; [Found: C, 50.93, 50.91; H, 5.06, 5.08; N, 2.16, 2.25; Br, 25.93, 26.18. C₂₆H₃₁NO₆Br₂ requires C, 50.92; H, 5.09; N, 2.28; Br, 26.06].

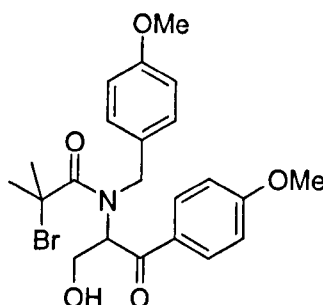
2-Bromo-N-[1-(4-methoxybenzoyl)-vinyl]-N-(4-methoxybenzyl)-2-methyl-propionamide (315)



Potassium *tert*-butoxide (18.3 mg, 0.163 mmol) was added in small portions to a solution of 2-bromo-2-methyl-propionic acid 2-[(2-bromo-2-methyl-propionyl)-(4-methoxybenzyl)-amino]-3-(4-methoxyphenyl)-3-oxo-propyl ester (**314**) (100 mg, 0.163 mmol) in anhydrous THF (4 ml) at room temperature under nitrogen. The reaction was heated to reflux for 2 hours, cooled and partitioned between saturated NH₄Cl solution (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give 2-bromo-N-[1-(4-methoxybenzoyl)-vinyl]-N-(4-methoxybenzyl)-2-methyl-propionamide (**315**) as a colourless oil (54.0 mg, 74%), R_f (3:1 petrol:ethyl acetate) 0.33; ν_{\max} (film)/cm⁻¹ 2933, 2838, 1647, 1600, 1512, 1461, 1394, 1358, 1305, 1250, 1167, 1110, 1031, 974, 843; δ_{H} (300 MHz, CDCl₃) 7.88 (2H, d, J 8.9 Hz, Ar C-H), 7.35 (2H, d, J 8.7 Hz, Ar C-H), 6.91 (2H, d, J 8.9 Hz, Ar C-H), 6.88 (2H, d, J 8.7 Hz, Ar C-H), 5.44 (1H, br s, C=CH_aH_b), 5.37 (1H, br s, C=CH_aH_b), 5.20 (2H, br s, CH₂N), 3.85 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 2.00 (6H, s, CBr[CH₃]₂); δ_{C} (75.5 MHz, CDCl₃) 190.7 (C=O, ketone), 170.6 (C=O, amide), 163.1 and 158.8 (Ar quat.), 145.1 (N-C=CH₂), 132.1 (Ar C-H),

128.9 (Ar quat.), 128.5 (Ar C-H), 128.1 (Ar quat.), 118.0 (N-C=CH₂), 113.7 and 113.3 (Ar C-H), 55.3 and 55.0 (2 x OCH₃), 52.6 (CH₂N), 43.7 (BrC[CH₃]₂), 32.4 (BrC[CH₃]₂); m/z (FAB, with TFA) 448 (MH)⁺, 446 (MH)⁺, 366, 341, 307, 289, 219, 206, 154, 136, 121; [Found: (MH)⁺ 446.0977, C₂₂H₂₄NO₄⁷⁹Br requires (MH)⁺ 446.0977].

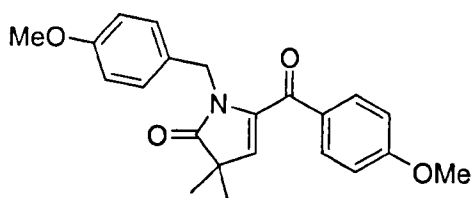
2-Bromo-N-[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-N-(4-methoxybenzyl)-2-methyl-propionamide (316)



Triethylamine (14.6 μ l, 0.105 mmol) and 2-bromoisobutyryl bromide (13.0 μ l, 0.105 mmol) were added dropwise to a stirred solution of 3-hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)-propan-1-one (**284**) (30.0 mg, 0.0951 mmol) in anhydrous acetonitrile (3 ml) at 0°C under nitrogen. After 30 minutes, the reaction was partitioned between water (10 ml) and ethyl acetate (10 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give *2-bromo-N-[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-N-(4-methoxybenzyl)-2-methyl-propionamide (316)* as a pale yellow oil (8.0 mg, 18%), R_f (1:1 petrol:ethyl acetate) 0.29; ν_{\max} (film)/cm⁻¹ 3476 (br, OH), 2930, 2841, 1680, 1601, 1512, 1462, 1417, 1365, 1307, 1250, 1171, 1111, 1030, 954, 838; δ_{H} (300 MHz, CDCl₃) 7.69 (2H, br d, Ar C-H), 7.29 (2H, d, J 8.7 Hz, Ar C-H), 6.89 (4H, d, J 8.7 Hz, Ar C-H), 5.28-5.13 (1H, br d, CH_aH_bN), 4.83-4.66 (2H, m, CH_aH_bN and OCH₂CHN), 4.02 (1H, dd, J 12.0, 5.3 Hz, CH_aH_bO), 3.86 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.82-3.69 (1H, m, CH_aH_bO), 1.99 (3H, br s, CBr[CH₃][CH₃]), 1.95 (1H, br, OH), 1.92 (3H, br

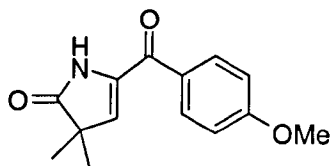
s, CBr[CH₃][CH₃]); m/z (FAB, with TFA) 466 (MH)⁺, 464 (MH)⁺, 384, 341, 307, 289, 219, 154, 136, 121; [Found: (MH)⁺ 466.1047, C₂₂H₂₆NO₅⁸¹Br requires (MH)⁺ 466.1052].

5-(4-Methoxybenzoyl)-1-(4-methoxybenzyl)-3,3-dimethyl-1,3-dihydropyrrol-2-one (317)



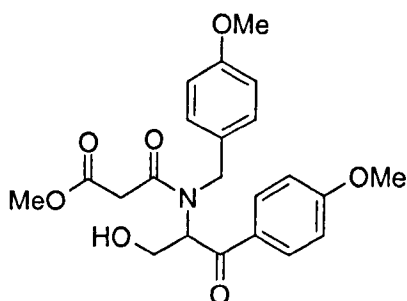
TPA (16.3 mg, 0.0560 mmol) and copper (I) bromide (8.0 mg, 0.0560 mmol) were added to a stirred solution of 2-bromo-*N*-[1-(4-methoxybenzoyl)-vinyl]-*N*-(4-methoxybenzyl)-2-methyl-propionamide (**315**) (50.0 mg, 0.112 mmol) in anhydrous toluene (0.93 ml) under nitrogen. The reaction was heated to reflux for 2 hours, cooled and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 1:1 petrol:ethyl acetate) to give 5-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-3,3-dimethyl-1,3-dihydropyrrol-2-one (**317**) as a colourless gum (34.0 mg, 83%), R_f (1:1 petrol:ethyl acetate) 0.43; ν_{max} (film)/cm⁻¹ 2966, 2932, 2939, 1707, 1645, 1596, 1511, 1461, 1441, 1394, 1342, 1306, 1254, 1167, 1140, 1112, 1029, 901, 845, 773, 613; δ_H (300 MHz, CDCl₃) 7.67 (2H, d, J 8.9 Hz, Ar C-H), 7.08 (2H, d, J 8.7 Hz, Ar C-H), 6.88 (2H, d, J 8.9 Hz, Ar C-H), 6.72 (2H, d, J 8.7 Hz, Ar C-H), 5.77 (1H, s, CH=C-N), 4.96 (2H, s, CH₂N), 3.86 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 1.32 (6H, s, C[CH₃]₂); δ_C (75.5 MHz, CDCl₃) 186.7 (C=O), 182.5 (C=O), 164.2 and 159.1 (Ar quat.), 139.5 (N-C=CH), 132.2 (Ar C-H), 130.3 and 129.8 (Ar quat.), 129.7 (Ar C-H), 129.5 (CH=C-N), 114.2 and 114.0 (Ar C-H), 55.9 and 55.5 (2 x OCH₃), 47.1 (C[CH₃]₂), 43.8 (CH₂N), 23.3 (C[CH₃]₂); m/z (EI) 365 (M)⁺, 337, 247, 206, 144, 121, 115, 91, 77, 69; [Found: (M)⁺ 365.1642, C₂₂H₂₃NO₄ requires (M)⁺ 365.1627].

5-(4-Methoxybenzoyl)-3,3-dimethyl-1,3-dihydropyrrol-2-one (313)



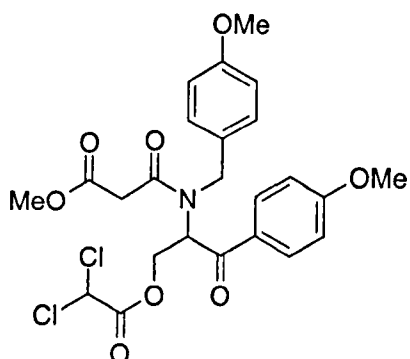
A solution of 5-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-3,3-dimethyl-1,3-dihydropyrrol-2-one (**317**) (14.0 mg, 0.0383 mmol) in trifluoroacetic acid (1 ml) was heated to reflux for 2 hours. The reaction mixture was partitioned between saturated NaHCO₃ solution (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, ethyl acetate) to give 5-(4-methoxybenzoyl)-3,3-dimethyl-1,3-dihydropyrrol-2-one (**313**) as an off-white solid (6.8 mg, 72%), R_f (ethyl acetate) 0.50; m.p. 153.7-154.2 °C; ν_{\max} (film)/cm⁻¹ 3300 (NH), 2969, 2931, 2361, 1715, 1639, 1599, 1510, 1462, 1416, 1384, 1310, 1256, 1170, 1028, 849; δ_{H} (300 MHz, CDCl₃) 7.92 (1H, br s, NH), 7.84 (2H, d, J 8.9 Hz, Ar C-H), 6.97 (2H, d, J 8.9 Hz, Ar C-H), 6.01 (1H, d, J 1.9 Hz, NH-C=CH), 3.88 (3H, s, OCH₃), 1.33 (6H, s, C[CH₃]₂[CO]); δ_{C} (75.5 MHz, CDCl₃) 184.5 (C=O, ketone), 182.0 (C=O, amide), 163.5 (Ar quat.), 137.5 (C=C-NH), 131.0 (Ar C-H), 128.6 (Ar quat.), 128.5 (CH=C-NH), 113.7 (Ar C-H), 55.3 (OCH₃), 48.6 (C[CH₃]₂[CO]), 22.6 (C[CH₃]₂[CO]); m/z (EI) 245 (M)⁺, 230, 202, 187, 174, 159, 135, 107, 92, 82, 77, 64; [Found: (M)⁺ 245.1055, C₁₄H₁₅NO₃ requires (M)⁺ 245.1052].

N-[1-Hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (323)



Triethylamine (48.6 μ l, 0.349 mmol) and methyl-3-chloro-3-oxopropionate (37.4 μ l, 0.349 mmol) were added dropwise to a stirred solution of 3-hydroxy-2-(4-methoxybenzylamino)-1-(4-methoxyphenyl)propan-1-one (**284**) (100 mg, 0.317 mmol) in anhydrous acetonitrile (10 ml) at 0°C under nitrogen. After 1 hour, the reaction was partitioned between water (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , ethyl acetate) to give *N*-[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (**323**) as a pale yellow oil (86.0 mg, 65%), R_f (ethyl acetate) 0.40; ν_{max} (film)/ cm^{-1} 3450 (br, OH), 2952, 2841, 1742, 1645, 1601, 1513, 1438, 1311, 1250, 1173, 1028, 836; δ_{H} (300 MHz, CDCl_3) 7.89 (2H, d, J 8.9 Hz, Ar C-H), 6.97 (2H, d, J 8.7 Hz, Ar C-H), 6.91 (2H, d, J 8.9 Hz, Ar C-H), 6.76 (2H, d, J 8.7 Hz, Ar C-H), 6.03 (1H, dd, J 6.0, 6.0 Hz, OCH_2CHN), 4.47 (2H, s, CH_2N), 4.10-4.00 (1H, m, $\text{CH}_a\text{H}_b\text{O}$), 4.00-3.89 (1H, m, $\text{CH}_a\text{H}_b\text{O}$), 3.88 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.68 (3H, s, $[\text{CO}]\text{OCH}_3$), 3.42 (2H, s, $[\text{CO}]\text{CH}_2[\text{CO}]$), 2.64 (1H, br, OH); δ_{C} (75.5 MHz, CDCl_3) 195.8 ($\text{C}=\text{O}$), 167.7 and 167.5 ($\text{C}=\text{O}$, ester and amide), 163.8 and 158.8 (Ar quat.), 130.7 (Ar C-H), 128.2 and 127.7 (Ar quat.), 127.5, 114.0 and 113.7 (Ar C-H), 60.5 (CH_2O), 59.0 (OCH_2CHN), 55.3 (ArOCH_3), 54.9 (ArOCH_3), 51.8 ($[\text{CO}]\text{OCH}_3$), 49.0 (CH_2N), 41.2 ($[\text{CO}]\text{CH}_2[\text{CO}]$); m/z (FAB, with TFA) 416 (MH)⁺, 369, 307, 219, 193, 154, 136, 121; [Found: (MH)⁺ 416.1710, $\text{C}_{22}\text{H}_{25}\text{NO}_7$ requires (MH)⁺ 416.1709].

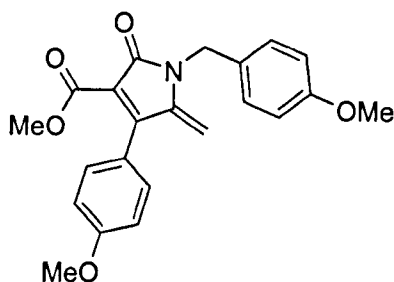
N-[1-(2,2-Dichloro-acetoxymethyl)-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (324)



Triethylamine (48.3 μ l, 0.347 mmol) and dichloroacetyl chloride (33.4 μ l, 0.347 mmol) were added dropwise to a stirred solution of *N*-[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (**323**) (131 mg, 0.315 mmol) in anhydrous acetonitrile (4 ml) at room temperature under nitrogen. After 30 minutes, the reaction was partitioned between water (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 1:1 petrol:ethyl acetate) to give *N*-[1-(2,2-dichloroacetoxymethyl)-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (**324**) as a pale yellow oil (48.0 mg, 29%), R_f (1:1 petrol:ethyl acetate) 0.47; ν_{max} (film)/ cm^{-1} 2954, 2839, 1743, 1650, 1597, 1512, 1413, 1302, 1247, 1164, 1024, 909, 812, 730, 663, 607; δ_{H} (300 MHz, CDCl_3) 7.90 (2H, d, J 9.0 Hz, Ar C-H), 6.92 (2H, d, J 8.7 Hz, Ar C-H), 6.90 (2H, d, J 9.0 Hz, Ar C-H), 6.72 (2H, d, J 8.7 Hz, Ar C-H), 6.55 (1H, dd, J 8.9, 5.1 Hz, OCH_2CHN), 5.99 (1H, s, CHCl_2), 4.69 (1H, dd, J 11.9, 5.1 Hz, $\text{CH}_a\text{H}_b\text{O}$), 4.54 (1H, dd, J 11.9, 9.1 Hz, $\text{CH}_a\text{H}_b\text{O}$), 4.51 (1H, d, J 17.5 Hz, $\text{CH}_a\text{H}_b\text{N}$), 4.40 (1H, d, J 17.5 Hz, $\text{CH}_a\text{H}_b\text{N}$), 3.89 (3H, s, ArOCH_3), 3.75 (3H, s, ArOCH_3), 3.67 (3H, s, $[\text{CO}]\text{OCH}_3$), 3.45 (1H, d, J 15.6 Hz, $[\text{CO}]\text{CH}_a\text{H}_b[\text{CO}]$), 3.38 (1H, d, J 15.6 Hz, $[\text{CO}]\text{CH}_a\text{H}_b[\text{CO}]$); δ_{C} (75.5 MHz, CDCl_3) 194.1 ($\text{C}=\text{O}$, ketone), 168.2 and 167.8 (2 x $\text{C}=\text{O}$), 164.8 and 164.6 ($\text{C}=\text{O}$ and Ar quat.), 159.5 (Ar quat.), 131.5 (Ar C-H), 128.1 (Ar quat.), 127.9 (Ar C-H), 127.7 (Ar quat.), 114.6 and 114.5 (Ar C-H), 64.5 (CHCl_2), 64.3

($\underline{\text{C}}\text{H}_2\text{O}$), 56.0 and 55.7 (2 x $\text{ArO}\underline{\text{C}}\text{H}_3$), 55.2 ($\text{OCH}_2\underline{\text{C}}\text{HN}$), 52.9 ($[\text{CO}]\underline{\text{O}}\text{CH}_3$), 48.5 ($\underline{\text{C}}\text{H}_2\text{N}$), 41.6 ($[\text{CO}]\underline{\text{C}}\text{H}_2[\text{CO}]$); m/z (EI) 525 (M^+), 448, 424, 379, 347, 316, 296, 262, 236, 135, 121, 84, 77; [Found: (M^+) 525.0970, $\text{C}_{24}\text{H}_{25}\text{NO}_8^{35}\text{Cl}_2$ requires (M^+) 525.0957].

1-(4-Methoxybenzyl)-4-(4-methoxyphenyl)-5-methylene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (325)



Method A:

Oxalyl chloride (67.6 μl , 0.776 mmol) was added dropwise over 15 minutes to a stirred solution of *N*-[1-hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (**323**) (293 mg, 0.705 mmol) and triethylamine (217 μl , 1.55 mmol) in anhydrous DCM (10 ml) at 0°C under nitrogen. After 1 hour, the reaction was partitioned between water (20 ml) and ethyl acetate (20 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , 1:1 petrol:ethyl acetate) to give *1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-5-methylene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (325)* as a yellow oil (81.0 mg, 30%), R_f (1:1 petrol:ethyl acetate) 0.39; ν_{max} (film)/ cm^{-1} 2926, 2846, 1735, 1705, 1608, 1512, 1439, 1374, 1296, 1250, 1179, 1138, 1031; δ_{H} (300 MHz, CDCl_3) 7.32 (2H, d, J 8.9 Hz, Ar C-H), 7.22 (2H, d, J 8.7 Hz, Ar C-H), 6.95 (2H, d, J 8.9 Hz, Ar C-H), 6.85 (2H, d, J 8.7 Hz, Ar C-H), 5.14 (1H, d, J 2.3 Hz, C= $\underline{\text{C}}\text{H}_a\text{H}_b$), 4.89 (1H, d, J 2.3 Hz, C= $\underline{\text{C}}\text{H}_a\text{H}_b$), 4.84 (2H, s, $\underline{\text{C}}\text{H}_2\text{N}$), 3.85 (3H, s, OCH_3),

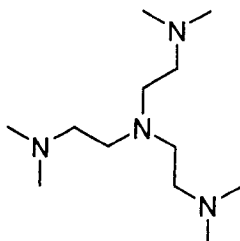
3.79 (3H, s, OCH₃), 3.78 (3H, s, OCH₃); δ_C (125.8 MHz, CDCl₃) 165.6, 163.1, 160.9, 159.0, 152.9 and 144.6 (2 x C=O, 3 x olef. quat. and 2 x Ar quat., 2 signals coincident), 131.1 and 128.7 (Ar C-H), 122.2 and 121.7 (Ar quat.), 114.1 and 113.6 (Ar C-H), 101.7 (C=CH₂), 55.3 (2 x OCH₃), 52.2 (OCH₃), 42.9 (CH₂N); m/z (FAB, with TFA) 380 (MH)⁺, 348, 257, 219, 173, 154, 136, 121; [Found: (MH)⁺ 380.1499, C₂₂H₂₁NO₅ requires (MH)⁺ 380.1498].

Method B:

DBU (22.0 μl, 0.148 mmol) was added to a solution of *N*-[1-(2,2-dichloroacetoxyethyl)-2-(4-methoxyphenyl)-2-oxo-ethyl]-*N*-(4-methoxybenzyl)-malonamic acid methyl ester (**324**) (39.0 mg, 0.0741 mmol) in dry acetonitrile (1 ml) at room temperature under nitrogen. After 10 minutes, the reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO₂, 3:1 petrol:ethyl acetate) to give *1*-(4-methoxybenzyl)-4-(4-methoxyphenyl)-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid methyl ester (**325**) as a yellow oil (26.0 mg, 92%).

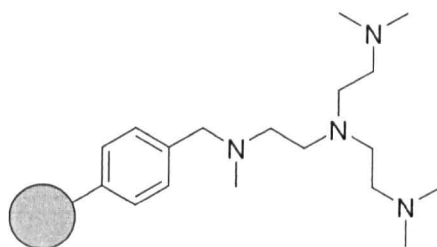
6.5 Experimental for Chapter 5

N,N-Bis-(2-dimethylamino-ethyl)-*N',N'*-dimethyl-ethane-1,2-diamine (*Me₆-tren*) (43)¹⁹²



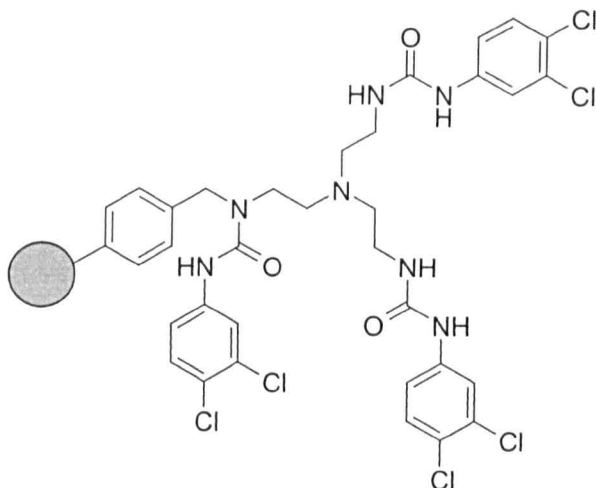
Tris (2-aminoethyl)amine (2.99ml, 20.0 mmol) was cooled to 0°C in an ice bath. Formic acid (12.8 ml, 340 mmol) was added by syringe over 10 minutes, followed by aqueous formaldehyde (22.5 ml, 36% aqueous solution, 292 mmol). The reaction mixture was heated to reflux for 16 hours. The reaction was cooled, concentrated *in vacuo*, brought to pH 12 with 1M NaOH solution, and extracted with chloroform (3 x 25 ml). The combined organic extracts were washed with brine (25 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil (4.97 g, 100%). Purification by vacuum distillation gave *N,N*-bis-(2-dimethylamino-ethyl)-*N',N'*-dimethyl-ethane-1,2-diamine (*Me₆-tren*) (43) as a colourless oil (3.04 g, 66%, bp 69-70°C, 0.6 mm Hg); ν_{\max} (film)/cm⁻¹ 3376, 2940, 2857, 2814, 2761, 1683, 1458, 1262, 1154, 1122, 1030, 936, 856, 775; δ_{H} (400 MHz, CDCl₃) 2.50 (6H, t, J 7.0 Hz, NCH₂CH₂N), 2.27 (6H, t, J 7.0 Hz, NCH₂CH₂N), 2.12 (18H, s, N[CH₃]₂); δ_{C} (75.5 MHz, CDCl₃) 57.2 and 52.8 (NCH₂CH₂N), 45.6 (N[CH₃]₂); *m/z* (EI) 231 (MH)⁺, 229 (M-H)⁺, 228 (M-2H)⁺, 186, 172, 133, 114, 97, 83, 72; [Found: (M-2H)⁺ 228.2310, C₁₂H₃₀N₄ requires (M-2H)⁺ 228.2314].

Polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (PS-Me₆-tren) (338)



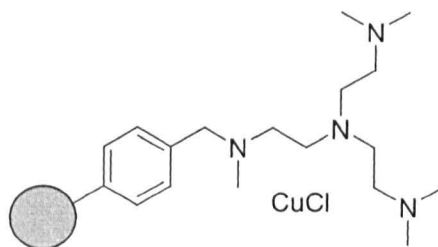
Tris (2-aminoethyl)amine polystyrene (**326**) (*ex* Argonaut; [Found: C, 81.83, 81.80; H, 8.15, 8.17; N, 6.64, 6.54; Cl, 0.58, 0.58]; 1.18 mmol tetramine/g) (3.00 g, 3.53 mmol) was cooled to 0°C in an ice bath. Formic acid (6.79 ml, 180 mmol) was added by syringe over 10 minutes, followed by aqueous formaldehyde (11.9 ml, 36% aqueous solution, 154 mmol). The reaction mixture was heated to reflux for 16 hours. The mixture was cooled and the resin filtered through a pre-tared filter funnel. The resin was washed well with water, DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* to give *polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (PS-Me₆-tren) (338)* (2.99 g) as a white solid; ν_{\max} (solid)/cm⁻¹ 3057, 3023, 2920, 2847, 2766, 1679, 1599, 1491, 1448, 1361, 1113, 1025, 754, 695; [Found: C, 84.27, 84.41; H, 8.52, 8.55; N, 5.67, 5.71; Cl, 0.14, 0.13]; 1.02 mmol tetramine/g; Kaiser test (resin colourless); *p*-chloranil test (resin stained blue). Polymer supported *N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (PS-Me₆-tren) (338)* (100 mg, 0.102 mmol) was added to a solution of 3,4-dichlorophenyl isocyanate (288 mg, 1.53 mmol) in anhydrous DCM (10 ml) under nitrogen. After stirring at room temperature for 16 hours, the resin was filtered, washed with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and dried *in vacuo* at room temperature to give *product (340)* (107 mg); ν_{\max} (solid)/cm⁻¹ 3360, 3056, 3024, 2920, 2845, 2769, 1683, 1599, 1490, 1449, 1023, 754, 696; [Found: C, 81.76, 81.69; H, 8.23, 8.41; N, 4.23, 4.34; Cl, 1.76, 1.68].

Urea (339)



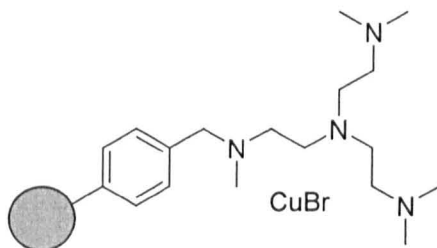
(2-Aminoethyl)amine polystyrene (**326**) (*ex* Argonaut, 1.18 mmol/g) (0.300 g, 0.354 mmol) was added to a solution of 3,4-dichlorophenyl isocyanate (1.41 g, 7.51 mmol) in anhydrous DCM (20 ml) at room temperature under nitrogen. After 16 hours, the reaction mixture was filtered through a pre-tared filter funnel. The resin was washed well with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* to give *urea* (**339**) (432 mg); ν_{\max} (solid)/cm⁻¹ 3312, 3024, 2919, 2849, 1652, 1583, 1513, 1473, 1451, 1403, 1378, 1296, 1223, 1130, 1025, 813, 754, 696; [Found: C, 70.36, 70.25; H, 6.06, 6.05; N, 6.26, 6.31; Cl, 12.72, 12.83].

Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine copper (I) chloride complex (PS-Me₆-tren.CuCl) (341a)



Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (PS-Me₆-tren) (**338**) (0.800 g, 0.816 mmol) was added to a stirred solution of copper (I) chloride (96.9 mg, 0.979 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the bright green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine copper (I) chloride complex (PS-Me₆-tren.CuCl) (341a)* (932 mg); ν_{\max} (solid)/cm⁻¹ 3350, 3057, 3024, 2322, 1664, 1597, 1492, 1451, 1366, 1179, 1024, 942, 908, 757, 698; [Found: C, 70.06, 69.89; H, 7.06, 7.04; N, 4.75, 4.86; Cu, 8.10]; 1.28 mmol Cu/g; 0.858 mmol ligand/g.

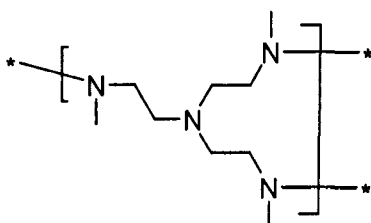
Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine copper (I) bromide complex (PS-Me₆-tren.CuBr) (341b)



Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (PS-Me₆-tren) (**338**) (1.20 g, 1.22 mmol) was added to a stirred solution of copper (I) bromide (211 mg, 1.47 mmol) in dry acetonitrile (15 ml) at room temperature

under nitrogen. After 30 minutes, the bright green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine copper (I) bromide complex (PS-Me₆-tren.CuBr) (341b)* (1.50 g); ν_{\max} (solid)/cm⁻¹ 3409, 3056, 3024, 2919, 2321, 1665, 1598, 1492, 1449, 1367, 1179, 1023, 941, 908, 756, 698; [Found: C, 68.13, 67.95; H, 6.87, 6.86; N, 4.71, 4.62; Cu, 6.79, 6.77]; 1.07 mmol Cu/g; 0.834 mmol ligand/g.

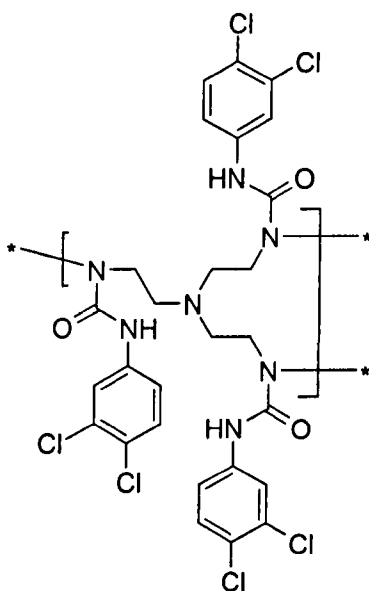
Polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (cross-linked) (PS(CL)-Me₆-tren) (343)



Tris (2-aminoethyl)amine, polymer bound (**342**) (*ex* Aldrich; [Found; C, 82.24, 82.14; H, 8.15, 8.14; N, 6.36, 6.31; Cl, 0.40, 0.35]; 1.13 mmol tetramine/g) (4.70 g, 5.32 mmol) was cooled to 0°C in an ice bath. Formic acid (10.2 ml, 271 mmol) was added by syringe over 10 minutes, followed by aqueous formaldehyde (18.0 ml, 36% aqueous solution, 239 mmol). The reaction mixture was heated to reflux for 16 hours. The mixture was cooled and the resin filtered through a pre-tared filter funnel. The resin was washed well with water, DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* at room temperature to give *polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (cross-linked) (PS(CL)-Me₆-tren) (343)* (4.70 g) as a white solid; ν_{\max} (solid)/cm⁻¹ 3057, 3023, 2920, 2846, 2765, 1677, 1600, 1491, 1448, 1360, 1113, 1024, 754, 696; [Found: C, 84.07, 84.14; H, 8.55, 8.54; N, 5.99, 6.00; Cl, 0.22, 0.07]; 1.07 mmol tetramine/g; Kaiser test (resin colourless); *p*-chloranil test (resin stained orange brown). Polystyrene supported *N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (cross-linked) (PS(CL)-Me₆-tren) (343)* (100 mg, 0.107 mmol) was added to a solution of 3,4-dichlorophenyl

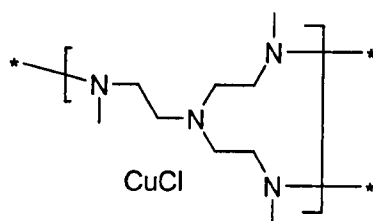
isocyanate (302 mg, 1.61 mmol) in anhydrous DCM (10 ml) under nitrogen. After stirring at room temperature for 16 hours, the resin was filtered, washed with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and dried *in vacuo* at room temperature to give *product (345)* (107 mg) as a cream solid; ν_{\max} (solid)/cm⁻¹ 3377, 3056, 3023, 2918, 2846, 2773, 1686, 1600, 1490, 1448, 1361, 1115, 1022, 755, 696; [Found: C, 80.39, 80.56; H, 8.38, 8.35; N, 5.45, 5.39; Cl, 3.88, 3.37].

Urea (344)



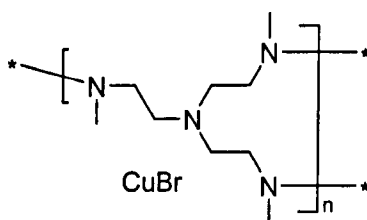
Tris (2-aminoethyl)amine, polymer bound (**342**) (*ex* Aldrich, 1.13 mmol/g) (100 mg, 0.113 mmol) was added to a solution of 3,4-dichlorophenyl isocyanate (369 mg, 1.96 mmol) in anhydrous DCM (20 ml) at room temperature under nitrogen. After 16 hours, the reaction mixture was filtered through a pre-tared filter funnel. The resin was washed well with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* at room temperature to give *urea (344)* (140 mg); ν_{\max} (solid)/cm⁻¹ 3300, 3055, 3023, 2919, 2849, 1660, 1583, 1511, 1473, 1450, 1403, 1379, 1295, 1223, 1130, 1024, 753, 696; [Found: C, 71.60, 71.58; H, 6.25, 6.24; N, 6.45, 6.43; Cl, 10.55, 10.63].

Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (cross-linked) copper (I) chloride complex (PS- Me_6 -tren.CuCl) (346a)



Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (cross-linked) (PS(CL)- Me_6 -tren) (**343**) (1.00g, 1.07 mmol) was added to a stirred solution of copper (I) chloride (127 mg, 1.28 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (cross-linked) copper (I) chloride complex (PS- Me_6 -tren.CuCl) (346a)* (1.19 g); ν_{\max} (solid)/ cm^{-1} 3357, 3057, 3024, 2929, 2321, 2169, 2047, 1985, 1664, 1582, 1493, 1450, 1363, 1180, 1023, 942, 821, 757, 698; [Found: C, 70.73, 70.53; H, 7.15, 7.16; N, 4.98, 4.95; Cu, 6.81, 6.75]; 1.07 mmol Cu/g; 0.888 mmol ligand/g.

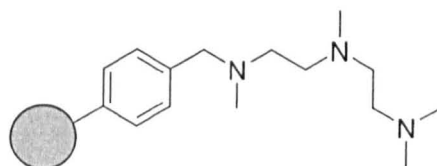
Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (cross-linked) copper (I) bromide complex (PS- Me_6 -tren.CuBr) (346b)



Polystyrene supported N,N -bis-(2-dimethylamino-ethyl)- N',N' -dimethyl-ethane-1,2-diamine (cross-linked) (PS(CL)- Me_6 -tren) (**343**) (1.00 g, 1.07 mmol) was added to a

stirred solution of copper (I) bromide (184 mg, 1.28 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N,N-bis-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine (cross-linked) copper (I) bromide complex (PS-Me₆-tren.CuBr) (346b)* (1.22 g); ν_{\max} (solid)/cm⁻¹ 3378, 3055, 3024, 2918, 2321, 2169, 2049, 1986, 1664, 1598, 1493, 1449, 1363, 1179, 1023, 821, 757, 698; [Found: C, 68.52, 68.33; H, 6.93, 6.89; N, 4.79, 4.73; Cu, 6.40, 6.39]; 1.01 mmol Cu/g; 0.850 mmol ligand/g.

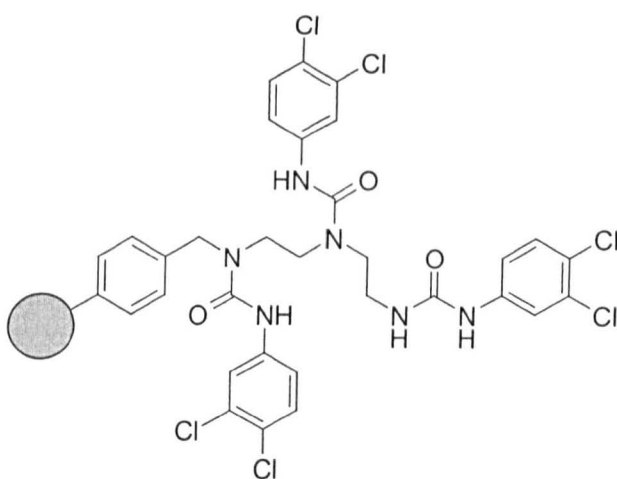
Polystyrene supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine (PS-PMDETA) (347)



Stratospheres PL-DETA (diethylenetriamine) resin (**327**) (*ex* Aldrich; [Found: C, 77.36, 77.54; H, 8.78, 8.76; N, 11.30, 11.58; Cl 0.07, 0.07]; 2.72 mmol triamine/g) (4.50 g, 12.2 mmol) was cooled to 0°C in an ice bath. Formic acid (23.4 ml, 622 mmol) was added by syringe over 10 minutes, followed by aqueous formaldehyde (41.2 ml, 36% aqueous solution, 549 mmol). The reaction mixture was heated to reflux for 16 hours. The mixture was cooled and the resin filtered through a pre-tared filter funnel. The resin was washed well with water, DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* at room temperature to give *polystyrene supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine (PS-PMDETA) (347)* (5.07 g) as a white solid; ν_{\max} (solid)/cm⁻¹ 3024, 2924, 2764, 1673, 1602, 1489, 1448, 1361, 1285, 1119, 1025, 788, 760, 699; [Found: C, 78.82, 78.97; H, 9.23, 9.25; N, 9.90, 9.86; Cl, 0.05, 0.00]; 2.35 mmol triamine/g; Kaiser test (resin colourless); *p*-chloranil test (resin stained orange brown then green). Polystyrene supported *N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine* (PS-

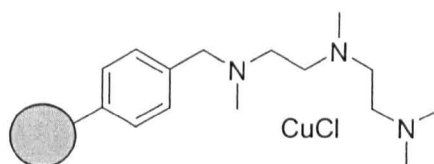
PMDETA) (**347**) (150 mg, 0.353 mmol) was added to a solution of 3,4-dichlorophenyl isocyanate (799 mg, 4.25 mmol) in anhydrous DCM (10 ml) at room temperature under nitrogen. After stirring for 16 hrs, the resin was filtered, washed with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and dried *in vacuo* at room temperature to give *product* (**349**) (165 mg); ν_{\max} (solid)/cm⁻¹ 3349, 3022, 2922, 2765, 1725, 1668, 1595, 1448, 1362, 1299, 1220, 1120, 1024, 760, 699; [Found: C, 75.26, 75.19; H, 8.85, 8.80; N, 9.51, 9.36; Cl, 3.39, 3.57].

Urea (**348**)



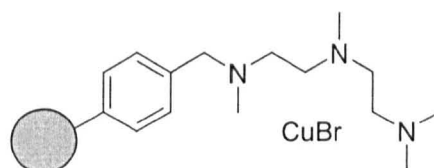
Stratospheres PL-DETA (diethylenetriamine)resin (**327**) (*ex* Aldrich, 2.72 mmol/g) (100 mg, 0.272 mmol) was added to a solution of 3,4-dichlorophenyl isocyanate (614 mg, 3.26 mmol) in anhydrous DCM (10 ml) under nitrogen. After 16 hours at room temperature, the reaction mixture was filtered through a pre-tared filter funnel. The resin was washed well with DCM, MeOH, DMF, Et₃N, MeOH, DCM, Et₃N, MeOH, DCM, MeOH, DCM and MeOH, and was dried *in vacuo* at room temperature to give *urea* (**348**) (271 mg); ν_{\max} (solid)/cm⁻¹ 3338, 3309, 3085, 2920, 2359, 1649, 1585, 1521, 1472, 1406, 1375, 1298, 1224, 1129, 1025, 811, 697; [Found: C, 56.48, 56.40; H, 4.57, 4.50; N, 8.61, 8.56; Cl, 22.14, 21.74].

Polystyrene supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine copper (I) chloride complex (PS-PMDETA.CuCl) (350a)



Polystyrene supported *N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine (PS-PMDETA) (**347**) (1.50 g, 3.53 mmol) was added to a stirred solution of copper (I) chloride (422 mg, 4.27 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the dark green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine copper (I) chloride complex (PS-PMDETA.CuCl) (350a)* (2.02 g); ν_{\max} (solid)/ cm^{-1} 3366, 3023, 2917, 2322, 2169, 2047, 1985, 1659, 1599, 1453, 1368, 1160, 1022, 963, 804, 765, 702; [Found: C, 58.74, 58.80; H, 7.30, 7.34; N, 7.59, 7.60; Cu, 12.63, 12.54]; 1.98 mmol Cu/g; 1.81 mmol ligand/g.

Polystyrene supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine copper (I) bromide complex (PS-PMDETA.CuBr) (350b)

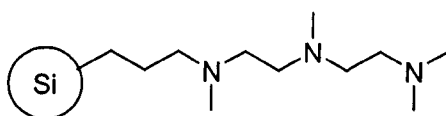


Polystyrene supported *N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine (PS-PMDETA) (**347**) (1.50 g, 3.53 mmol) was added to a stirred solution of copper (I) bromide (612 mg, 4.27 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the dark green resin was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N-(2-dimethylamino-ethyl)-*

N,N,N'-trimethyl-ethane-1,2-diamine copper (I) bromide complex (PS-PMDETA.CuBr) (**350b**) (2.17 g); ν_{\max} (solid)/ cm^{-1} 3380, 3023, 2919, 2322, 2170, 2054, 1987, 1659, 1600, 1022, 963, 803, 765, 702; [Found: C, 54.20, 54.48; H, 6.50, 6.73; N, 6.85, 6.36; Cu, 11.32, 11.24]; 1.78 mmol Cu/g; 1.57 mmol ligand/g.

Attempted synthesis of:

Silica supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine (Si-PMDETA) (352) and (353)



Using Eschweiler-Clarke methylation (method A):

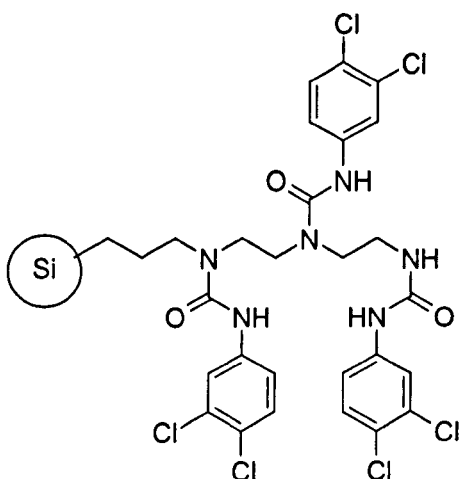
3-Propyldiethylenetriamine functionalised silica gel (**351**) (*ex* Aldrich; [Found: C, 12.28, 12.27; H, 3.00, 3.00; N, 5.33, 5.38; Cl, 0.24, 0.38]; 1.28 mmol triamine/g) (4.50 g, 5.76 mmol) was cooled to 0°C in an ice bath. Formic acid (11.0 ml, 294 mmol) was added by syringe over 10 minutes, followed by aqueous formaldehyde (19.4 ml, 36% aqueous solution, 259 mmol). The reaction mixture was heated to reflux for 16 hours. The mixture was cooled and the resin filtered through a pre-tared filter funnel. The resin was washed repeatedly with 19:1 DCM:MeOH, and was dried *in vacuo* at room temperature to give a white solid (**352**) (3.75 g); ν_{\max} (solid)/ cm^{-1} 3245, 1591, 1044, 795; [Found: C, 7.55, 7.35; H, 1.90, 1.90; N, 1.80, 1.78; Cl, 0.00, 0.00]; Kaiser test (solid initially colourless, stains pale black after 30 seconds); *p*-chloranil test (silica stained dark green). The white solid (**352**) (150 mg) was added to a solution of 3,4-dichlorophenyl isocyanate (144 mg, 0.767 mmol) in anhydrous DCM (10 ml) at room temperature under nitrogen. After stirring at room temperature for 16 hours, the solid was filtered, washed with 19:1 DCM:MeOH, and dried *in vacuo* at room temperature to give a white solid (**355**) (148

mg); ν_{\max} (solid)/ cm^{-1} 1050, 797; [Found: C, 8.33, 8.12; H, 1.69, 1.64; N, 1.92, 1.89; Cl, 0.88, 0.81].

Using methyl iodide (method B):

Methyl iodide (1.27 ml, 20.4 mmol) was added to a suspension of 3-propyldiethylenetriamine functionalised silica gel (**351**) (*ex* Aldrich; [Found: C, 12.28, 12.27; H, 3.00, 3.00; N, 5.33, 5.38; Cl, 0.24, 0.38]; 1.28 mmol triamine/g) (4.00 g, 5.10 mmol) in anhydrous DCM (40 ml) at room temperature under nitrogen. After 16 hours, the solid was filtered through a pre-tared filter funnel, washed repeatedly with 19:1:0.5 DCM:MeOH:Et₃N, and dried *in vacuo* at room temperature to give a white solid (**353**) (4.43 g); [Found: C, 12.31, 12.21; H, 2.73, 2.71; N, 4.81, 4.79; I, 6.62, 6.55]. The white solid (**353**) (150 mg) was added to a solution of 3,4-dichlorophenyl isocyanate (387 mg, 2.06 mmol) in anhydrous DCM (10 ml) at room temperature under nitrogen. After stirring at room temperature for 16 hours, the solid was filtered, washed with 19:1 DCM:MeOH, and dried *in vacuo* at room temperature to give a white solid (**356**) (161 mg); [Found: C, 15.23, 15.43; H, 2.63, 2.66; N, 5.00, 5.01; Cl, 3.79, 3.82].

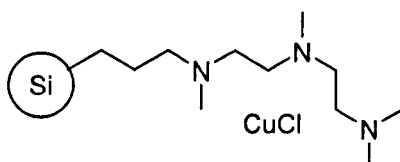
Urea (354)



3-Propyldiethylenetriamine functionalised silica gel (**351**) (*ex* Aldrich; 1.28 mmol triamine/g) (100 mg, 0.128 mmol) was added to a stirred solution of 3,4-dichlorophenyl

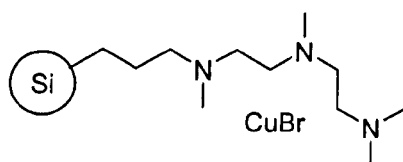
isocyanate (289 mg, 1.54 mmol) in anhydrous DCM (10 ml) at room temperature under nitrogen. After 16 hours, the reaction mixture was filtered through a pre-tared filter funnel. The solid was washed well with 19:1 DCM:MeOH, and dried *in vacuo* at room temperature to give a white solid (**354**) (127 mg); ν_{\max} (solid)/ cm^{-1} 3303, 2938, 1652, 1589, 1534, 1476, 1041, 792; [Found: C, 17.15, 17.16; H, 2.71, 2.54; N, 5.94, 5.67; Cl, 5.86, 5.87].

Silica supported *N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine copper chloride complex (Si-PMDETA.CuCl) (357a**)**



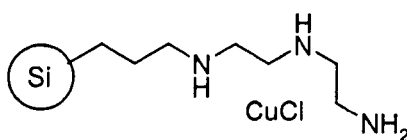
Silica supported *N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine (Si-PMDETA) (**353**) (1.50 g, 1.71 mmol) *ex methyl iodide* reaction was added to a stirred solution of copper (I) chloride (204 mg, 2.06 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the turquoise solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *silica supported N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine copper chloride complex (Si-PMDETA.CuCl) (**357a**) (1.60 g); ν_{\max} (solid)/ cm^{-1} 3233, 2941, 2647, 1465, 1039, 793; [Found: C, 11.50, 11.42; H, 2.55, 2.53; N, 4.53, 4.48; Cu, 4.88, 4.84]; 0.765 mmol Cu/g; 1.07 mmol ligand/g.

Silica supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine copper bromide complex (Si-PMDETA.CuBr) (357b)



Silica supported *N*-(2-dimethylamino-ethyl)-*N,N',N'*-trimethyl-ethane-1,2-diamine (Si-PMDETA) (**353**) (1.50 g, 1.71 mmol) *ex* methyl iodide reaction was added to a stirred solution of copper (I) bromide (295 mg, 2.06 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the turquoise solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *silica supported N-(2-dimethylamino-ethyl)-N,N',N'-trimethyl-ethane-1,2-diamine copper bromide complex (Si-PMDETA.CuBr) (357b)* (1.63 g); ν_{\max} (solid)/ cm^{-1} 3249, 2944, 2321, 1648, 1465, 1037, 793; [Found: C, 11.29, 11.22; H, 2.48, 2.47; N, 4.42, 4.42; Cu, 4.26, 4.23]; 0.668 mmol Cu/g; 1.05 mmol ligand/g.

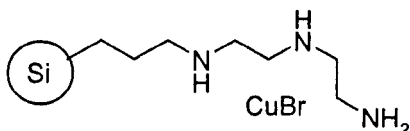
3-Propyldiethylenetriamine functionalised silica gel copper chloride complex (Si-DETA.CuCl) (358a)



3-Propyldiethylenetriamine functionalised silica gel (Si-DETA) (**351**) (*ex* Aldrich; [Found: C, 12.28, 12.27; H, 3.00, 3.00; N, 5.33, 5.38; Cl, 0.24, 0.38]; 1.28 mmol triamine/g) (1.50 g, 1.91 mmol) was added to a stirred solution of copper (I) chloride (227 mg, 2.30 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the turquoise solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *3-propyldiethylenetriamine functionalised silica gel copper chloride complex (Si-*

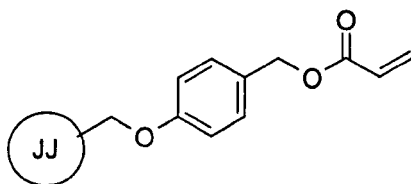
DETA.CuCl (**358a**) (1.73 g); ν_{\max} (solid)/ cm^{-1} 3227, 2942, 1041, 794; [Found: C, 10.37, 10.34; H, 2.36, 2.35; N, 4.63, 4.60; Cu, 6.92, 6.92]; 1.09 mmol Cu/g; 1.10 mmol ligand/g.

3-Propyldiethylenetriamine functionalised silica gel copper bromide complex (Si-DETA.CuBr) (358b)



3-Propyldiethylenetriamine functionalised silica gel (Si-DETA) (**351**) (ex Aldrich; [Found: C, 12.28, 12.27; H, 3.00, 3.00; N, 5.33, 5.38; Cl, 0.24, 0.38]; 1.28 mmol triamine/g) (1.50 g, 1.91 mmol) was added to a stirred solution of copper (I) bromide (329 mg, 2.30 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the turquoise solid was filtered, washed well with acetonitrile and dried *in vacuo* to give 3-propyldiethylenetriamine functionalised silica gel copper bromide complex (*Si-DETA.CuBr*) (**358b**) (1.75 g); ν_{\max} (solid)/ cm^{-1} 3246, 2938, 2321, 1647, 1038, 793; [Found: C, 10.15, 10.13; H, 2.24, 2.27; N, 4.50, 4.49; Cu, 6.15, 6.08]; 0.962 mmol Cu/g; 1.07 mmol ligand/g.

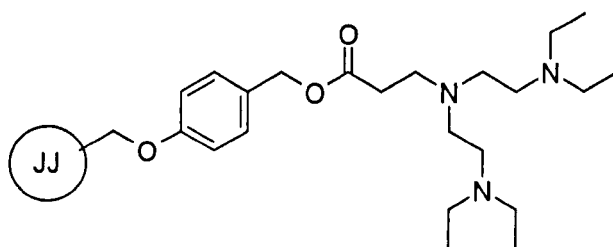
JandaJel supported acrylate (JJ-Acrylate) (360)¹⁹¹



JandaJel-OH (**359**) (ex Aldrich; [Found: C, 89.10, 89.05; H, 7.91, 7.90; N, 0.10, 0.08]; 0.916 mmol OH/g) (4.90 g, 4.46 mmol) was dispersed in anhydrous THF (70 ml) under nitrogen and was cooled to 0°C. Triethylamine (6.22 ml, 44.6 mmol) was added,

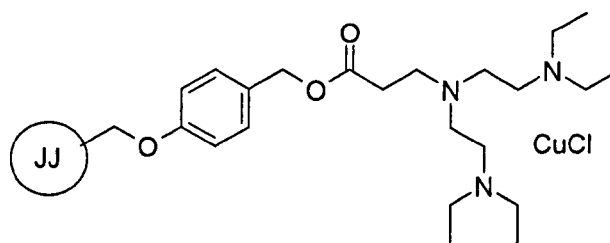
followed by the dropwise addition of acryloyl chloride (3.62 ml, 44.6 mmol). After stirring at room temperature for 11 days, the solids were collected by filtration and washed 10 times with water and 5 times with THF. The gel was dried to constant weight under reduced pressure to give *JandaJel supported acrylate (JJ-Acrylate) (360)* (5.73 g) as an orange solid; ν_{\max} (solid)/ cm^{-1} 3371, 3059, 3025, 2918, 2849, 2323, 1721 (C=O), 1602, 1493, 1448, 1401, 1267, 1178, 1062, 1025, 981, 754, 696; [Found: C, 82.45, 82.60; H, 7.47, 7.49; N, 0.77, 0.66]; 1.93 mmol acrylate/g.

***JandaJel supported N,N,N,N',N'-tetraethyldiethylenetriamine (JJ-TEDETA) (334)*¹⁹¹**



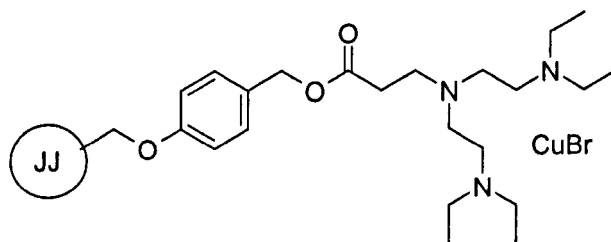
N,N,N,N',N'- Tetraethyldiethylenetriamine (5.00 ml, 19.4 mmol) was added to a suspension of *JandaJel supported acrylate (JJ-Acrylate) (360)* (4.50 g, 8.69 mmol) in anhydrous THF (100 ml) at room temperature under nitrogen. After 48 hours, the solids were filtered, washed several times with THF and dried *in vacuo* to give *JandaJel supported N,N,N,N',N'-tetraethyldiethylenetriamine (JJ-TEDETA) (334)* (4.42 g) as an orange solid; ν_{\max} (solid)/ cm^{-1} 3296, 3060, 3025, 2920, 2848, 1724 (C=O), 1602, 1493, 1448, 1374, 1244, 1175, 1065, 1027, 908, 815, 753, 696; [Found: C, 83.99, 83.94; H, 8.01, 8.02; N, 2.10, 2.08]; 0.497 mmol ligand/g.

JandaJel supported *N,N,N,N',N'*- tetraethyldiethylenetriamine copper (I) chloride complex (JJ-TEDETA.CuCl) (361a)



JandaJel supported *N,N,N,N',N'*- tetraethyldiethylenetriamine (JJ-TEDETA) (**334**) (1.90g, 0.945 mmol) was added to a stirred solution of copper (I) chloride (93.5 mg, 0.945 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *JandaJel supported N,N,N,N',N'*- tetraethyldiethylenetriamine copper (I) chloride complex (JJ-TEDETA.CuCl) (**361a**) as a dark green solid (1.96 g); ν_{\max} (solid)/ cm^{-1} 3371, 3059, 3026, 2920, 2321, 2169, 1723, 1601, 1493, 1451, 1401, 1268, 1178, 1026, 816, 754, 697; [Found: C, 79.87, 79.71; H, 7.47, 7.46; N, 1.89, 1.85; Cu, 2.8, 2.6]; 0.425 mmol Cu/g; 0.445 mmol ligand/g.

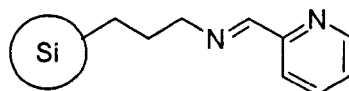
JandaJel supported *N,N,N,N',N'*- tetraethyldiethylenetriamine copper (I) bromide complex (JJ-TEDETA.CuBr) (361b)¹⁹¹



JandaJel supported *N,N,N,N',N'*- tetraethyldiethylenetriamine (JJ-TEDETA) (**334**) (1.90g, 0.945 mmol) was added to a stirred solution of copper (I) bromide (136 mg, 0.945 mmol) in dry acetonitrile (20 ml) at room temperature under nitrogen. After 30 minutes, the

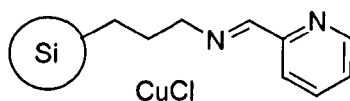
solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *JandaJel* supported *N,N,N,N',N'*- tetraethyldiethylenetriamine copper (I) bromide complex (*JJ-TEDETA.CuBr*) (**361b**) as a dark green solid (1.96 g); ν_{\max} (solid)/ cm^{-1} 3396, 3058, 3026, 2921, 2321, 2169, 2046, 1984, 1723, 1601, 1509, 1493, 1452, 1400, 1267, 1177, 1026, 817, 755, 697; [Found: C, 78.31, 78.26; H, 7.33, 7.32; N, 1.90, 1.87; Cu, 2.8, 2.7]; 0.433 mmol Cu/g; 0.449 mmol ligand/g.

Silica supported N-alkyl-2-pyridylmethanimine (Si-NPMI) (363)³⁵



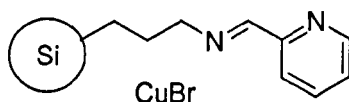
A mixture of aminopropylated silica gel (**362**) (*ex* Aldrich; [Found: C, 7.50, 7.42, 7.06; H, 1.82, 1.78, 1.82; N, 2.21, 1.17, 1.90]; 1.26 mmol $-\text{NH}_2/\text{g}$) (4.00 g, 5.04 mmol) and pyridine-2-carboxaldehyde (4.26 ml, 45.0 mmol) in dry toluene (100 ml) was heated to reflux for 24 hours with a soxhlet containing crushed 4Å molecular sieves (10.0 g). The orange solid was filtered, washed with toluene (3 x 50 ml), DCM (3 x 20 ml) and ethanol (10 ml), and dried *in vacuo* to give *silica supported N-alkyl-2-pyridylmethanimine (Si-NPMI) (363)* as an orange solid (4.35 g); ν_{\max} (solid)/ cm^{-1} 1045, 796; [Found: C, 15.27, 15.23; H, 1.81, 1.74; N, 3.56, 3.51]; 1.26 mmol ligand /g.

Silica supported *N*-alkyl-2-pyridylmethanimine copper (I) chloride complex (Si-NPMI.CuCl) (336a)³⁵



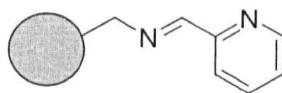
Silica supported *N*-alkyl-2-pyridylmethanimine (Si-NPMI) (**363**) (1.00g, 1.26 mmol) was added to a stirred solution of copper (I) chloride (125 mg, 1.26 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give silica supported *N*-alkyl-2-pyridylmethanimine copper (I) chloride complex (Si-NPMI.CuCl) (**336a**) as a brown solid (1.12 g); ν_{\max} (solid)/ cm^{-1} 3346, 1642, 1601, 1043, 792; [Found: C, 14.01, 13.76; H, 1.68, 1.75; N, 2.48, 2.42; Cu, 5.17, 5.14]; 0.812 mmol Cu/g; 0.875 mmol ligand/g.

Silica supported *N*-alkyl-2-pyridylmethanimine copper (I) bromide complex (Si-NPMI.CuBr) (336b)³⁵



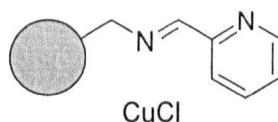
Silica supported *N*-alkyl-2-pyridylmethanimine (Si-NPMI) (**363**) (1.00g, 1.26 mmol) was added to a stirred solution of copper (I) bromide (181 mg, 1.26 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give silica supported *N*-alkyl-2-pyridylmethanimine copper (I) bromide complex (Si-NPMI.CuBr) (**336b**) as a brown solid (1.16 g); ν_{\max} (solid)/ cm^{-1} 3357, 1641, 1601, 1045, 793; [Found C, 13.58, 13.52; H, 1.76, 1.67; N, 3.42, 3.07; Cu, 4.38, 4.38]; 0.689 mmol Cu/g; 1.16 mmol ligand/g.

*Polystyrene supported N-alkyl-2-pyridylmethanimine (PS-NPMI) (329)*¹⁸⁶



A mixture of (aminomethyl)polystyrene (**364**) (*ex* Aldrich, 1% cross linked; [Found: C, 86.40, 86.44; H, 7.82, 7.89; N, 2.35, 2.29]; 1.66 mmol -NH₂/g) (4.50 g, 7.47 mmol) and pyridine-2-carboxaldehyde (6.41 ml, 67.5 mmol) in dry toluene (100 ml) was heated to reflux for 24 hours with a soxhlet containing crushed 4Å molecular sieves (10.0 g). The resin was filtered, washed with anhydrous toluene (10 x 25 ml) and dried *in vacuo* to give *polystyrene supported N-alkyl-2-pyridylmethanimine (PS-NPMI) (329)* as an orange solid (4.97 g); ν_{\max} (solid)/cm⁻¹ 3057, 3025, 2919, 2850, 2320, 1700, 1646 (C=N), 1594, 1492, 1452, 1361, 1152, 1072, 1025, 994, 755, 697; [Found: C, 88.05, 88.21; H, 7.28, 7.30; N, 3.29, 3.30]; 1.18 mmol ligand /g.

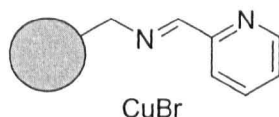
Polystyrene supported N-alkyl-2-pyridylmethanimine copper (I) chloride complex (PS-NPMI.CuCl) (365a)



Polystyrene supported *N*-alkyl-2-pyridylmethanimine (PS-NPMI) (**329**) (1.00g, 1.18 mmol) was added to a stirred solution of copper (I) chloride (117 mg, 1.18 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N-alkyl-2-pyridylmethanimine copper (I) chloride complex (PS-NPMI.CuCl) (365a)* as a black solid (1.06 g); ν_{\max} (solid)/cm⁻¹ 3057, 3025, 2919, 2851, 2320, 1744, 1643 (C=N), 1600, 1492, 1448, 1371, 1303, 1223, 1156, 1024, 907, 842, 755, 697; [Found: C, 82.12,

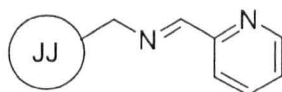
82.00; H, 6.65, 6.63; N, 3.33, 3.32; Cu, 3.30, 3.22]; 0.513 mmol Cu/g; 1.19 mmol ligand/g.

*Polystyrene supported N-alkyl-2-pyridylmethanimine copper (I) bromide complex (PS-NPMI.CuBr) (365b)*¹⁸⁶



Polystyrene supported *N*-alkyl-2-pyridylmethanimine (PS-NPMI) (**329**) (1.00g, 1.18 mmol) was added to a stirred solution of copper (I) bromide (169 mg, 1.18 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give *polystyrene supported N-alkyl-2-pyridylmethanimine copper (I) bromide complex (PS-NPMI.CuBr) (365b)* as a black solid (1.29 g); ν_{\max} (solid)/ cm^{-1} 3057, 3024, 2919, 2850, 2289, 1643 (C=N), 1599, 1492, 1447, 1370, 1303, 1221, 1154, 1070, 1024, 907, 841, 755, 697; [Found: C, 78.65, 79.23; H, 6.35, 6.43; N, 3.29, 3.27; Cu, 3.40, 3.27]; 0.526 mmol Cu/g; 1.17 mmol ligand/g.

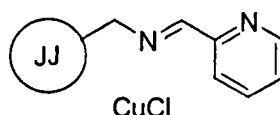
*JandaJel supported N-alkyl-2-pyridylmethanimine (JJ-NPMI) (335)*¹⁹¹



A mixture of JandaJel-NH₂ (**366**) (ex Aldrich; [Found: C, 89.17, 89.16; H, 7.85, 7.88; N, 0.90, 0.88]; 0.635 mmol -NH₂/g) (5.08 g, 3.22 mmol) and pyridine-2-carboxaldehyde (613 μl , 6.45 mmol) in dry toluene (100 ml) was heated to reflux for 16 hours with a soxhlet containing crushed 4Å molecular sieves (5.0 g). The resin was filtered, washed with anhydrous toluene (10 x 25 ml) and dried *in vacuo* to give *JandaJel supported N-*

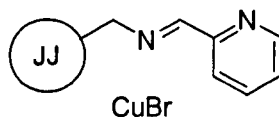
N-alkyl-2-pyridylmethanimine (JJ-NPMI) (**335**) as a yellow solid (5.02 g); ν_{\max} (solid)/ cm^{-1} 3058, 3025, 2917, 2850, 1645 (C=N), 1601, 1510, 1493, 1452, 1368, 1239, 1178, 1111, 1024, 906, 825, 754, 695; [Found: C, 89.11, 89.09; H, 7.64, 7.64; N, 1.46, 1.46]; 0.521 mmol ligand/g.

JandaJel supported *N*-alkyl-2-pyridylmethanimine copper (I) chloride complex (JJ-NPMI.CuCl) (367a)



JandaJel supported *N*-alkyl-2-pyridylmethanimine (JJ-NPMI) (**335**) (1.00g, 0.521 mmol) was added to a stirred solution of copper (I) chloride (51.6 mg, 0.521 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was filtered, washed well with acetonitrile and dried *in vacuo* to give JandaJel supported *N*-alkyl-2-pyridylmethanimine copper (I) chloride complex (JJ-NPMI.CuCl) (**367a**) as a brown solid (952 mg); ν_{\max} (solid)/ cm^{-1} 3391, 3058, 3025, 2919, 2850, 2320, 1674, 1601, 1509, 1493, 1451, 1370, 1240, 1177, 1025, 907, 828, 754, 696; [Found: C, 85.92, 85.72; H, 7.26, 7.17; N, 1.49, 1.47; Cu, 1.62]; 0.255 mmol Cu/g; 0.528 mmol ligand/g.

JandaJel supported *N*-alkyl-2-pyridylmethanimine copper (I) bromide complex (JJ-NPMI.CuBr) (367b)¹⁹¹



JandaJel supported *N*-alkyl-2-pyridylmethanimine (JJ-NPMI) (**335**) (1.00g, 0.521 mmol) was added to a stirred solution of copper (I) bromide (74.7 mg, 0.521 mmol) in dry acetonitrile (10 ml) at room temperature under nitrogen. After 30 minutes, the solid was

filtered, washed well with acetonitrile and dried *in vacuo* to give *JandaJel supported N-alkyl-2-pyridylmethanimine copper (I) bromide complex (JJ-NPMI.CuBr) (367b)* as a brown solid (1.01g); ν_{\max} (solid)/ cm^{-1} 3402, 3058, 3025, 2919, 2851, 1601, 1509, 1493, 1452, 1370, 1240, 1178, 1025, 828, 754, 696; [Found: C, 83.99, 83.94; H, 7.09, 7.07; N, 1.45, 1.46; Cu, 2.87]; 0.452 mmol Cu/g; 0.519 mmol ligand/g.

***Kaiser test for determining primary amines on solid supports*¹⁹⁶**

One drop of each of the following solutions was added to 1-2 mg of solid:

- i) 5 g ninhydrin in 100 ml ethanol
- ii) 80 g phenol in 20 ml ethanol
- iii) 2 ml 0.001M KCN (aq) mixed with 98 ml pyridine

The mixture was heated for a few seconds. Colouration of the solid indicates the presence of primary amines on the solid support.

p-Chloranil test for determining secondary amines on solid supports

One drop of each of the following solutions was added to 1-2 mg of solid:

- i) 2% acetaldehyde in DMF
- ii) 2% *p*-chloranil (tetrachloro-1,4-benzoquinone) in DMF
- iii) 2 ml 0.001M KCN (aq) and 98 ml pyridine

The mixture was allowed to stand for 5 minutes at room temperature. Colouration of the solid indicates the presence of secondary amines on the solid support.

General procedure for radical cyclisation with solution ligand/copper (I) halide mixtures:

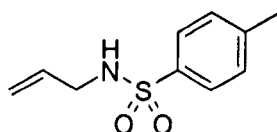
Copper (I) chloride or copper (I) bromide (0.0360 mmol) was added to a solution of the cyclisation substrate (0.120 mmol) and the solution ligand (0.036 mmol) in anhydrous DCE (1 ml) under nitrogen. The mixture was stirred at an appropriate temperature, and was monitored by tlc or ^1H NMR until no further change in reaction composition was observed. The crude reaction mixture was filtered through a short plug of silica, which was washed well with DCM and then EtOAc. The filtrate was concentrated *in vacuo*, and was characterised by ^1H NMR. Reaction products were purified by flash column chromatography (SiO_2 ; an appropriate solvent) where necessary.

General procedure for radical cyclisation with solid supported copper (I) catalysts:

Solid supported catalyst (0.0360 mmol Cu) was added to a solution of the cyclisation substrate (0.120 mmol) in anhydrous DCE (1 ml) under nitrogen. The mixture was stirred at an appropriate temperature, and was monitored by tlc or ^1H NMR until no further change in reaction composition was observed. The crude reaction mixture was filtered, and the resin was washed well with DCM and then EtOAc. The filtrate was concentrated *in vacuo*, and was characterised by ^1H NMR. Reaction products were purified by flash column chromatography (SiO_2 ; an appropriate solvent) where necessary.

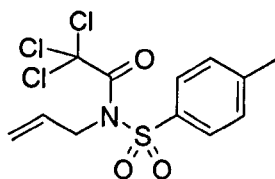
Radical Precursors:

N-Allyl-4-methyl-benzenesulfonamide (369)²¹⁰



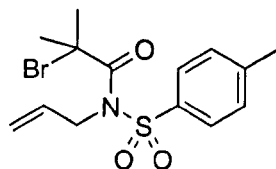
Triethylamine (8.36 ml, 60.0 mmol), and *p*-toluenesulfonyl chloride (11.4 g, 60.0 mmol) dissolved in DCM (70 ml), was added dropwise to a solution of allylamine (4.50 ml, 60.0 mmol) in DCM (70 ml) under nitrogen at 0°C. The solution was allowed to warm to room temperature, and was stirred for 3 days. The reaction was quenched with 1M HCl solution (150 ml), the layers were separated and the aqueous layer was extracted with DCM (3 x 150 ml). The combined organic extracts were washed with brine (150 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give *N*-allyl-4-methyl-benzenesulfonamide (369) as a pale beige crystalline solid (12.5 g, 99%), *R*_f (3:1 petrol:ethyl acetate) 0.22; m.pt. 64.3-64.8 °C; ν_{\max} (film)/cm⁻¹ 3277 (br, -NH), 1598 (C=C), 1428, 1321, 1306, 1290, 1155, 1093, 1065, 922, 814, 666; δ_{H} (300 MHz, CDCl₃) 7.76 (2H, d, *J* 8.1 Hz, Ar C-H), 7.32 (2H, d, *J* 8.1 Hz, Ar C-H), 5.73 (1H, ddt, *J* 17.1, 10.2, 5.8 Hz, H₂C=CH), 5.17 (1H, ddt, *J* 17.1, 1.5, 1.5 Hz, H_aH_bC=CH), 5.10 (1H, ddt, *J* 10.2, 1.5, 1.5 Hz, H_aH_bC=CH), 4.62 (1H, br t, *J* 6.0 Hz, NH), 3.58 (2H, dddd, *J* 6.0, 5.8, 1.5, 1.5 Hz, CH₂N), 2.45 (3H, s, CH₃); δ_{C} (75.5 MHz, CDCl₃) 143.9 and 137.3 (Ar quat.), 133.4 (H₂C=CH), 130.1 and 127.5 (Ar C-H), 117.9 (H₂C=CH), 46.1 (CH₂N), 21.9 (CH₃); *m/z* (EI) 211 (M)⁺, 155, 147, 139, 120, 105, 91, 84, 65; [Found: (M)⁺ 211.0667, C₁₀H₁₃NO₂S requires (M)⁺ 211.0667]; [Found: C, 56.52; H, 6.11; N, 6.53. C₁₀H₁₃NO₂S requires C, 56.85; H, 6.20; N, 6.63].

N-Allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**7b**)¹³



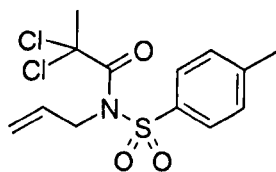
A 2.5 M solution of *n*-butyllithium in hexanes (4.40 ml, 11.0 mmol) was added dropwise over 5 minutes to a stirred solution of *N*-allyl-4-methyl-benzenesulfonamide (**369**) (2.11 g, 10.0 mmol) in anhydrous THF (100 ml) under nitrogen at -78°C . After 30 minutes, trichloroacetyl chloride (1.34 ml, 12.0 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO_3 solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO_2 , 5:1, petrol:ethyl acetate), and then recrystallisation from hexane, gave *N*-allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (**7b**) as a white solid (3.22g, 90%), R_f (3:1 petrol:ethyl acetate) 0.46; m.pt. $71.4\text{--}71.9^{\circ}\text{C}$; ν_{max} (film)/ cm^{-1} 3089, 2989, 2925, 1708, 1595, 1492, 1442, 1361, 1320, 1219, 1188, 1168, 1119, 1083, 989, 925, 836, 810, 709, 668; δ_{H} (300 MHz, CDCl_3) 7.93 (2H, d, J 8.5 Hz, Ar C-H), 7.34 (2H, d, J 8.5 Hz, Ar C-H), 5.96 (1H, ddt, J 17.2, 10.4, 5.5 Hz, $\text{H}_2\text{C}=\text{CH}$), 5.46 (1H, br dd, J 17.2, 0.8 Hz, $\text{H}_a\text{H}_b\text{C}=\text{CH}$), 5.38 (1H, br dd, J 10.4, 0.8 Hz, $\text{H}_a\text{H}_b\text{C}=\text{CH}$), 4.92 (2H, dt, J 5.5, 1.5 Hz, CH_2N), 2.45 (3H, s, Ar- CH_3); δ_{C} (100.6 MHz, CDCl_3) 159.0 ($\text{C}=\text{O}$), 146.0 and 129.0 (Ar quat.), 132.7 ($\text{H}_2\text{C}=\text{CH}$), 129.9 and 129.8 (Ar C-H), 119.9 ($\text{H}_2\text{C}=\text{CH}$), 92.5 (CCl_3), 51.5 (CH_2N), 22.2 (CH_3); m/z (FAB) 356 (MH^+), 321, 289, 154, 137; [Found: (MH^+) 355.9693, $\text{C}_{12}\text{H}_{12}\text{NO}_3\text{S}^{35}\text{Cl}_3$ requires (MH^+) 355.9682]; [Found: C, 40.47; H, 3.33; N, 3.76. $\text{C}_{12}\text{H}_{12}\text{NO}_3\text{S}\text{Cl}_3$ requires C, 40.41; H, 3.39; N, 3.93].

N-Allyl-*N*-(2-bromo-2-methyl-propionyl)-4-methyl-benzenesulfonamide (370)³⁵



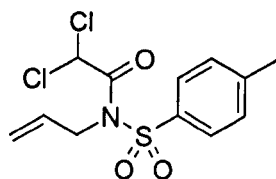
A 2.5 M solution of *n*-butyllithium in hexanes (4.40 ml, 11.0 mmol) was added dropwise over 5 minutes to a stirred solution of *N*-allyl-4-methyl-benzenesulfonamide (369) (2.11 g, 10.0 mmol) in anhydrous THF (100 ml) under nitrogen at -78°C. After 30 minutes, 2-bromoisobutyryl bromide (1.48 ml, 12.0 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO₃ solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate), and then recrystallisation from hexane, gave *N*-allyl-4-methyl-*N*-(2,2,2-trichloro-acetyl)-benzenesulfonamide (370) as a white solid (2.74g, 76%), R_f (3:1 petrol:ethyl acetate) 0.41; m.pt. 81.9-82.5 °C; ν_{\max} (film)/cm⁻¹ 2983, 2931, 1681, 1596, 1459, 1351, 1315, 1239, 1166, 1187, 1121, 1080, 927, 813, 775, 716, 658; δ_{H} (300 MHz, CDCl₃) 7.87 (2H, d, J 8.3 Hz, Ar C-H), 7.31 (2H, d, J 8.3 Hz, Ar C-H), 5.99 (1H, ddt, J 17.1, 10.4, 4.7 Hz, H₂C=CH), 5.42 (1H, br d, J 17.1 Hz, H_aH_bC=CH), 5.34 (1H, br d, J 10.4 Hz, H_aH_bC=CH), 4.96 (2H, dt, J 4.7, 1.7 Hz, CH₂N), 2.43 (3H, s, Ar-CH₃), 1.88 (6H, s, BrC[CH₃]₂); δ_{C} (100.6 MHz, CDCl₃) 170.0 (C=O), 145.1 and 136.5 (Ar quat.), 134.0 (H₂C=CH), 129.6 and 129.3 (Ar C-H), 118.5 (H₂C=CH), 57.5 (BrC[CH₃]₂), 51.0 (CH₂N), 32.4 (BrC[CH₃]₂), 22.1 (Ar-CH₃); m/z (EI) 360 (MH)⁺, 358 (M-H)⁺, 295, 216, 188, 155, 121, 91; [Found: (M-H)⁺ 358.0118, C₁₄H₁₈NO₃S⁷⁹Br requires (M-H)⁺ 358.0113].

N-Allyl-*N*-(2,2-dichloro-propionyl)-4-methyl-benzenesulfonamide (**44**)²⁰¹



A 2.5 M solution of *n*-butyllithium in hexanes (4.40 ml, 12.0 mmol) was added dropwise over 5 minutes to a stirred solution of *N*-allyl-4-methyl-benzenesulfonamide (**369**) (2.11 g, 10.0 mmol) in anhydrous THF (100 ml) under nitrogen at -78°C. After 30 minutes, 2,2-dichloro-propionyl chloride (2.88 g, 18.0 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO₃ solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) gave *N*-allyl-*N*-(2,2-dichloro-propionyl)-4-methyl-benzenesulfonamide (**44**) as a white solid (2.98 g, 88%), R_f (3:1 petrol:ethyl acetate) 0.33; m.pt. 70.0-71.0 °C; ν_{\max} (film)/cm⁻¹ 3073, 2957, 2872, 1692 (C=O), 1596 (C=C), 1440, 1359, 1325, 1293, 1235, 1188, 1169, 1064, 931, 815, 783, 713, 666; δ_{H} (300 MHz, CDCl₃) 7.88 (2H, d, J 8.5 Hz, Ar C-H), 7.30 (2H, d, J 8.5 Hz, Ar C-H), 6.00 (1H, ddt, J 17.0, 10.4, 5.5 Hz, H₂C=CH), 5.46 (1H, ddt, J 17.0, 1.1, 1.5 Hz, H_aH_bC=CH), 5.34 (1H, ddt, J 10.4, 1.1, 1.3, H_aH_bC=CH), 4.99 (2H, ddd, J 5.5, 1.3, 1.1 Hz, NCH₂), 2.43 (3H, s, Ar-CH₃), 2.18 (3H, s, Cl₂C[CH₃]); δ_{C} (75.5 MHz, CDCl₃); 164.5 (C=O), 145.5 and 135.9 (Ar quat.), 133.3 (H₂C=CH), 129.7 and 129.6 (Ar C-H), 119.6 (H₂C=CH), 80.2 (Cl₂C[CH₃]), 51.1 (NCH₂), 36.1 (Cl₂C[CH₃]), 22.1 (Ar-CH₃); m/z (EI) 338 (MH)⁺, 336 (MH)⁺, 300, 271, 236, 180, 164, 155, 139, 91, 65; [Found: (MH)⁺ 338.0192, C₁₃H₁₅NO₃SBr³⁵Cl³⁷Cl requires (MH)⁺ 338.0198]; [Found: C, 46.12; H, 4.39; N, 3.95. C₁₃H₁₅NO₃SBrCl₂ requires C, 46.44; H, 4.50; N, 4.17].

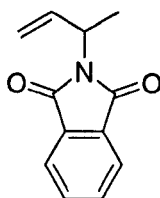
N-Allyl-*N*-(2,2-dichloro-acetyl)-4-methyl-benzenesulfonamide (**371a-b**)²⁰¹



A 1.6 M solution of *n*-butyl lithium in hexanes (17.0 ml, 27.2 mmol) was added dropwise over 5 minutes to a stirred solution of *N*-allyl-4-methyl-benzenesulfonamide (**369**) (2.5 g, 11.8 mmol) in anhydrous THF (150 ml) under nitrogen at -78°C. After 30 minutes, dichloroacetyl chloride (2.96 ml, 30.8 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO₃ solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) gave *isomer A* of *N*-allyl-*N*-(2,2-dichloro-acetyl)-4-methyl-benzenesulfonamide (**371a**) as a white solid (2.55 g, 67%), R_f (3:1 petrol:ethyl acetate) 0.35; m.pt. 94.2-94.9 °C; ν_{\max} (film)/cm⁻¹ 1716 (C=O), 1596 (C=C), 1363, 1320, 1171, 1119, 1087, 926, 810, 665; δ_{H} (300 MHz, CDCl₃) 7.81 (2H, d, J 8.5 Hz, Ar C-H), 7.34 (2H, d, J 8.5 Hz, Ar C-H), 6.82 (1H, s, CHCl₂), 5.77 (1H, ddt, J 17.3, 10.2, 5.3 Hz, H₂C=CH), 5.20 (1H, dd, J 10.2, 0.9 Hz, H_aH_bC=CH), 5.19 (1H, dd, J 17.3, 0.9 Hz, H_aH_bC=CH), 4.39 (2H, dt, J 5.3, 0.9 Hz, CH₂N), 2.42 (3H, s, CH₃); δ_{C} (75.5 MHz, CDCl₃) 163.4 (C=O), 145.8 and 134.5 (Ar quat.), 131.0 (H₂C=CH), 129.9 and 128.0 (Ar C-H), 118.9 (H₂C=CH), 64.5 (CHCl₂), 48.9 (CH₂N), 21.5 (CH₃); m/z (CI) 339 (MNH₄)⁺, 322 (MH)⁺, 286, 257, 222, 166, 155, 108, 9; [Found: (MH)⁺ 322.0058, C₁₂H₁₄NO₃SCl requires (MH)⁺ 322.0071]; [Found: C, 44.53; H, 4.04; N, 4.20. C₁₂H₁₄NO₃SCl requires C, 44.73; H, 4.07; N, 4.35], and *isomer B* of *N*-allyl-*N*-(2,2-dichloro-acetyl)-4-methyl-benzenesulfonamide (**371b**) as a pale yellow oil (0.506 g, 13%), R_f (3:1 petrol:ethyl acetate) 0.44; ν_{\max} (film)/cm⁻¹ 1790, 1714 (C=O), 1596 (C=C), 1360, 1165, 1107, 1088, 1049, 969, 932, 907, 811, 730, 659; δ_{H} (300 MHz, CDCl₃) 7.79 (2H, d, J 8.5 Hz, Ar C-H), 7.33 (2H, d, J 8.5 Hz, Ar C-H), 5.97 (1H, s, CHCl₂), 5.80 (1H,

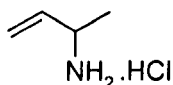
ddt, J 17.0, 10.2, 6.6 Hz, H₂C=CH), 5.25 (1H, ddt, J 17.0, 1.1, 1.1 Hz, H_aH_bC=CH), 5.20 (1H, ddt, J 10.2, 1.1, 1.1 Hz, H_aH_bC=CH), 3.97 (2H, dt, J 6.6, 1.1 Hz, CH₂N), 2.44 (3H, s, CH₃); δ_C (75.5 MHz, CDCl₃) 159.4 (C=O), 144.6 and 135.6 (Ar quat.), 131.1 (H₂C=CH), 129.8 and 127.8 (Ar C-H), 120.2 (H₂C=CH), 63.0 (CHCl₂), 52.0 (CH₂N), 21.4 (CH₃); m/z (CI) 339 (MNH₄)⁺, 322 (MH)⁺, 304, 288, 252, 212, 185, 155, 139, 132, 91.

2-(1-Methyl-allyl)-isoindole-1,3-dione (373)²¹¹



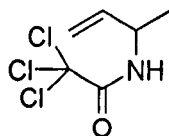
3-Chloro-1-butene (8.05 ml, 80.0 mmol) was added to a stirred suspension of potassium phthalimide (15.9 g, 85.6 mmol) in DMF (60 ml), and the reaction was heated to reflux for 3 hours. The reaction mixture was poured into ice (200ml), and the aqueous phase was extracted with chloroform (3 x 200ml). The combined organic extracts were washed with aqueous 1M NaOH solution (100 ml), aqueous 0.5 M HCl solution (100 ml) and saturated brine (100 ml), was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol to give 2-(1-methyl-allyl)-isoindole-1,3-dione (373) as white needles (11.9 g, 74%), R_f (5:1 petrol:ethyl acetate) 0.28; m.pt. 87.5-87.9 °C; ν_{max} (solid)/cm⁻¹ 1771, 1707 (C=O), 1642, 1471, 1388, 1357, 1330, 1139, 1074, 1039, 940, 716; δ_H (300 MHz, CDCl₃) 7.81 (2H, dd, J 5.5, 3.0 Hz, Ar C-H), 7.68 (2H, dd, J 5.5, 3.0 Hz, Ar C-H), 6.18 (1H, ddd, J 17.0, 10.2, 7.2 Hz, H₂C=CH), 5.21 (1H, ddd, J 17.0, 1.2, 1.2 Hz, H_aH_bC=CH), 5.14 (1H, ddd, J 10.2, 1.2, 1.2 Hz, H_aH_bC=CH), 4.91 (1H, dqt, J 7.2, 7.2, 1.2 Hz, CHN), 1.56 (3H, d, J 7.2 Hz, CH₃); δ_C (75.5 MHz, CDCl₃) 167.7 (C=O), 136.6 (H₂C=CH), 133.7 and 122.9 (Ar C-H), 131.8 (Ar quat.), 116.1 (H₂C=CHC), 48.7 (CHN), 18.0 (CH₃); m/z (EI) 201 (M)⁺, 186, 160, 147, 130, 104, 76; [Found: (M)⁺ 201.0796, C₁₂H₁₁NO₂ requires (M)⁺ 201.0790].

1-Methyl-allylamine hydrochloride (374)



A 55% solution of hydrazine in water (4.35 ml, 77.1 mmol) was added to a stirred solution of 2-(1-methyl-allyl)-isoindole-1,3-dione (**373**) (9.70 g, 48.2 mmol) in ethanol (100 ml), and the mixture was heated to reflux for 1 hour. After cooling to room temperature, aqueous 10M HCl solution (20 ml) was added, the reaction was stirred for 30 minutes, and was then diluted with water (300 ml). The reaction mixture was filtered through a pad of celite, which was washed well with water. The filtrate was evaporated to dryness, and the white residue was heated in refluxing ethanol (300 ml) for 15 minutes. The remaining solid was filtered, and the filtrate was concentrated *in vacuo* to give *1-methyl-allylamine hydrochloride (374)* as a hygroscopic white solid (4.30 g, 83%); m.pt. 123.0-124.0 °C; ν_{\max} (solid)/ cm^{-1} 3391 (br), 2916 (br), 1608, 1503, 1424, 1383, 940; δ_{H} (300 MHz, d_6 -DMSO) 8.41 (3H, br, $\text{NH}_2\cdot\text{HCl}$), 5.91 (1H, ddd, J 17.1, 10.6, 6.2 Hz, $\text{H}_2\text{C}=\underline{\text{C}}\text{H}$), 5.32 (1H, ddd, J 17.1, 1.1, 1.1 Hz, $\underline{\text{H}}_a\text{H}_b\text{C}=\text{CH}$), 5.23 (1H, ddd, J 10.6, 1.1, 1.1 Hz, $\text{H}_a\text{H}_b\text{C}=\text{CH}$), 3.75 (1H, m, CHNH_2), 1.28 (3H, d, J 6.8 Hz, CH_3); δ_{C} (75.5 MHz, d_6 -DMSO); 136.7 ($\text{H}_2\text{C}=\underline{\text{C}}\text{H}$), 118.0 ($\text{H}_2\underline{\text{C}}=\text{CH}$), 48.5 ($\underline{\text{C}}\text{H}\text{NH}_2$), 18.7 ($\underline{\text{C}}\text{H}_3$); m/z (EI) 70 (M-H)⁺, 56; [Found: (M-H)⁺ 70.0658, $\text{C}_4\text{H}_8\text{N}$ requires (M-H)⁺ 70.0657].

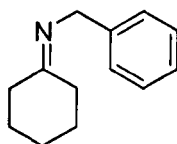
2,2,2-Trichloro-N-(1-methyl-allyl)-acetamide (375)²⁰⁴



Triethylamine (10.4 ml, 75.0 mmol) was added to a stirred suspension of 1-methyl-allylamine hydrochloride (**374**) (2.69 g, 25.0 mmol) in anhydrous DCM (50 ml) under nitrogen at 0°C. After 30 minutes, trichloroacetyl chloride (3.07 ml, 37.5 mmol) was added by syringe. After 16 hours, water (20 ml) was added, the layers were separated,

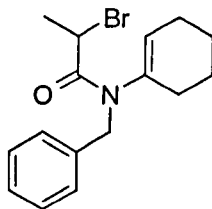
and the aqueous layer was extracted with DCM (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *2,2,2-trichloro-N-(1-methyl-allyl)-acetamide* (**375**) as a white solid (4.76 g, 88%), R_f (5:1 petrol:ethyl acetate) 0.34; m.pt. 43.7-44.4 °C; ν_{\max} (film)/cm⁻¹ 3302 (NH), 1688 (C=O), 1526 (C=C), 1252, 925, 823; δ_{H} (300 MHz, CDCl₃) 6.62 (1H, br, NH), 5.84 (1H, ddd, J 17.3, 10.6, 5.1 Hz, H₂C=CH), 5.21 (1H, br d, J 17.3 Hz, H_aH_bC=CH), 5.15 (1H, br d, J 10.6, H_aH_bC=CH), 4.50 (1H, m, CHNH), 1.32 (3H, d, J 6.8 Hz, CH₃); δ_{C} (75.5 MHz, CDCl₃) 160.8 (C=O), 137.4 (H₂C=CH), 115.3 (H₂C=CH), 92.5 (CCl₃) 48.9 (CNH), 19.6 (CH₃); m/z (EI) 224, 181, 135, 113, 96; [Found: C, 33.11; H, 3.68; N, 6.30. C₆H₈NOCl₃ requires C, 33.29; H, 3.72; N, 6.47].

Benzyl-cyclohexylidene-amine (**377**)



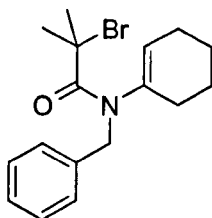
A solution of cyclohexanone (6.22 ml, 60.0 mmol) and benzylamine (6.55 ml, 60.0 mmol) in toluene (40 ml) was heated to reflux in a Dean-Stark apparatus for 24 hours. The reaction mixture was concentrated *in vacuo* to give *benzyl-cyclohexylidene-amine* (**377**) as a pale yellow oil (11.2 g, 100%, purity >85%), R_f (5:1, petrol:ethyl acetate) 0.43; ν_{\max} (film)/cm⁻¹ 2927, 2856, 1657 (C=N), 1603; δ_{H} (300 MHz, CDCl₃) 7.31-7.29 (5H, m, Ar C-H), 4.53 (2H, s, NCH₂), 2.36 (4H, m, 2 x CH₂), 1.72 (2H, m, CH₂), 1.64 (4H, m, 2 x CH₂); δ_{C} (75.5 MHz, CDCl₃) 174.0 (C=N), 140.4 (Ar quat.), 128.8, 128.2 and 126.3 (Ar C-H), 53.9 (CH₂N), 39.9, 29.0, 27.5, 26.8 and 25.8 (5 x CH₂); m/z (EI) 187 (M)⁺, 149, 106, 98, 91, 77, 65.

***N*-Benzyl-2-bromo-*N*-cyclohex-1-enyl-propionamide (378)**



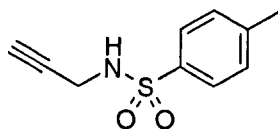
2-Bromopropionyl bromide (1.68 ml, 16.0 mmol) was added dropwise over 10 minutes to a solution of benzyl-cyclohexylidene-amine (**377**) (3.00g, 16.0 mmol) and *N,N*-diethylaniline (2.55 ml, 16.0 mmol) in anhydrous toluene (90 ml) at 0°C. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (40 ml) and then 1M HCl (40 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *N*-benzyl-2-bromo-*N*-cyclohex-1-enyl-propionamide (**378**) as an off-white solid (3.59 g, 70%), R_f (5:1 petrol:ethyl acetate) 0.29; m.pt. 87.5-88.2°C; ν_{max} (film)/cm⁻¹ 2931, 1656 (C=O), 1496, 1446, 1401, 700; δ_H (300 MHz, CDCl₃) 7.28-7.18 (5H, m, Ar C-H), 5.48 (1H, br s, C=CH), 4.70-4.45 (3H, m, NCH₂ and CHBr), 2.22-1.84 (4H, m, 2 x CH₂), 1.78 (3H, d, J 8.0 Hz, CH₃), 1.70-1.58 (2H, m, CH₂), 1.56-1.47 (2H, m, CH₂); δ_C (75.5 MHz, CDCl₃) 169.7 (C=O), 138.0 and 137.8 (Ar quat. and N-C=C), 129.4 (NC=CH), 129.0, 128.7 and 127.7 (Ar C-H), 50.4 (CH₂N), 39.9 (CHBr), 28.4, 25.1, 23.1 and 21.7 (4 x CH₂), 22.6 (CH₃); m/z (CI) 322 (MH)⁺, 321 (M)⁺, 146, 97, 91, 69; [Found: (M)⁺ 321.0735, C₁₆H₂₀NO⁷⁹Br requires (M)⁺ 321.0728]; [Found: C, 59.60, 59.70; H, 6.21, 6.25; N, 4.41, 4.34; Br, 24.78. C₁₆H₂₀NOBr requires C, 59.64; H, 6.26; N, 4.35; Br, 24.80].

N-Benzyl-2-bromo-*N*-cyclohex-1-enyl-2-methyl-propionamide (**69**)³⁵



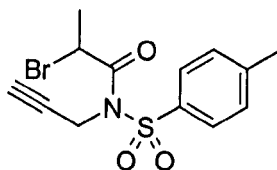
2-Bromoisobutyryl bromide (1.98 ml, 16.0 mmol) was added dropwise over 10 minutes to a stirred solution of benzyl-cyclohexylidene-amine (**377**) (3.00g, 16.0 mmol) and *N,N*-diethylaniline (2.55 ml, 16.0 mmol) in anhydrous toluene (90 ml) at 0°C. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (40 ml) and then 1M HCl (40 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *N*-benzyl-2-bromo-*N*-cyclohex-1-enyl-2-methyl-propionamide (**69**) as a yellow oil (3.69 g, 69%), R_f (5:1 petrol:ethyl acetate) 0.38; ν_{\max} (film)/cm⁻¹ 2934, 1633 (C=O), 1391; δ_{H} (300 MHz, CDCl₃) 7.27-7.17 (5H, m, Ar C-H), 5.56 (1H, m, C=CH), 5.20-4.00 (2H, 2 x br, NCH₂), 2.20-2.00 (4H, m, 2 x CH₂), 1.97 (6H, s, BrC[CH₃]₂), 1.70-1.62 (2H, m, CH₂), 1.57-1.40 (2H, m, CH₂); δ_{C} (75.5 MHz, CDCl₃) 170.2 (C=O), 137.4 (Ar quat. and N-C=C), 129.3 (NC=CH), 128.2, 128.0 and 126.9 (Ar C-H), 58.2 (CH₂N), 52.2 (BrC[CH₃]₂), 34.0 (BrC[CH₃]₂), 27.8, 24.4, 22.4 and 21.0 (4 x CH₂); m/z (CI) 336 (MH)⁺, 256, 166, 91; [Found: (MH)⁺ 336.0970, C₁₇H₂₃NO⁷⁹Br requires (MH)⁺ 336.0963].

4-Methyl-N-prop-2-ynyl-benzenesulfonamide (380)



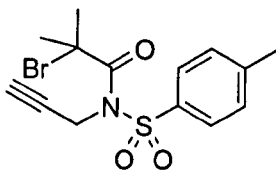
A stirred suspension of propagylamine hydrochloride (5.49 g, 60.0 mmol) in anhydrous dichloromethane (70 ml) was cooled to 0°C in an ice bath. Triethylamine (18.4 ml, 132 mmol) was added by syringe, followed by a solution of *p*-toluenesulfonyl chloride (11.4 g, 60.0 mmol) in anhydrous DCM (70 ml). The reaction was stirred at room temperature for 16 hours. The reaction was quenched with 1M HCl solution (150 ml), the layers were separated, and the aqueous layer was extracted with DCM (3 x 150 ml). The combined organic extracts were washed with brine (150 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give 4-methyl-N-prop-2-ynyl-benzenesulfonamide (380) as an off-white crystalline solid (11.9 g, 95%), R_f (3:1 petrol:ethyl acetate) 0.15; m.pt. 75.5-76.0 °C; ν_{\max} (film)/cm⁻¹ 3274 (br, -NH), 2125 (alkyne), 1597, 1426, 1320, 1152, 1067, 812, 660; δ_{H} (300 MHz, CDCl₃) 7.78 (2H, d, J 8.5 Hz, Ar C-H), 7.31 (2H, d, J 8.5 Hz, Ar C-H), 4.98 (1H, br, NH), 3.82 (2H, br, NCH₂), 2.43 (3H, s, CH₃), 2.10 (1H, t, J 2.6 Hz, HCCCH₂); δ_{C} (75.5 MHz, CDCl₃) 143.6 and 136.2 (Ar quat.), 129.5 and 127.2 (Ar C-H), 72.7 (HCCCH₂N), 32.6 (NCH₂), 21.3 (CH₃), HCCCH₂N not visible; m/z (CI) 210 (MH)⁺, 209 (M)⁺, 144, 118, 91; [Found: (M)⁺ 209.0514, C₁₀H₁₁NO₂S requires (M)⁺ 209.0511]; [Found: C, 57.31; H, 5.30; N, 6.66. C₁₀H₁₁NO₂S requires C, 57.40; H, 5.30; N, 6.69].

N-(2-Bromo-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**381**)²⁴



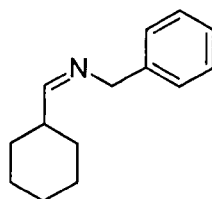
A 2.5 M solution of *n*-butyllithium in hexanes (6.60 ml, 16.5 mmol) was added dropwise over 5 minutes to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**380**) (3.14 g, 15.0 mmol) in anhydrous THF (150 ml) under nitrogen at -78°C. After 30 minutes, 2-bromopropionyl bromide (1.89 ml, 18.0 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO₃ solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) gave *N*-(2-bromo-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**381**) as a yellow solid (4.45 g, 86%), R_f (3:1 petrol:ethyl acetate) 0.26; m.pt. 73.3-74.0 °C; ν_{\max} (film)/cm⁻¹ 3281, 2127 (alkyne), 1703 (C=O), 1595, 1443, 1353, 1291, 1214, 1166, 1112, 1087, 1047, 996, 810, 719, 662; δ_{H} (300 MHz, CDCl₃) 7.93 (2H, d, J 8.5 Hz, Ar C-H), 7.36 (2H, d, J 8.5 Hz, Ar C-H), 5.00 (1H, q, J 6.5 Hz, CHBr), 4.86 (1H, dd, J 18.7, 2.5 Hz, NCH_aH_b), 4.62 (1H, dd, J 18.7, 2.5 Hz, NCH_aH_b), 2.45 (3H, s, Ar-CH₃), 2.36 (1H, t, J 2.5 Hz, HCC), 1.75 (3H, d, J 6.5 Hz, [CH₃]CHBr); δ_{C} (75.5 MHz, CDCl₃) 168.7 (C=O), 145.3 and 135.0 (Ar quat.), 129.6 and 128.1 (Ar C-H), 77.5 (HCC), 73.2 (HCC), 39.0 ([CH₃]CHBr), 35.4 (NCH₂), 21.5 (Ar-CH₃), 20.9 ([CH₃]CHBr); m/z (EI) 345 (M)⁺, 343 (M)⁺, 200, 174, 172, 155, 139, 91, 65; [Found: (M)⁺ 344.9846, C₁₃H₁₄NO₃S⁸¹Br requires (M)⁺ 344.9857]; [Found: C, 45.30, 45.27; H, 4.06, 4.01; N, 3.93, 3.78; Br, 23.13. C₁₃H₁₄NO₃SBr requires C, 45.36; H, 4.10; N, 4.07; Br, 23.21].

N-(2-Bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**55**)²⁰



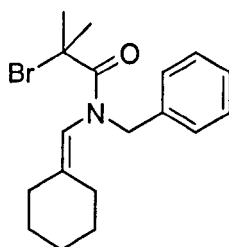
A 2.5 M solution of *n*-butyllithium in hexanes (6.60 ml, 16.5 mmol) was added dropwise over 5 minutes to a stirred solution of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**380**) (3.14 g, 15.0 mmol) in anhydrous THF (150 ml) under nitrogen at -78°C. After 30 minutes, 2-bromoisobutyryl bromide (2.22 ml, 18.0 mmol) was added, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (10 ml), and was partitioned between DCM (200 ml) and saturated NaHCO₃ solution (200 ml). The layers were separated and the aqueous layer was extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO₂, 5:1, petrol:ethyl acetate) gave *N*-(2-bromo-2-methyl-propionyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (**55**) as a yellow solid (5.04 g, 94%), R_f (3:1 petrol:ethyl acetate) 0.27; m.pt. 72.0-73.0 °C; ν_{\max} (film)/cm⁻¹ 3278, 2126 (alkyne) 1685 (C=O), 1596, 1457, 1352, 1309, 1165, 1084, 709; δ_{H} (300 MHz, CDCl₃) 7.96 (2H, d, J 8.5 Hz, Ar C-H), 7.29 (2H, d, J 8.5 Hz, Ar C-H), 5.11 (2H, d, J 2.5 Hz, NCH₂), 2.45 (1H, t, J 2.5 Hz, HCC), 2.47 (3H, s, Ar-CH₃), 1.92 (6H, s, BrC[CH₃]₂); δ_{C} (75.5 MHz, CDCl₃) 169.4 (C=O), 144.7 and 135.4 (Ar quat.), 129.3 and 128.8 (Ar C-H), 78.5 (HCC), 73.7 (HCC), 37.8 (BrC[CH₃]₂), 37.6 (CH₂N), 31.5 (BrC[CH₃]₂), 21.5 (Ar-CH₃); m/z (EI) 359 (M)⁺, 357 (M)⁺, 186, 155, 121, 91, 84, 65; [Found: (M)⁺ 357.0031, C₁₄H₁₆NO₃S⁷⁹Br requires (M)⁺ 357.0034]; [Found: C, 46.86; H, 4.46; N, 3.84. C₁₄H₁₆NO₃SBr requires C, 46.94; H, 4.50; N, 3.91].

Benzyl-cyclohexylmethylene-amine (383)



A stirred solution of cyclohexanecarboxaldehyde (7.27 ml, 60.0 mmol) and benzylamine (6.55 ml, 60.0 mmol) in toluene (40 ml) was heated to reflux in a Dean-Stark apparatus for 24 hours. The reaction mixture was concentrated *in vacuo* to give *benzyl-cyclohexylmethylene-amine (383)* as a colourless oil (12.1 g, 100%, purity >90%), R_f (5:1, petrol:ethyl acetate) 0.47; ν_{\max} (film)/ cm^{-1} 2922, 2849, 1665 (C=N), 1603, 1495, 1448, 731, 695; δ_{H} (300 MHz, CDCl_3) 7.63 (1H, dt, J 5.1, 1.3 Hz, $\text{HC}=\text{N}$), 7.33-7.19 (5H, m, Ar-H), 4.54 (2H, d, J 1.3 Hz, NCH_2), 2.22 (1H, m, $\text{CHCH}=\text{N}$), 1.90-1.60 (6H, m, 3 x CH_2), 1.40-1.10 (4H, m, 2 x CH_2); δ_{C} (75.5 MHz, CDCl_3) 170.6 ($\text{C}=\text{N}$), 139.9 (Ar quat.), 128.8, 128.2 and 127.2 (Ar C-H), 65.4 (CH_2N), 44.0 ($\text{CHCH}=\text{N}$), 30.1, 26.4 and 25.9 (3 x CH_2); m/z (CI) 202 (MH)⁺, 196, 136, 91.

N-Benzyl-2-bromo-N-cyclohexylidenemethyl-2-methyl-propionamide (384)

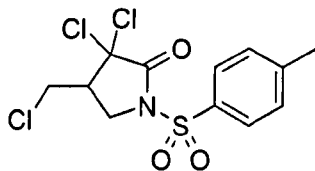


2-Bromoisobutyryl bromide (1.98 ml, 16.0 mmol) was added dropwise over 10 minutes to a stirred solution of benzyl-cyclohexylidene-amine (**383**) (3.22g, 16.0 mmol) and *N,N*-diethylaniline (2.55 ml, 16.0 mmol) in anhydrous toluene (90 ml) at 0°C. After stirring for 16 hours at room temperature, the reaction mixture was washed with water (40 ml)

and then 1M HCl (40 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, 9:1, petrol:ethyl acetate) to give *N*-benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methylpropionamide (**384**) as a colourless oil (4.86 g, 87%), R_f (5:1 petrol:ethyl acetate) 0.44; ν_{\max} (film)/cm⁻¹ 2928, 2853, 1636 (C=O), 1463, 1389, 1365, 1178, 1108, 838, 698; δ_{H} (300 MHz, CDCl₃) 7.33-7.20 (5H, m, Ar C-H), 6.30 (1H, s, C=CHN), 4.67 (2H, s, NCH₂), 2.13-2.06 (4H, m, 2 x CH₂), 1.98 (6H, s, BrC[CH₃]₂), 1.58-1.46 (6H, m, 3 x CH₂); δ_{C} (75.5 MHz, CDCl₃) 171.0 (C=O), 141.5 and 137.7 (C=CHN and Ar quat.), 128.8, 128.3 and 127.5 (Ar C-H), 123.2 (C=CHN), 58.9 (BrC[CH₃]₂), 55.5 (CH₂N), 33.2 (CH₂), 32.7 (BrC[CH₃]₂), 29.0, 27.9, 26.6 and 26.5 (4 x CH₂); m/z (EI) 352 (MH)⁺, 350 (MH)⁺, 270, 178, 136, 111, 91, 65; [Found: (MH)⁺ 352.1112, C₁₈H₂₄NO⁸¹Br requires (MH)⁺ 352.1099]; [Found: C, 61.68, 61.68; H, 6.89, 6.91; N, 3.97, 3.99; Br, 22.65. C₁₈H₂₄NOBr requires C, 61.72; H, 6.91; N, 4.00; Br, 22.81].

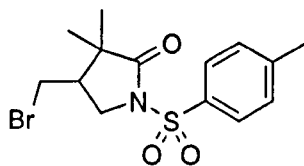
Cyclisation Products:

*3,3-Dichloro-4-chloromethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (16b)*¹³



White solid, R_f (3:1 petrol:ethyl acetate) 0.34; m.pt. 167.0-167.5 °C; ν_{\max} (film)/ cm^{-1} 2960, 1757 (C=O), 1595, 1475, 1445, 1368, 1237, 1172, 1129, 1088, 984, 814, 662; δ_H (300 MHz, CDCl_3) 7.94 (2H, d, J 8.3 Hz, Ar C-H), 7.38 (2H, d, J 8.3 Hz, Ar C-H), 4.25 (1H, dd, J 10.4, 7.0 Hz, NCH_aH_b), 3.94 (1H, dd, J 11.5, 4.4 Hz, ClCH_aH_b), 3.69 (1H, dd, J 11.5, 10.0 Hz, ClCH_aH_b), 3.56 (1H, dd, J 10.4, 8.7 Hz, NCH_aH_b), 3.14-3.04 (1H, m, CHCl₂), 2.46 (3H, s, CH₃); δ_C (75.5 MHz, CDCl_3) 163.4 (C=O), 146.8 and 133.7 (Ar quat.), 130.5 and 128.7 (Ar C-H), 83.0 (CCl₂), 51.1 (CHCl₂), 47.8 (CH₂N), 40.5 (CH₂Cl), 22.2 (CH₃); m/z (EI) 356 (MH)⁺, 322, 291, 257, 155, 138, 109, 91, 65; [Found: (MH)⁺ 355.9676, C₁₂H₁₂NO₃S³⁵Cl requires (MH)⁺ 355.9682]; [Found: C, 40.39; H, 3.36; N, 3.82. C₁₂H₁₂NO₃S³⁵Cl requires C, 40.41; H, 3.39; N, 3.93].

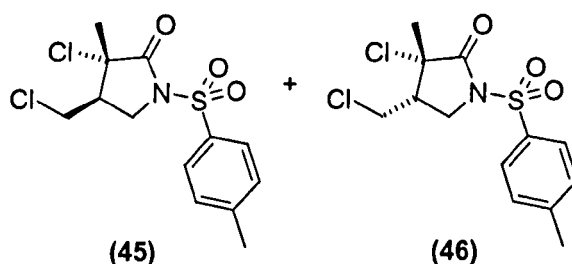
*4-Bromomethyl-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (385)*³⁵



White solid, R_f (3:1 petrol:ethyl acetate) 0.21; m.pt. 132.8-133.2 °C; ν_{\max} (film)/ cm^{-1} 2969, 2930, 1732 (C=O), 1596, 1487, 1463, 1357, 1236, 1169, 1112, 1090, 881, 814, 784, 727, 660; δ_H (300 MHz, CDCl_3) 7.90 (2H, d, J 8.3 Hz, Ar C-H), 7.33 (2H, d, J 8.3 Hz, Ar C-H), 4.14 (1H, dd, J 10.4 and 7.5 Hz, NCH_aH_b), 3.46 (1H, dd, J 10.4 and 8.7 Hz,

NCH_aH_b), 3.43 (1H, dd, J 10.4 and 4.7 Hz, CH_aH_bBr), 3.20 (1H, dd, J 10.4 and 10.4 Hz, CH_aH_bBr), 2.50-2.38 (1H, m, CHCH₂Br), 2.43 (3H, s, Ar-CH₃), 1.16 (3H, s, C[CH₃][CH₃]), 0.88 (3H, s, C[CH₃][CH₃]); δ_c (75.5 MHz, CDCl₃) 177.3 (C=O), 145.7 and 135.2 (Ar quat.), 130.1 and 128.4 (Ar C-H), 49.2 (CH₂N), 45.8 (C[CH₃]₂), 45.4 (CHCH₂Br), 30.2 (CH₂Br), 23.8 and 18.2 (C[CH₃][CH₃]), 22.1 (Ar-CH₃); m/z (EI) 360 (MH)⁺, 358 (M-H)⁺, 295, 202, 155, 133, 119, 91, 84, 69; [Found: (M-H)⁺ 358.0107, C₁₄H₁₈NO₃S⁷⁹Br requires (M-H)⁺ 358.0113]; [Found: C, 46.53; H, 4.95; N, 3.72. C₁₄H₁₈NO₃SBr requires C, 46.67; H, 5.04; N, 3.89].

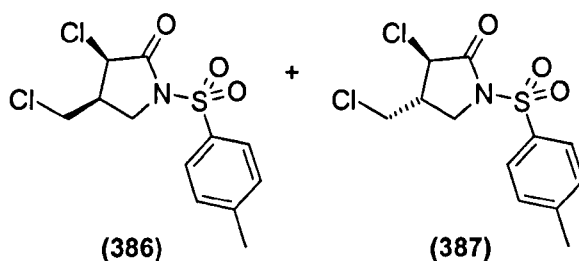
(3*S,4*S**) 3-chloro-4-chloromethyl-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (45) and (3*S**,4*R**) 3-chloro-4-chloromethyl-3-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (46)**²⁰¹



White solid, R_f (3:1 petrol:ethyl acetate) 0.40; m.pt. 161.0-162.0 °C; ν_{max} (film)/cm⁻¹ 2959, 2929, 1744 (C=O), 1596, 1476, 1446, 1363, 1272, 1241, 1170, 1188, 1170, 1106, 1037, 900, 814, 772, 732, 703, 662; δ_H (300 MHz, C₆D₆) 8.00 (2H, d, J 8.3 Hz, Ar C-H, (46)), 7.97 (2H, d, J 8.3 Hz, Ar C-H, (45)), 6.71 (2H, d, J 8.3 Hz, Ar C-H, (45)), 6.71 (2H, d, J 8.3 Hz, Ar C-H, (46)), 3.85 (1H, dd, J 9.8 and 7.0 Hz, NCH_aH_b, (45)), 3.72 (1H, dd, J 10.5 and 6.6 Hz, NCH_aH_b, (46)), 3.52 (1H, dd, J 10.5 and 3.6 Hz, NCH_aH_b, (46)), 3.03-2.84 (3H, m, NCH_aH_b, CH₂Cl, (45)), 2.66 (1H, dd, J 11.5 and 4.3 Hz, CH_aH_bCl, (46)), 2.42 (1H, dd, J 11.5 and 8.7 Hz, CH_aH_bCl, (46)), 2.05-1.97 (1H, m, CHCH₂Cl, (46)), 1.76 (3H, s, Ar-CH₃, (45)), 1.76 (3H, s, Ar-CH₃, (46)), 1.49 (1H, m, CHCH₂Cl, (45)), 1.18 (3H, s, ClC[CH₃], (45)), 1.02 (3H, s, ClC[CH₃], (46)); δ_H (300 MHz, CDCl₃) 7.89 (2H, d, J 8.5 Hz, Ar C-H, (46)), 7.88 (2H, d, J 8.5 Hz, Ar C-H, (45)), 7.34 (2H, d, J 8.5 Hz, Ar C-H, (46)), 7.34 (2H, d, J 8.5 Hz, Ar C-H, (45)), 4.19 (1H, dd, J 10.1 and 7.0 Hz,

NCH_aH_b, (**46**)), 4.13 (1H, dd, J 10.7 and 8.5 Hz, NCH_aH_b, (**45**)), 3.84 (1H, dd, J 10.7 and 3.7 Hz, NCH_aH_b, (**45**)), 3.77 (1H, dd, J 11.3 and 5.8 Hz, CH_aH_bCl, (**46**)), 3.65 (1H, dd, 11.6, 4.3 Hz, CH_aH_bCl, (**45**)), 3.61 (1H, dd, J 11.3 and 8.5 Hz, CH_aH_bCl, (**46**)), 3.41 (1H, dd, J 10.1 and 10.1 Hz, CH_aH_bN, (**46**)), 3.37 (1H, dd, J 11.6 and 8.5 Hz, CH_aH_bCl, (**45**)), 2.83 (1H, m, CHCH₂Cl, (**45**)), 2.53 (1H, m, CHCH₂Cl, (**46**)), 2.43 (3H, s, Ar-CH₃, (**45**)), 2.43 (3H, s, Ar-CH₃, (**46**)), 1.70 (3H, s, ClC[CH₃], (**46**)), 1.58 (3H, s, ClC[CH₃], (**45**)); m/z (EI) 336 (MH)⁺, 300, 271, 236, 200, 186, 155, 139; [Found: (MH)⁺ 336.0230, C₁₃H₁₅NO₃S³⁵Cl₂ requires (MH)⁺ 336.0228].

(3R*,4S*) 3-chloro-4-chloromethyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-one (386) and (3R*,4R*) 3-chloro-4-chloromethyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-one (387)²⁰¹



White solid, R_f (3:1 petrol:ethyl acetate) 0.26; m.pt. 156.0-157.0 °C; ν_{max} (film)/cm⁻¹ 2957, 2924, 2855, 1745 (C=O), 1596, 1478, 1445, 1363, 1167, 1126, 1088, 961, 814, 662; δ_H (300 MHz, C₆D₆) 7.98 (2H, d, J 8.3 Hz, Ar C-H, (**386**)), 7.98 (2H, d, J 8.3 Hz, Ar C-H, (**387**)), 6.73 (2H, d, J 8.3 Hz, Ar C-H, (**387**)), 6.73 (2H, d, J 8.3 Hz, Ar C-H, (**386**)), 3.62 (1H, dd, J 10.0 and 7.9 Hz, NCH_aH_b, (**386**)), 3.52 (1H, dd, J 10.0 and 7.0 Hz, NCH_aH_b, (**387**)), 3.40 (1H, d, J 9.5 Hz, CHCl, (**386**)), 3.15 (1H, dd, J 10.2 and 8.5 Hz, NCH_aH_b, (**386**)), 3.09 (1H, dd, J 10.0 and 8.1 Hz, NCH_aH_b, (**387**)), 2.84 (1H, dd, J 11.3 and 7.2 Hz, CH_aH_bCl, (**387**)), 2.73 (1H, dd, J 11.7 and 4.3 Hz, CH_aH_bCl, (**386**)), 2.63 (1H, dd, J 11.7 and 7.0 Hz, CH_aH_bCl, (**386**)), 2.63 (1H, dd, J 11.7 and 7.0 Hz, CH_aH_bCl, (**387**)), 1.79 (3H, s, CH₃, (**386**)), 1.78 (3H, s, CH₃, (**387**)), 1.77-1.64 (1H, m, CHCH₂Cl, (**386**)), 1.62-1.48 (1H, m, CHCH₂Cl, (**387**)); δ_H (300 MHz, CDCl₃) 7.86 (2H, d, J 8.3 Hz, Ar C-H, (**386**)), 7.84 (2H, d, J 8.3 Hz, Ar C-H, (**387**)), 7.29 (2H, d, J 8.3 Hz, Ar C-H,

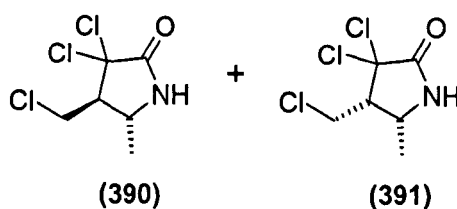
(386)), 7.29 (2H, d, J 8.3 Hz, Ar C-H, (387)), 4.39 (1H, d, J 6.0 Hz, CHCl, (387)), 4.29 (1H, d, J 9.2 Hz, CHCl, (386)), 4.06 (1H, dd, J 10.4, 7.0 Hz, NCH_aH_b, (387)), 4.05 (1H, dd, J 10.2, 7.9 Hz, NCH_aH_b, (386)), 3.72-3.60 (3H, m, NCH_aH_b, CH₂Cl, (386)), 3.54-3.43 (3H, m, NCH_aH_b, CH₂Cl, (387)), 2.97-2.83 (1H, m, CHCH₂Cl, (387)), 2.82-2.69 (1H, m, CHCH₂Cl, (386)), 2.38 (3H, s, CH₃, (386)), 2.36 (3H, s, CH₃, (387)); m/z (CI) 322 (MH)⁺, 257, 208, 155, 139, 120, 91, 75, 65;

N-Allyl-N-(2-chloro-acetyl)-4-methyl-benzenesulfonamide (388)



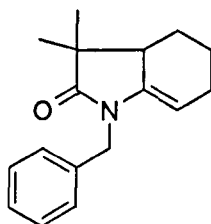
White solid, R_f (3:1 petrol:ethyl acetate) 0.35; m.pt. 93.2-94.3 °C; ν_{max} (film)/cm⁻¹ 2954, 1712, 1597, 1493, 1403, 1357, 1194, 1160, 1126, 1088, 1017, 928, 845, 797, 727, 665; δ_H (300 MHz, CDCl₃) 7.81 (2H, d, J 8.5 Hz, Ar C-H), 7.37 (2H, d, J 8.5 Hz, Ar C-H), 5.83 (1H, ddt, J 17.1, 10.3, 5.6 Hz, H₂C=CH), 5.26 (1H, br dd, J 17.1, 1.0 Hz, H_aH_bC=CH), 5.24 (1H, br dd, J 10.2, 1.0 Hz, H_aH_bC=CH), 4.48 (2H, s, CH₂Cl), 4.43 (2H, dt, J 5.6, 1.5 Hz, CH₂N), 2.46 (3H, s, CH₃); δ_C (100.6 MHz, CDCl₃) 165.9 (C=O), 145.7 (Ar. quat.), 135.7 (Ar quat.), 131.9 (CH=CH₂), 130.1 (Ar C-H), 128.0 (Ar C-H), 119.0 (CH=CH₂), 49.2 (CH₂N), 44.1 (CH₂Cl), 21.7 (CH₃); m/z (EI) 288 (MH)⁺, 252, 223, 188, 154, 132, 116, 91, 76, 65; [Found: (MH)⁺ 288.0471, C₁₂H₁₄NO₃S³⁵Cl requires (MH)⁺ 288.0461]; [Found: C, 49.75; H, 4.88; N, 4.75. C₁₂H₁₄NO₃SCl requires C, 50.09; H, 4.90; N, 4.87].

(4*S,5*R**) 3,3-dichloro-4-chloromethyl-5-methyl-pyrrolidin-2-one (390) and (4*R**,5*R**) 3,3-dichloro-4-chloromethyl-5-methyl-pyrrolidin-2-one (391)** ²⁰⁴



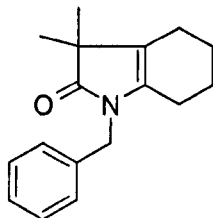
All data was identical to that previously reported.

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (70) ³⁵



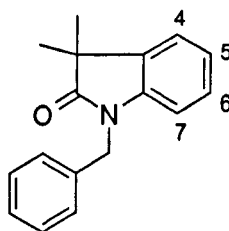
R_f (3:1 petrol:ethyl acetate) 0.48; ν_{\max} (film)/ cm^{-1} 2929, 2859, 1708 (C=O), 1679 (C=C), 1456, 1400; δ_H (300 MHz, CDCl_3) 7.34-7.18 (5H, m, Ar C-H), 4.79 (1H, dd, J 6.4, 3.0 Hz, C=CHCH₂), 4.66 (1H, d, J 15.5 Hz, NCH_aH_b), 4.56 (1H, d, J 15.5 Hz, NCH_aH_b), 2.46-2.38 (1H, m, CH of CH₂), 2.10-1.95 (2H, m, CH₂), 1.95-1.85 (1H, m, CH of CH₂), 1.82-1.71 (1H, m, CH of CH₂), 1.58-1.30 (2H, m, CH₂), 1.26 (6H, s, C[CH₃][CH₃]); δ_C (75.5 MHz, CDCl_3) 181.0 (C=O), 140.1 (N-C=CH), 137.4 (Ar quat.), 128.9, 127.6 and 127.6 (Ar C-H), 98.8 (N-C=CH), 46.2 (HC-C=C), 43.9 (NCH₂), 30.1 (CMe₂), 23.9, 22.6 and 23.5 (3 x CH₂), 23.5 and 21.2 (2 x CH₃); m/z (EI) 255 (M)⁺, 240, 230, 227, 212, 106, 91, 65.

1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (71)³⁵



R_f (3:1 petrol:ethyl acetate) 0.38; ν_{\max} (film)/ cm^{-1} 2962, 2929, 2863, 1705 (C=O), 1677 (C=C), 1452, 1387, 1352, 1177, 1139, 700; δ_H (300 MHz, CDCl_3) 7.32-7.13 (5H, m, Ar C-H), 4.61 (2H, s, NCH_2), 2.06-1.94 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.69-1.60 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.16 (6H, s, $\text{C}[\text{CH}_3]_2$); δ_C (75.5 MHz, CDCl_3) 184.0 ($\text{C}=\text{O}$), 138.7, 134.0 and 121.8 (N-C=C, N-C=C and Ar quat.), 129.0, 127.5 and 127.2 (Ar C-H), 46.7 ($\text{C}[\text{CH}_3]_2$), 43.3 (NCH_2), 22.9, 22.9, 21.6 and 19.9 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 22.5 ($\text{C}[\text{CH}_3]_2$); m/z (EI) 255 (M)⁺, 240, 212, 176, 162, 136, 106, 91, 65.

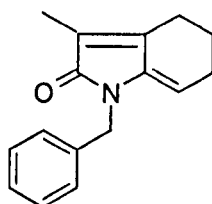
1-Benzyl-3,3-dimethyl-1,3-dihydro-indol-2-one (392)²¹²



White solid, R_f (3:1 petrol:ethyl acetate) 0.45; m.pt. 76.0-77.0 °C; ν_{\max} (film)/ cm^{-1} 2966, 2927, 2861, 1751, 1708 (C=O), 1612 (C=C), 1490, 1457, 1381, 1358, 1172, 1114, 1084, 1004, 741, 700, 664; δ_H (300 MHz, CDCl_3) 7.39-7.24 (5H, m, Ph C-H), 7.22 (1H, dd, J 7.5, 1.1 Hz, H-4), 7.14 (1H, td, J 7.5, 1.1 Hz, H-6), 7.02 (1H, td, J 7.5, 1.1 Hz, H-5), 6.72 (1H, d, J 7.5 Hz, H-7), 4.92 (2H, s, CH_2N), 1.44 (6H, s, $\text{C}[\text{CH}_3]_2$); δ_C (125.8 MHz, CDCl_3) 181.5 ($\text{C}=\text{O}$), 141.7, 136.1 and 135.8 (Ar quat.), 129.9, 128.8, 127.5 and 127.2 (C-6 and Ph C-H), 122.5 and 122.3 (C-4 and C-5), 109.1 (C-7), 43.5 (CH_2N), 29.7

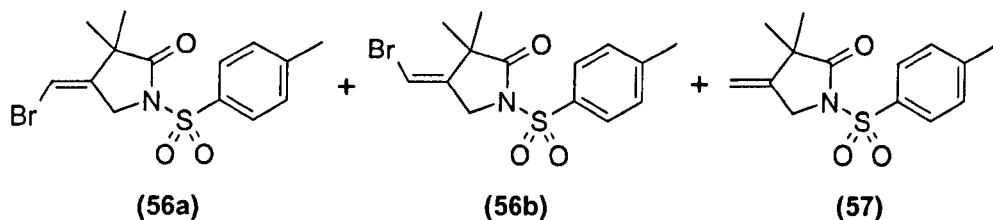
(C[CH₃]₂), 24.5 (C[CH₃]₂); m/z (EI) 251 (MH)⁺, 236, 230, 208, 176, 160, 91; [Found: (MH)⁺ 251.1296, C₁₇H₁₇NO requires (MH)⁺ 351.1310].

*1-Benzyl-3-methyl-1,4,5,6-tetrahydro-indol-2-one (393)*²¹³



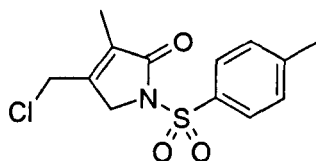
R_f (5:1 petrol:ethyl acetate) 0.26; ν_{\max} (film)/cm⁻¹ 3368, 2922, 2856, 1682 (C=O), 1653 (C=C), 1496, 1454, 1435, 1415, 1343, 1319, 1140, 1077, 700; δ_{H} (300 MHz, CDCl₃) 7.32-7.18 (5H, m, Ar C-H), 5.42 (1H, t, J 4.5 Hz, C=CHCH₂), 4.76 (2H, s, CH₂N), 2.53 (2H, m, CH₂), 2.24 (2H, m, CH₂), 1.89 (3H, s, CH₃), 1.78 (2H, m, CH₂); δ_{C} (125.8 MHz, CDCl₃) 171.5 (C=O), 140.4, 139.4, 138.3 and 123.8 (Ar quat. and 3 x olef. quat.), 128.9, 127.6 and 127.5 (3 x Ar C-H), 108.9 (C=CHCH₂), 43.2 (CH₂N), 24.7, 23.7, 22.9 (3 x CH₂), 8.8 (CH₃); m/z (EI) 239 (M)⁺, 216, 122, 105, 91, 77, 65; [Found: (M)⁺ 239.1311, C₁₆H₁₇NO requires (M)⁺ 239.1310].

Z-4-Bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**56a**), *E*-4-bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**56b**) and 3,3-dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidine-2-one (**57**)^{20,205}



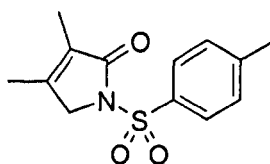
R_f (3:1 petrol:ethyl acetate) 0.19; ν_{\max} (film)/ cm^{-1} 3078, 2973, 2928, 2872, 1736 (C=O), 1596 (C=C), 1462, 1359, 1300, 1229, 1188, 1167, 1115, 1087, 812, 662; *Z*-4-Bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**56a**), δ_H (400 MHz, CDCl_3) 7.95 (2H, d, J 8.3 Hz, Ar C-H), 7.35 (2H, d, J 8.3 Hz, Ar C-H), 6.17 (1H, t, J 2.6 Hz, C=CHBr), 4.43 (2H, d, J 2.8 Hz, CH₂N), 2.45 (3H, s, Ar-CH₃), 1.22 (6H, s, C[CH₃]₂); *E*-4-bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**56b**), δ_H (400 MHz, CDCl_3) 7.92 (2H, d, J 8.3 Hz, Ar C-H), 7.34 (2H, d, J 8.3 Hz, Ar C-H), 6.19 (1H, t, J 2.0 Hz, C=CHBr), 4.40 (2H, d, J 2.0 Hz, CH₂N), 2.45 (3H, s, Ar-CH₃), 1.40 (6H, s, C[CH₃]₂); 3,3-dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidine-2-one (**57**), δ_H (400 MHz, CDCl_3) 7.93 (2H, d, J 8.3 Hz, Ar C-H), 7.33 (2H, d, J 8.3 Hz, Ar C-H), 5.11 (1H, t, J 1.8 Hz, C=CH_aH_b), 5.07 (1H, t, J 2.2 Hz, C=CH_aH_b), 4.45 (2H, t, J 2.0 Hz, CH₂N), 2.44 (3H, s, Ar-CH₃), 1.16 (6H, s, C[CH₃]₂); m/z (EI) 358 [MH^+ (**56a**) and (**56b**)], 293, 280 [MH^+ (**57**)], 214, 202, 161, 155, 91, 79, 65.

4-Chloromethyl-3-methyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (394)²⁰²



White solid, R_f (3:1 petrol:ethyl acetate) 0.16; m.pt. 147.5-148.0 °C; ν_{\max} (film)/ cm^{-1} 2925, 2857, 1722 (C=O), 1672, 1597, 1447, 1360, 1328, 1169, 1118, 1091, 1070, 811, 748, 706, 665; δ_H (300 MHz, CDCl_3) 7.79 (2H, d, J 8.1 Hz, Ar C-H), 7.34 (2H, d, J 8.1 Hz, Ar C-H), 4.44 (2H, s, CH_2N), 4.31 (2H, s, CH_2Cl), 2.43 (3H, s, Ar- CH_3), 1.80 (3H, s, CH_3); δ_C (75.5 MHz, CDCl_3) 168.5 (C=O), 147.6, 145.3, 135.3, 131.9 (2 x Ar quat. and 2 x olef. quat.), 129.8 and 128.0 (Ar C-H), 50.8 (CH_2N), 37.0 (CH_2Cl), 21.7 (Ar- CH_3), 8.7 (CH_3); m/z (FAB) 300 (MH)⁺, 266, 176, 154, 137, 120; [Found: (MH)⁺ 300.0459, $\text{C}_{13}\text{H}_{14}\text{NO}_3\text{S}^{35}\text{Cl}$ requires (MH)⁺ 300.0461]; [Found: C, 52.28, 52.14; H, 4.78, 4.75; N, 4.60, 4.58; Cl, 11.17. $\text{C}_{13}\text{H}_{14}\text{NO}_3\text{S}\text{Cl}$ requires C, 52.09; H, 4.71; N, 4.67; Cl, 11.83].

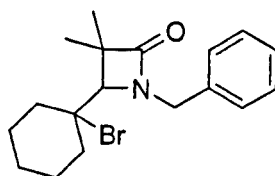
3,4-Dimethyl-1-(toluene-4-sulfonyl)-1,5-dihydro-pyrrol-2-one (395)



White solid, R_f (3:1 petrol:ethyl acetate) 0.13; m.pt. 198.5-199.0 °C; ν_{\max} (film)/ cm^{-1} 2922, 2854, 1714, 1672, 1596, 1447, 1356, 1319, 1166, 1122, 1087, 810, 748, 664; δ_H (300 MHz, CDCl_3) 7.95 (2H, d, J 8.6 Hz, Ar C-H), 7.32 (2H, d, J 8.6 Hz, Ar C-H), 4.24 (2H, s, CH_2N), 2.42 (3H, s, Ar- CH_3), 1.98 (3H, s, CH_3), 1.71 (3H, s, CH_3); δ_C (125.8 MHz, CDCl_3) 169.7 (C=O), 150.6, 144.9, 135.7 and 128.5 (2 x Ar quat. and 2 x olef. quat.), 129.8 and 128.1 (Ar C-H), 53.4 (CH_2N), 21.7 (Ar- CH_3), 13.5 (CH_3), 8.3 (CH_3);

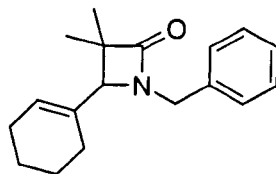
m/z (FAB) 266 (MH)⁺, 154, 137, 120; [Found: (MH)⁺ 266.0841, C₁₃H₁₅NO₃S requires (MH)⁺ 266.0851].

1-Benzyl-4-(1-bromo-cyclohexyl)-3,3-dimethyl-azetidine-2-one (396)



Colourless oil, R_f (3:1 petrol:ethyl acetate) 0.31; ν_{\max} (film)/cm⁻¹ 2930, 2859, 1752 (C=O), 1450, 1397, 1363, 1146, 1114, 701; δ_{H} (400 MHz, CDCl₃) 7.37-7.22 (5H, m, Ar C-H), 4.94 (1H, d, J 15.3 Hz, NCH_aH_b), 4.16 (1H, d, J 15.3 Hz, NCH_aH_b), 3.51 (1H, s, NCHC[CH₃]₂), 2.16-2.07 and 2.00-1.92 (2H, m, CH₂), 1.85-1.40 (6H, m, CH₂), 1.50 (3H, s, C[CH₃][CH₃]), 1.31 (3H, s, C[CH₃][CH₃]), 1.12-1.00 and 0.92-0.80 (2H, m, CH₂); δ_{C} (75.5 MHz, CDCl₃) 175.3 (C=O), 136.5 (Ar quat.), 129.1, 128.7 and 128.0 (Ar C-H), 72.3 (NCHC[CH₃]₂), 55.8 (CBr), 45.8 (NCH₂), 44.8 (C[CH₃]₂), 37.9, 37.7, 25.4, 22.9 and 22.0 (CH₂CH₂CH₂CH₂CH₂), 24.9 (CH₃), 18.7 (CH₃); m/z (FAB) 350 (MH)⁺, 307, 270, 154, 136; [Found: (MH)⁺ 350.1111, C₁₈H₂₄NO⁷⁹Br requires (MH)⁺ 350.1120].

1-Benzyl-4-cyclohex-1-enyl-3,3-dimethyl-azetidine-2-one (397)



Colourless oil, R_f (3:1 petrol:ethyl acetate) 0.31; ν_{\max} (film)/ cm^{-1} 2927, 1751, 1642, 1453, 1399, 1365; δ_H (300 MHz, CDCl_3) 7.37-7.21 (5H, m, Ar C-H), 5.57 (1H, m, C=CH), 4.83 (1H, d, J 14.9 Hz, NCH_aH_b), 3.86 (1H, d, J 14.9 Hz, NCH_aH_b), 3.36 (1H, s, $\text{NCHC}[\text{CH}_3]_2$), 2.14-2.05 (2H, m, CH_2), 1.85-1.45 (6H, m, 3 x CH_2), 1.26 (3H, s, CH_3), 1.06 (3H, s, CH_3); δ_C (75.5 MHz, CDCl_3) 174.1 ($\text{C}=\text{O}$), 136.1 and 132.8 (Ar quat. and $\text{NCHC}=\text{CH}$), 128.6, 128.2 and 127.4 (Ar C-H), 123.2 (C=CH), 66.2 ($\text{NCHC}[\text{CH}_3]_2$), 54.7 ($\text{C}[\text{CH}_3]_2$), 44.7 (NCH_2), 27.6, 25.2 and 22.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, 2 signals coincident), 22.8 (CH_3), 17.1 (CH_3); m/z (FAB) 270 (MH^+), 154, 136; [Found: (MH^+) 270.1859, $\text{C}_{18}\text{H}_{23}\text{NO}^{79}\text{Br}$ requires (MH^+) 270.1858].

APPENDIX

X-ray Crystallographic Data for (371a)

Empirical formula	C ₁₂ H ₁₃ Cl ₂ N O ₃ S	
Formula Weight	322.19	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.552(2) Å	α = 90°
	b = 7.1967(16) Å	β = 90°
	c = 22.972(5) Å	γ = 90°
U	1405.5(6) Å ³	
Z	4	
Density (calculated)	1.523 Mg/m ³	
Absorption coefficient	0.612 mm ⁻¹	
F(000)	664	
Crystal size	0.20 x 0.18 x 0.16 mm	
Maximum θ	29.18 °	
hkl ranges	-11/ 11, -7/ 9, -25/ 31.	
Reflections measured	8771	
Independent reflections	3486 [R(int) = 0.0616]	
Goodness-of-fit on F ²	0.949	
Final R indices [I>2σ(I)]	R1 = 0.0520, wR2 = 0.1140	
Largest diff. peak and hole	0.262 and -0.367 eÅ ⁻³	

Table 27: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **(371a)**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
S1	1803.9(9)	784.6(11)	4366.4(3)	30(1)
Cl1	-217.5(9)	-4584.3(12)	2929.0(3)	38(1)
Cl2	-2162.1(9)	-3994.1(13)	3878.5(4)	47(1)
O2	18(3)	-762(3)	3347.9(9)	41(1)
O6	2595(3)	798(3)	4945.6(9)	42(1)
C1	-231(3)	-3915(4)	3660.9(13)	27(1)
O5	481(2)	1979(3)	4227.5(9)	40(1)
C8	4741(4)	718(4)	4030.0(14)	35(1)
C14	1641(3)	-2854(4)	4720.0(12)	29(1)
C9	5832(4)	1030(4)	3640.3(15)	38(1)
C11	3809(4)	2136(4)	2931.4(14)	34(1)
C2	326(3)	-1894(4)	3733.1(13)	27(1)
C15	2973(3)	-4070(4)	4590.6(14)	32(1)
C16	3745(4)	-4014(4)	4136.7(15)	37(1)
C7	3177(3)	1121(4)	3862.6(13)	25(1)
C13	6566(4)	2024(5)	2653.4(16)	52(1)
N3	1171(3)	-1451(3)	4262.0(10)	25(1)
C12	2695(4)	1843(4)	3314.1(13)	29(1)
C10	5383(4)	1732(4)	3083.9(15)	35(1)

Table 28: Bond lengths [Å] and angles [deg] for (371a)

S1-O6	1.426(2)	O5-S1-C7	109.92(13)
S1-O5	1.429(2)	N3-S1-C7	105.22(12)
S1-N3	1.706(2)	C2-C1-C11	109.3(2)
S1-C7	1.753(3)	C2-C1-C12	106.70(19)
C11-C1	1.750(3)	C11-C1-C12	111.39(16)
C12-C1	1.778(3)	C9-C8-C7	119.2(3)
O2-C2	1.210(3)	N3-C14-C15	114.3(2)
C1-C2	1.534(4)	C8-C9-C10	121.1(3)
C8-C9	1.380(4)	C12-C11-C10	121.7(3)
C8-C7	1.382(4)	O2-C2-N3	122.6(3)
C14-N3	1.482(3)	O2-C2-C1	121.2(3)
C14-C15	1.492(4)	N3-C2-C1	116.1(2)
C9-C10	1.389(4)	C16-C15-C14	127.6(3)
C11-C12	1.381(4)	C8-C7-C12	121.0(3)
C11-C10	1.384(4)	C8-C7-S1	119.0(2)
C2-N3	1.382(4)	C12-C7-S1	119.9(2)
C15-C16	1.294(4)	C2-N3-C14	122.8(2)
C7-C12	1.383(4)	C2-N3-S1	117.96(19)
C13-C10	1.505(4)	C14-N3-S1	119.05(19)
O6-S1-O5	119.23(13)	C11-C12-C7	118.6(3)
O6-S1-N3	104.40(12)	C11-C10-C9	118.2(3)
O5-S1-N3	107.71(13)	C11-C10-C13	120.6(3)
O6-S1-C7	109.34(14)	C9-C10-C13	121.1(3)

Infra-Red Spectra of Homogeneous and Heterogeneous Ligands and Copper (I) Complexes

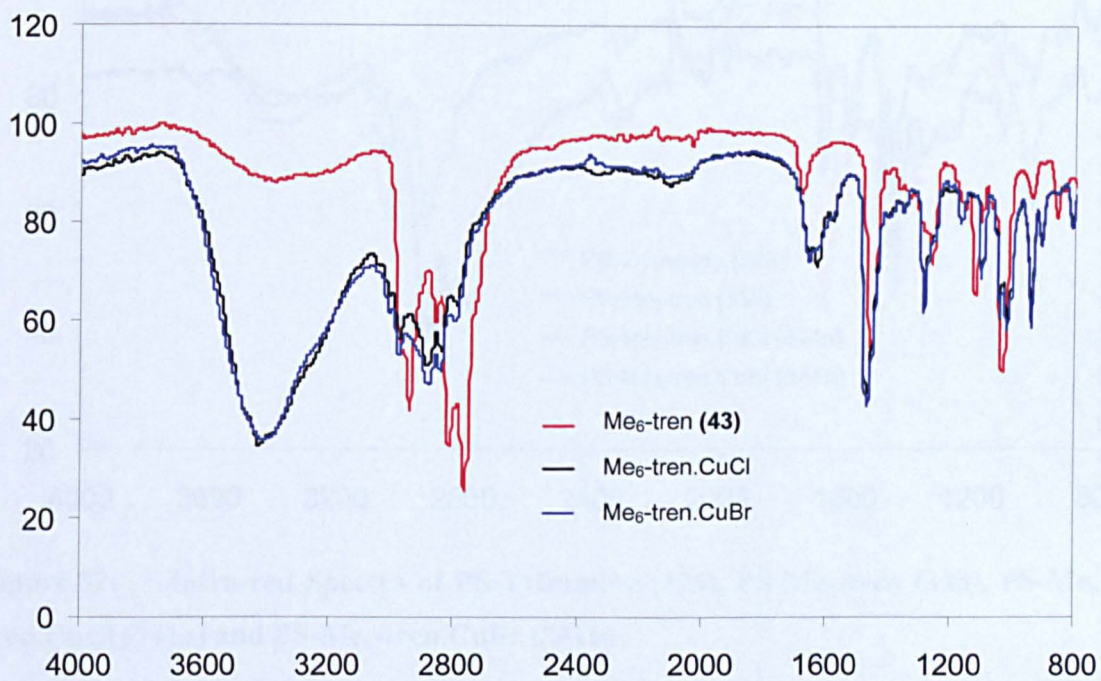


Figure 31: Infra-red Spectra of Me₆-tren (43), Me₆-tren.CuCl and Me₆-tren.CuBr

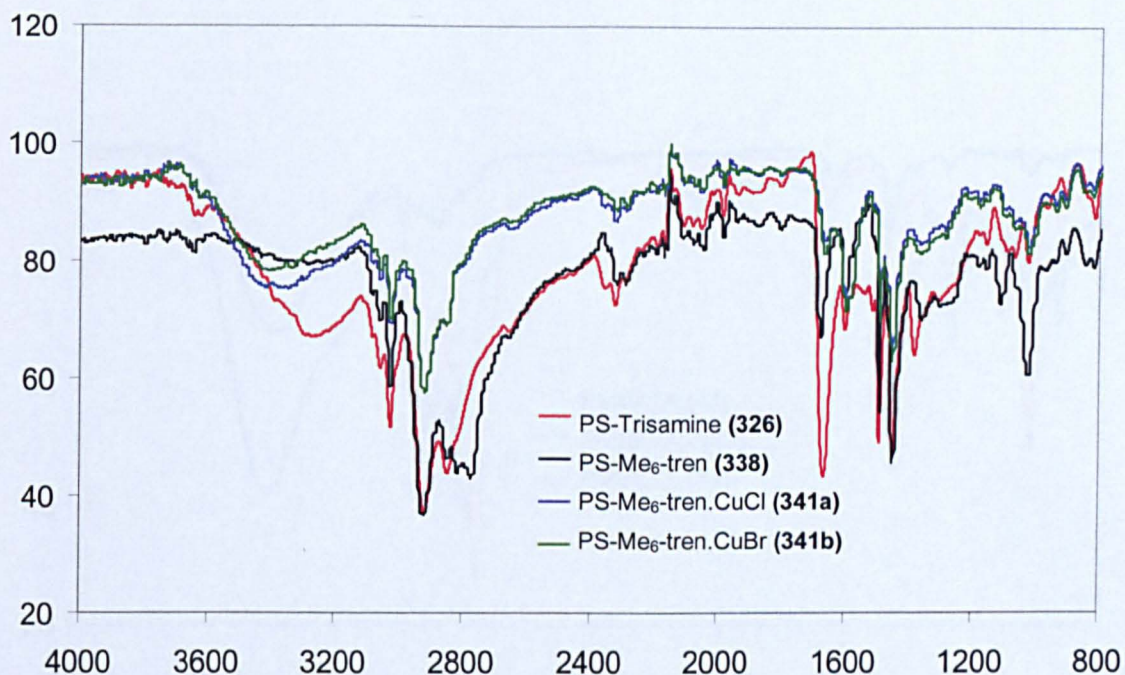


Figure 32: Infra-red Spectra of PS-Trisamine (326), PS-Me₆-tren (338), PS-Me₆-tren.CuCl (341a) and PS-Me₆-tren.CuBr (341b)

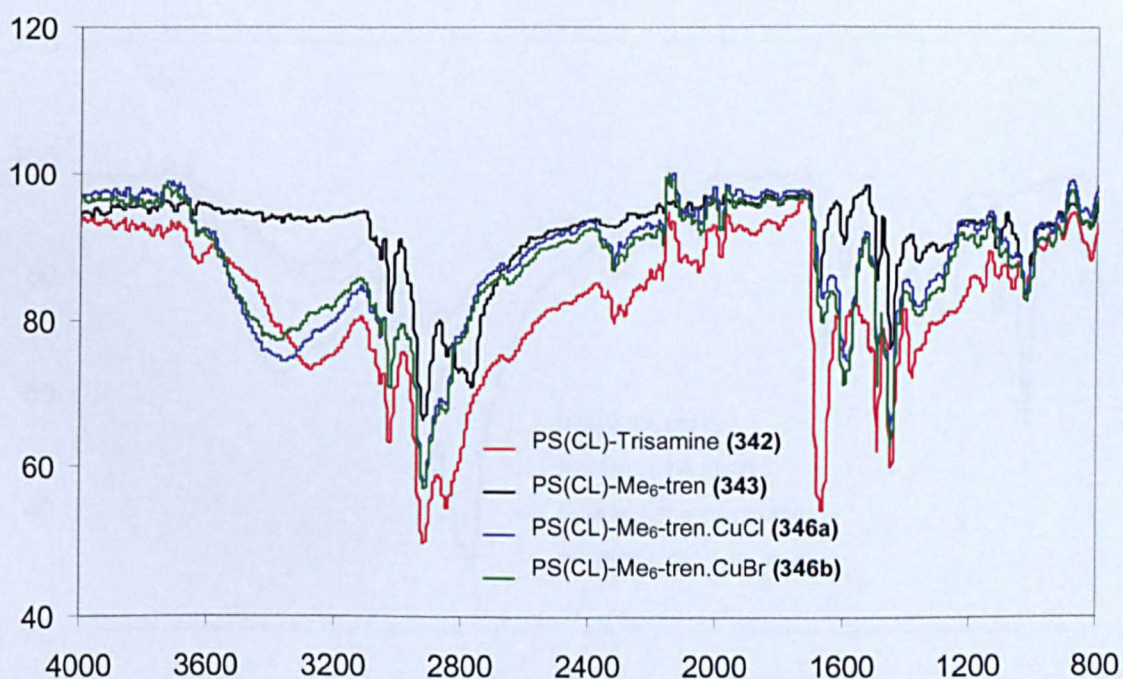


Figure 33: Infra-red Spectra of PS(CL)-Trisamine (342), PS(CL)-Me₆-tren (343), PS(CL)-Me₆-tren.CuCl (346a) and PS(CL)-Me₆-tren.CuBr (346b)

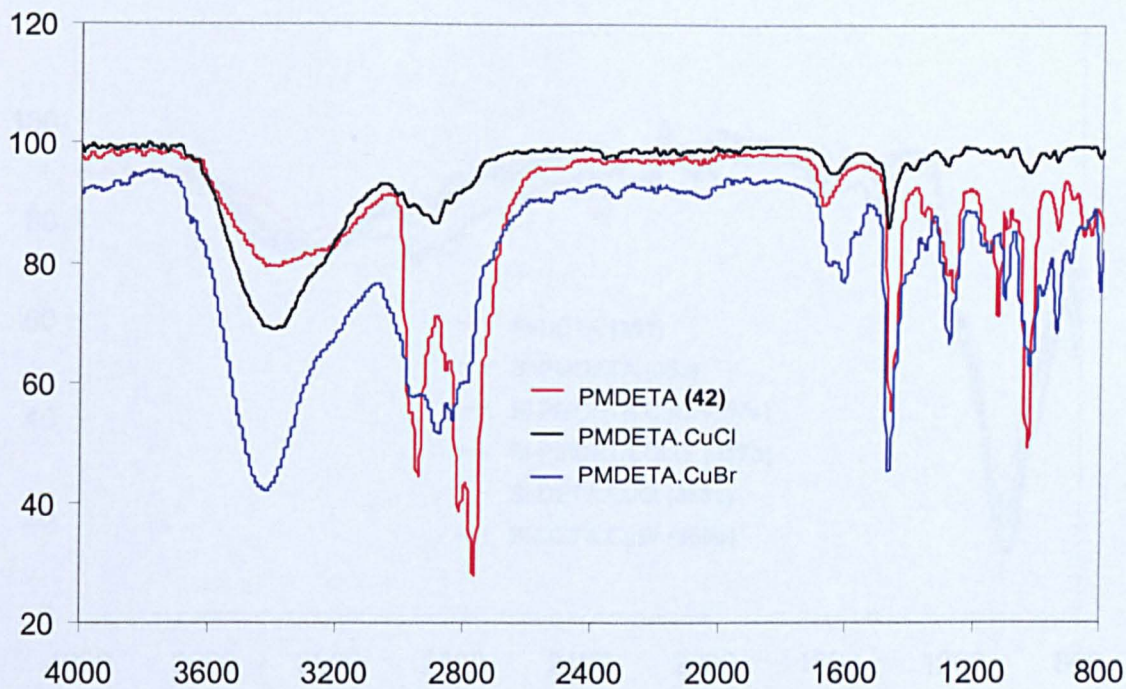


Figure 34: Infra-red Spectra of PMDETA (42), PMDETA.CuCl and PMDETA.CuBr

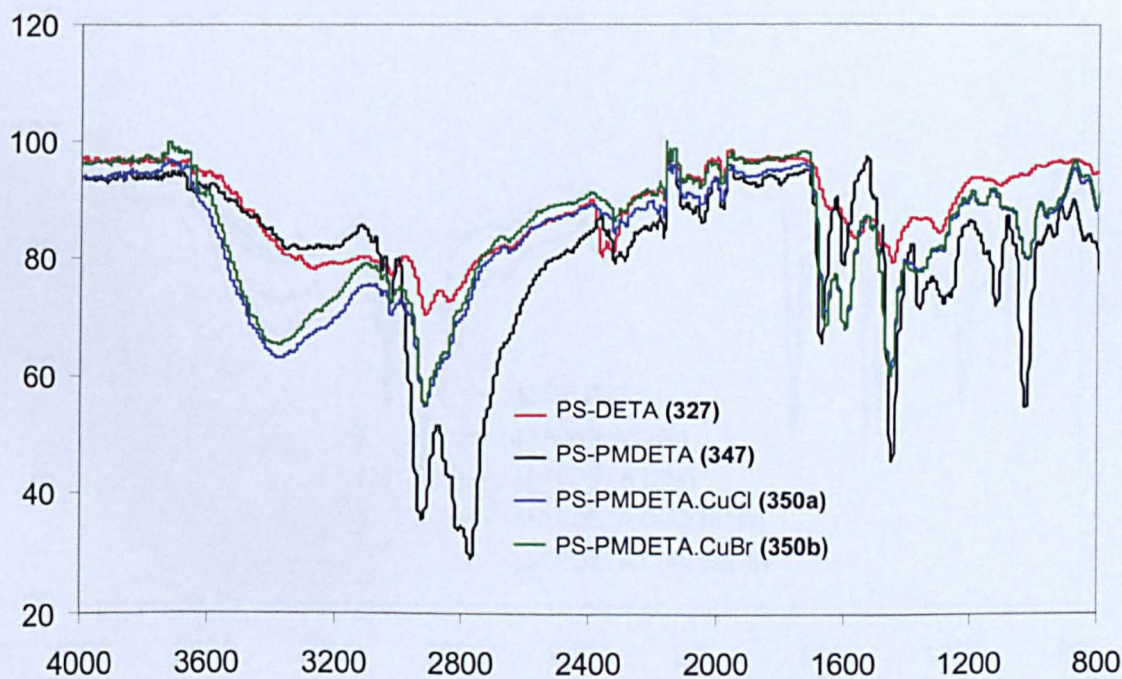


Figure 35: Infra-red Spectra of PS-DETA (327), PS-PMDETA (347), PS-PMDETA.CuCl (350a) and PS-PMDETA.CuBr (350b)

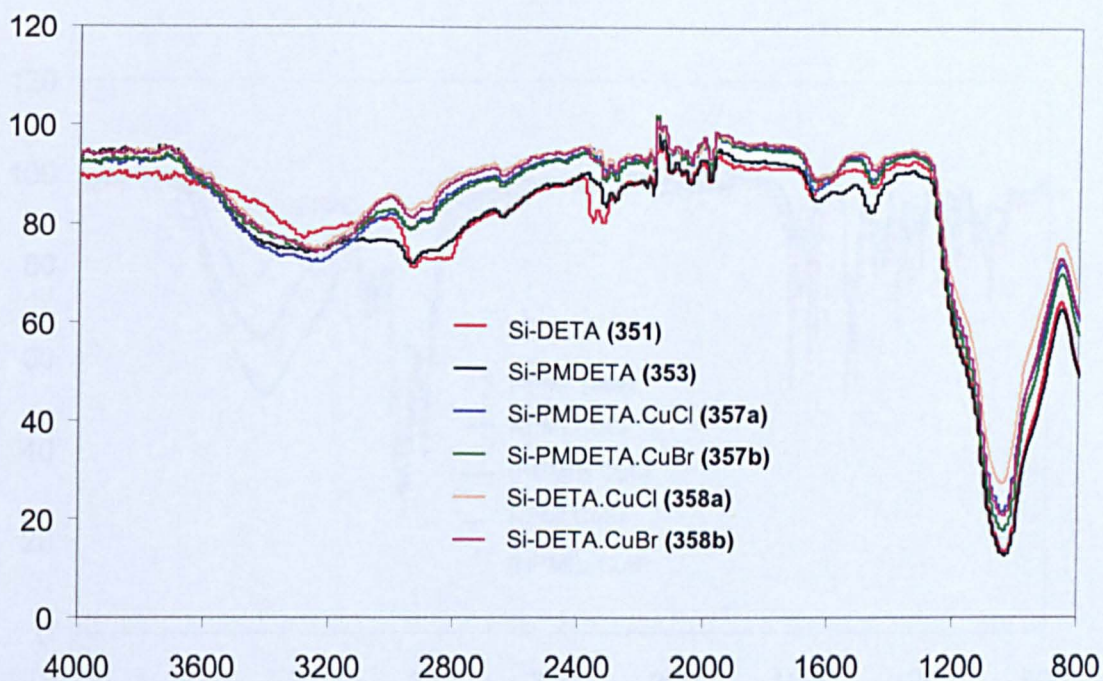


Figure 36: Infra-red Spectra of (351), (353), (357a), (357b), (358a) and (358b)

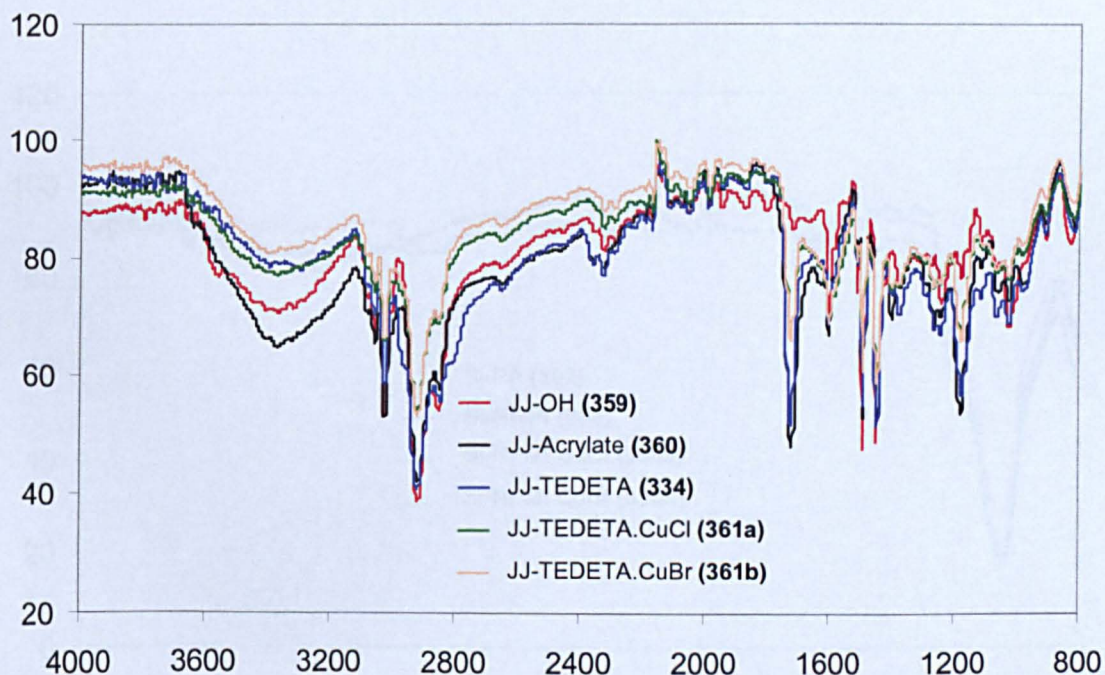


Figure 37: Infra-red Spectra of JJ-OH (359), JJ-Acrylate (360), JJ-TEDETA (334), JJ-TEDETA.CuCl (361a) and JJ-TEDETA.CuBr (361b)

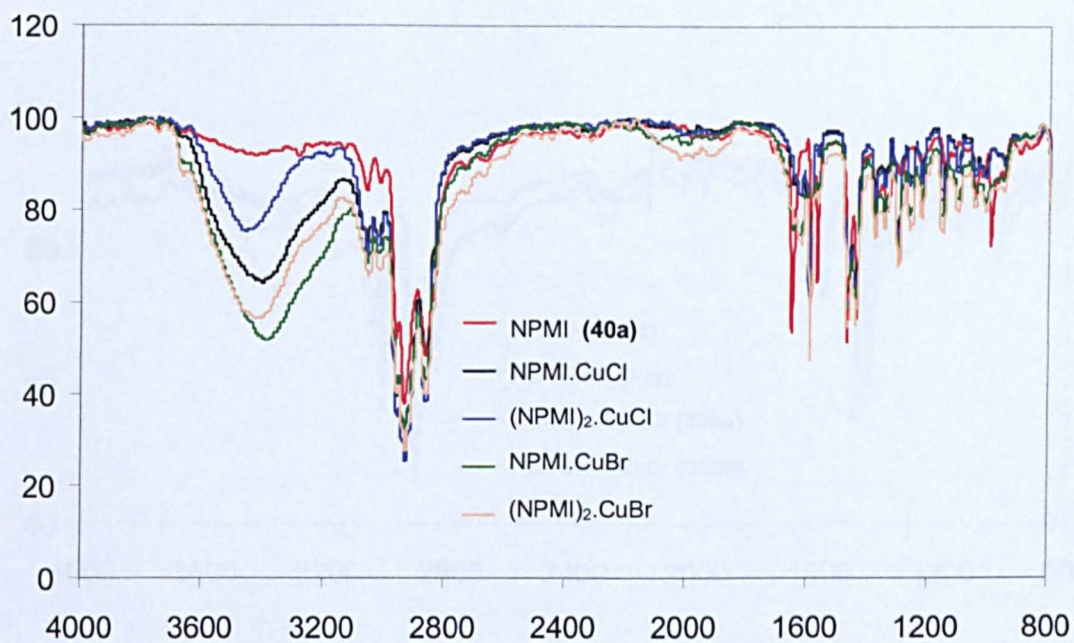


Figure 38: Infra-red Spectra of NPMI (40a), NPMI.CuCl, (NPMI)₂.CuCl, NPMI.CuBr and (NPMI)₂.CuBr

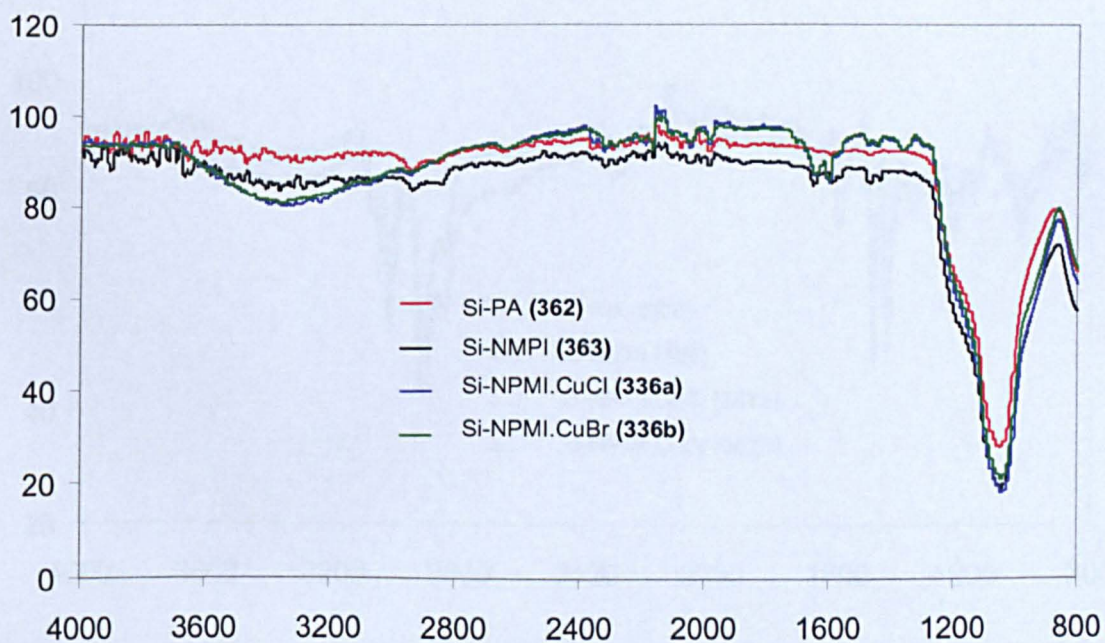


Figure 39: Infra-red Spectra of Si-PA (362), Si-NPMI (363), Si-NPMI.CuCl (336a) and Si-NPMI.CuBr (336b)

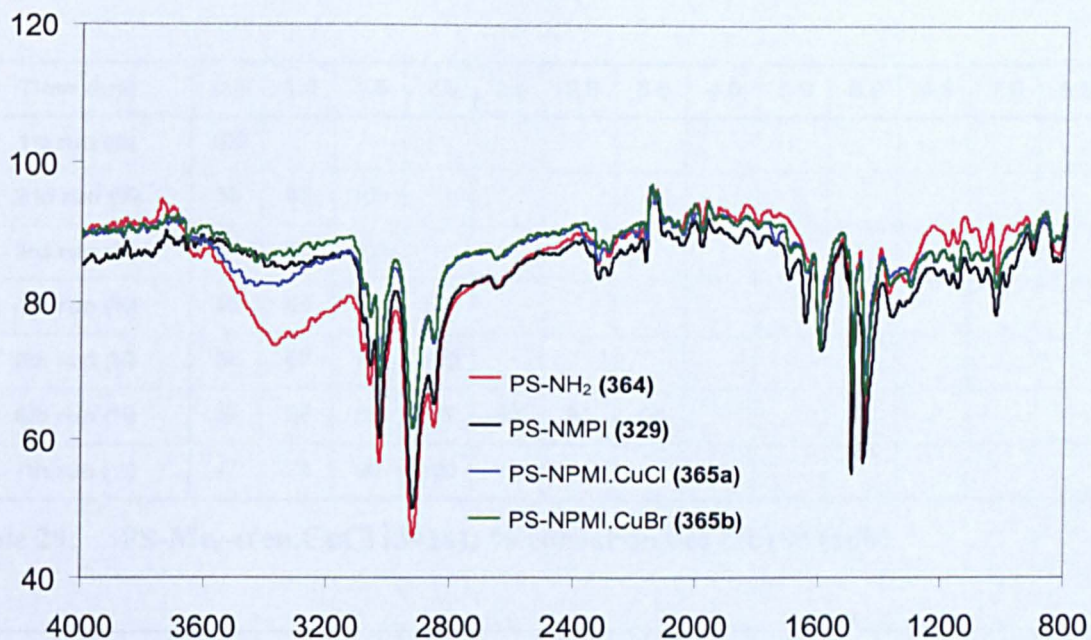


Figure 40: Infra-red Spectra of PS-NH₂ (364), PS-NMPI (329), PS-NMPI.CuCl (365a) and PS-NMPI.CuBr (365b)

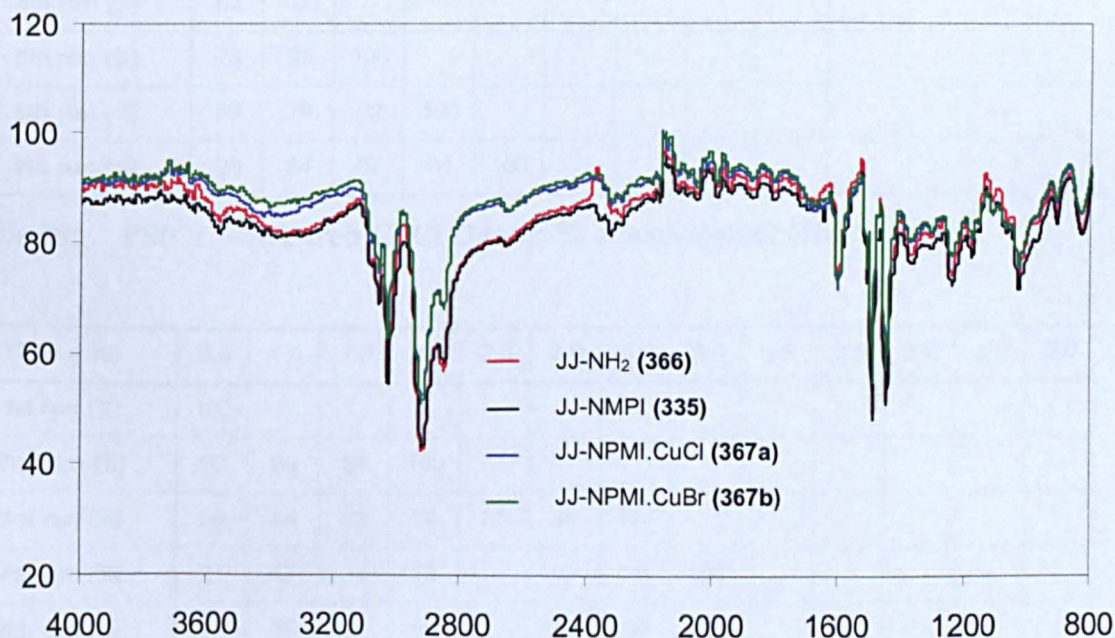


Figure 41: Infra-red Spectra of JJ-NH₂ (366), JJ-NMPI (335), JJ-NMPI.CuCl (367a) and JJ-NMPI.CuBr (367b)

Solid Supported Catalyst Reusability Data

Time (hrs)	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	6.5	7.0	8.0
1st run (%)	100												
2nd run (%)	58	82	100										
3rd run (%)	64	92	100										
4th run (%)	43	80	94	100									
5th run (%)	55	87	97	100									
6th run (%)	37	54	65	76	83	91	94						
7th run (%)	47	73	90	100									

Table 29: PS-Me₆-tren.CuCl (341a); % conversion of (7b) to (16b)

Time (hrs)	0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	6.5	7.0	8.0	9.0
1st run (%)	100												
2nd run (%)	94	100											
3rd run (%)	64	100											
4th run (%)	82	100											
5th run (%)	73	95	100										
6th run (%)	59	79	92	100									
7th run (%)	28	64	87	94	100								

Table 30: PS(CL)-Me₆-tren.CuCl (346a); % conversion of (7b) to (16b)

Time (hrs)	0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	6.5	7.0	8.0	9.0
1st run (%)	100												
2nd run (%)	56	69	81	100									
3rd run (%)	28	44	62	74	85	94	100						
4th run (%)	21	47		72		87	95	100					
5th run (%)		33		59		71	80	88		100			
6th run (%)		26		48		66	77	83	89			100	
7th run (%)		20		44		56	68	79	86		90		100

Table 31: PS-PMDETA.CuCl (350a); % conversion of (7b) to (16b)

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