New Approaches to Nitrogen Heterocycles *via* Radical Cyclisations

By

Collette Guy

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Contents

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Declaration

The work presented in this thesis is all the original work of the author. References to previous related results and ideas have been fully acknowledged. The work was all complete in the Department of Chemistry at the University of Warwick between October 2009 and October 2013 and has not been submitted for a degee at any other institution.

Collette Guy

Abstract

The work presented in this thesis focuses on the use of radical cyclisations to synthesise nitrogen heterocycles. Chapter 1 provides an introduction to radical cyclisations and the development of conditions over the past couple of decades. It also gives an introduction to atropisomerism, a phenomenon present in a number of cyclisation precursors, and how this has been exploited to achieve chirality transfer in the cyclisation of acrylanilides.

Chapter 2 describes investigations into the effects of alkene substitution on the barrier to rotation about the *N*-alkenyl bond in enamides. A range of enamides were synthesised and their barriers to rotation were investigated by both 1H VT NMR and racemisation of an enriched atropisomer. Tetrasubstituted enamides were found to have significantly higher barriers to rotation, and in some cases it was possible to separate the two atropisomers at room temperature by chiral HPLC.

Chapter 3 describes the results of 5-*endo* cyclisations of tetrasubstituted enamides. Dependant on the starting material, cyclisations were carried out mediated by both Bu_3SnH and copper. Cyclisations of tetrasubstituted enamides proved to be more challenging than previous reported cyclisations of less hindered substrates with a number of by products produced.We have also examined the possibility of whether chirality transfer would be possible in the cyclisation of an enamide with a high barrier to rotation.

In Chapter 4 studies into the cyclisations of 2-bromobenzyl enamides are presented. Initial cyclisations were carried out into the Bu_3SnH mediated cyclisation of a trisubstituted enamide and the rate of both the 5-*exo* and 6-*endo* cyclisation was calculated. The cyclisation of tetrasubstituted 2-bromobenzyl enamides was then

attempted, however it proved less successful. The hindered nature of the tetrasubstituted enamides was found to slow the rate of cyclisation significantly leading to the formation of other products.

Chapter 5 describes studies into the synthesis of oxindoles *via* radical cyclisation. Reactions in methanol with CuBr and TPA at 50 ^{o}C gave three main products, a reduced compound, an eliminated compound and the target oxindole. Reactions repeated in toluene at 110 ^{o}C were much cleaner giving the oxindole product in high conversions.

Abbreviations

Ac	Acetyl
ACN	1,1’-Azobis(cyclohexanecarbonitrile)
AGET	Activators generated by electron transfer
AIBN	Azabisisobutyronitrile
Ar	Aryl
ARGET	Activators regenerated by electron transfer
ATRC	Atom-Transfer Radical Addition
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bipy	Bipyridine
Bn	Benzyl
br	Broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
cy	Cyclohexyl
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets

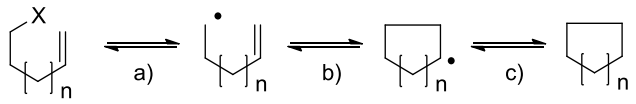
DMF	Dimethylformamide
dt	Doublet of triplets
ee	enantiomeric excess
EI	Electron Ionisation
eq	Equivalents
er	enantiomeric ratio
Et	Ethyl
$\Delta G^{\ddagger}$	Gibbs Free Energy (of rotation)
h	hours
h	Planck's Constant
HPLC	High Performance Liquid Chromatography
Hz	Hertz
ICAR	Initiators for Continuous Activator Regeneration
k_b	Boltzmann Constant
k_c	Rate of Cyclisation
k_{rot}	Rate of Rotation
KF	Potassium Fluoride
m	Multiplet
maj	Major

Me	Methyl
Me_6-Tren	*N, N, N', N', N'', N''*-hexamethyltriethylenetetramine
min	minute
mins	minutes
mpt	Melting Point
NHC	*N*-heterocylic carbene
NMR	Nuclear magnetic resonance
NMPI	Pyridine-imine ligand
nOe	Nuclear Overhauser Effect
PEG	Polyethylene glycol
Pet ether	Petroleum Ether 40-60 ^{o}C
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMDETA	pentamethyldiethylenetriamine
ppm	Parts per Million
q	Quartet
R	Gas Constant
rt	Room Temperature
s	Singlet

sec	Seconds
sept	Septet
t	Triplet
$t_{1/2}$	Half-Life
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
Tol	Toluene
TPA	Tripyridylamine
TsOH	*p*-Toluenesulfonic acid
VT NMR	Variable Temperature Nuclear Magnetic Resonance

1.0 Introduction

Radical cyclisation reactions are useful processes in organic synthesis as they allow for the formation of a variety of carbo- and heterocyclic ring systems.[1–5] They can offer high functional group tolerance and mild reaction conditions along with high levels of regio- and stereocontrol. In general, a radical cyclisation proceeds *via* three basic steps; generation of the radical , cyclisation of the radical, and then conversion of the cyclised radical to the product (Scheme 1.1).

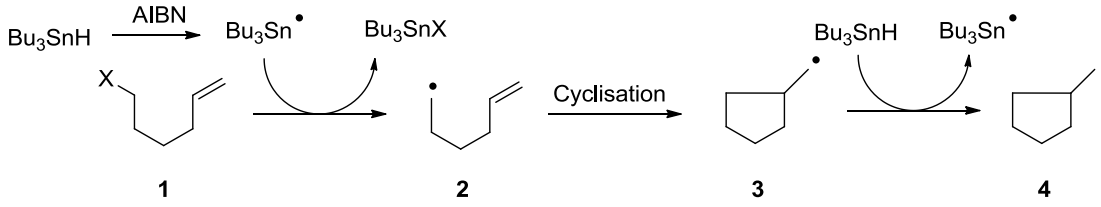


Scheme 1.1: General steps of a radical cyclisation: a) - Generation of radical, b) - Cyclisation of radical, c) – Conversion of cyclised radical to product.

The radical is predominantly generated from a halide (X),[5,6] but can be derived from a range of different functionalities in the cyclisation precursor, such as thio- and selenoethers,[7] aldehydes and ketones,[8] and xanthates.[9] The cyclisation step occurs *via* the intramolecular addition of a radical to a multiple bond, most commonly a carbon-carbon multiple bond, however cyclisations onto carbon-oxygen[10,11] and carbon-nitrogen[12,13] bonds are known. The radical formed in the cyclisation step can be quenched in a number of ways, depending on the reaction conditions; it can be trapped by a radical scavenger, undergo a fragmentation reaction, or be converted in an electron transfer reaction to a cation or anion.

1.1 Traditional Organnostannane Mediated Radical Cyclisations

Traditionally radical cyclisations were mediated by organostannane or organosilane reagents (e.g. Bu_3SnH[1,14] and $(SiMe_3)_3SiH$[15]) in the presence of radical initiators (e.g. AIBN) and for many years these were the only conditions used.

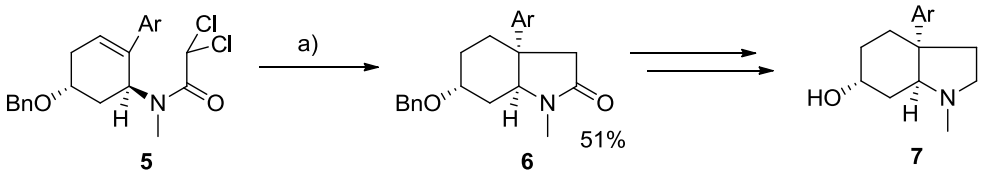


Scheme 1.2: Bu_3SnH mediated radical cyclisation.

The cleavage of the relatively weak Sn-H and Si-H bonds with an initiator generates the corresponding tin and silicon centred radicals which abstract the halogen (X) from the σ carbon-halogen bond in the precursor **1** to form radical **2**. Cyclisation of radical **2** onto a radical sink, such as an alkene, forms a third radical **3** which then is propagated by abstraction of a hydrogen atom from the organostannane or organosilane. This furnishes the reduced product **4** and regenerates another reactive tin or silicon centered radical (the chain carrier) to continue the radical chain reaction (Scheme 1.2).

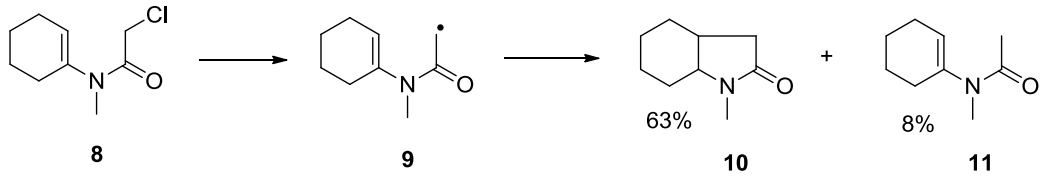
These conditions have been employed in the cyclisation of a variety of substrates to give a range of cyclised products such as lactams,[16] lactones,[17] carbocycles,[18] indoles[19] and oxindoles.[20] Ishibashi has applied these conditions to the cyclisation of α-chloroacetamides and α,α-dichloroacetamides and found that the dichlorosubstrates underwent cyclisation much more readily.[21] The cyclisation was then applied in the stereoselective synthesis of the natural products (±)-mesembranol

7 and (±)-elwesine.[16] Cyclisation of enamide **5** led to the cyclised product **6** in 51% yield, which was then converted into the natural product **7** after two further steps, (Scheme 1.3).



Scheme 1.3: Bu_3SnH mediated cyclisation in the synthesis of (±)-mesembranol. *Reagents and Conditions:* a) Bu_3SnH (2.1 eq.), AIBN (cat.), toluene, reflux, 4h.

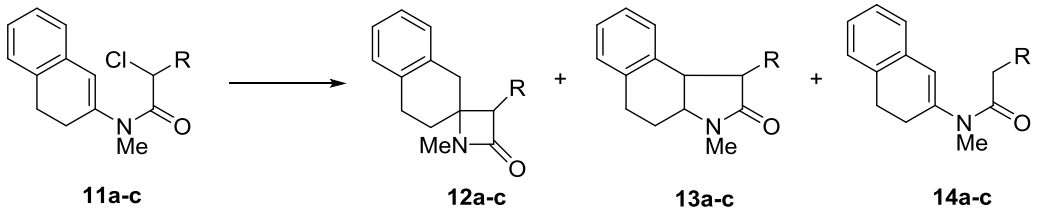
Ishibashi has used also Bu_3SnH to carry out the traditionally 'disfavoured'[22] 5-*endo-trig* cyclisation of *N*-vinylic α-chloroacetamides to give 5-membered lactams.[23] Treatment of enamide **8** with Bu_3SnH in the presence of AIBN led to the 5-*endo* cyclisation product **10** in 63% yield along with the reduced non-cyclised compound **11** as a minor product (Scheme 1.4).



Scheme 1.4: Tin mediated cyclisation of *N*-vinylic α-chloroacetamides: *Reagents and conditions*: Bu_3SnH (1.1 eq.), AIBN (cat.) toluene, reflux.

The type and level of substitution on the radical centre can affect the regiochemical outcome of the cyclisation and under certain conditions the 4-*exo* cyclisation is favoured. The difference in the reaction pathways of enamides **11a-c** can be explained in terms of electronic stability of the initial radicals and/or steric clashes in the cyclised radical intermediates **15** and **16** (Figure 1.1, Table 1). The authors suggest that enamide **11a** proceeds *via* the more electronically stable benzyl radical

intermediate **15** to give exclusively the 4-*exo* product **12a**. However when a larger R group is introduced (**11b** R=Me) steric clashing occurs between this R group and the neighbouring *gem*-dialkyl groups in **15**, destabilising the radical and as a result both pathways are followed. Increasing the size of the R group even further (**11c** R=Ph) results in severe steric clashing in the benzyl radical **15,** therefore the α-acylamino radical dominates leading to the 5-*endo* product **13c** as the major product. Another possible explanation is that for **11b-c** the 4-*exo trig* cyclisation has a greater degree of reversibility due to the methyl/phenyl group at the radical centre stabilising the initial radical, hence giving rise to greater percentages of the thermodynamic products **13b-c**.



Entry	R-Group	4-*exo* / %	5-*endo* / %	Reduced / %
1	H (**11a**)	50	0	32
2	Me (**11b**)	42	35	19
3	Ph (**11c**)	0	76	0

Table 1.1: Ratios of 5-*endo* and 4-*exo* products in cyclisation of enamides. *Reagents and Conditions:* Bu_3SnH (1.1 eq.), AIBN (cat.) toluene, reflux.

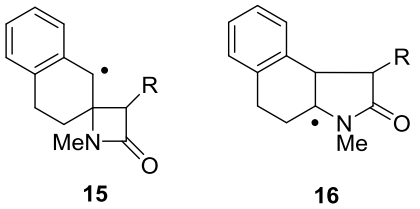


Figure 1.1: Radical intermediates in the cyclisation of enamides 11a-c.

1.1.1 Drawbacks of Organostannane Mediated Cyclisations

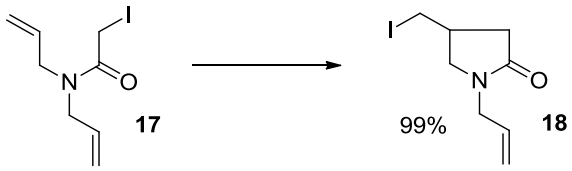
Whilst these reductive conditions have proven successful in many applications including the synthesis of a number of natural products[24–27] there are certain disadvantages that limit the usefulness of the process. The reductive nature of the reaction is a major drawback, the termination of the cyclised radical with a hydrogen atom results in the loss of two functional groups in the transformation of the starting material into the product. Organostannane reagents and their by-products are also particularly toxic and can be difficult to remove from the final product.[28] This causes particular concern for the pharmaceutical industry, where acceptable levels of tin compounds in final products are very low, and it is generally very hard to achieve these low levels during purification.[29] Other disadvantages of these procedures are the need for stoichiometric amounts of organostannane reagent and the relatively high cost of these reagents, issues which are magnified on a large scale making the process unattractive for industry.

1.1.2 Overcoming the Issues in Organostannane Mediated Reactions.

There have been attempts at overcoming these issues and Studer[30] and Baguley[31] have both written reviews covering developments in the area. As well as modified work-up and purification procedures,[32–34] a range of alternative tin hydrides have been developed to aid with the removal of any tin containing by-products from the reaction mixture. In particular solid-supported,[28,35–37] PEG-bound,[38] water soluble,[39] acid extractable[40] and perfluorous tin hydrides[41] have all shown significantly to improve the removal of any tin residues from reactions mixtures.

In 1979 Berge and Roberts reported that partitioning the concentrated reaction mixture between acetonitrile and pentane, followed by concentration of the acetonitrile extract could result in significantly reduced levels of tin compounds in the product.[32] Another method developed by Jacobus involves conversion of the organotin residue into the insoluble organotin fluoride by washing the reaction mixture with aqueous potassium fluoride. The organotin fluoride can then be removed by filtration and the organic phase dried and concentrated to yield the product.[42] More recently Harrowven has modified the method of Jacobus and Leibner, and has developed the use of a KF-silica stationary phase for column chromatography as a means of removing tin residues.[34] Using the hydrodehalogenation of an aryl halide with tributyltin hydride as a reagent he has shown that simply concentrating the reaction mixture and eluting it through a stationary phase comprising of 10% w/w of KF and 90% w/w silica resulted in levels of tin below 30 parts per million. Solid supported tin reagents have also been developed to facilitate the removal of tin at the end of the reaction.[43–45]

In the early 90's Curran looked at addressing the issues relating to the reductive nature of tin reagents, and the need for stoichiometric amounts in reactions. By replacing Bu_3SnH, with hexabutylditin, the possibility of reductive termination was removed and instead the reaction was found to be terminated by transfer of an iodine atom (an atom transfer radical cyclisation process, ATRC), either from the substrate **17** or a Bu_3SnI by-product (Scheme 1.5). This also allowed the loadings of tin reagent to be lowered sub-stoichiometric levels of 10 mol%.[17]

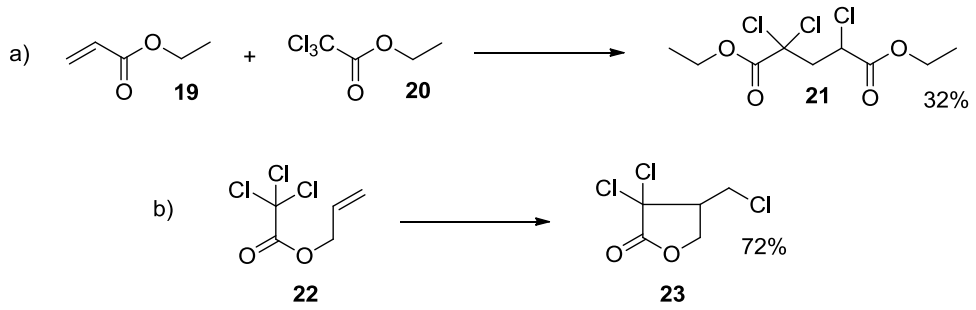


Scheme 1.5: A non-reductive, non-stoichiometric tin cyclisation. *Reagents and conditions:* 10 mol% $Bu_3SnSnBu_3$, benzene, hν.

The retention of functionality and the catalytic conditions achieved by Curran, along with the developments in purification techniques discussed earlier represent significant improvements in the area, however the toxicity and high cost of organotin reagents still remain major drawbacks. In order to address these issues research has focussed on the use of other metals such as copper,[5] nickel[46,47] and ruthenium[48–50] to mediate the reaction and has led to the development of atom transfer radical cyclisations.

1.2 Atom Transfer Radical Cyclisation

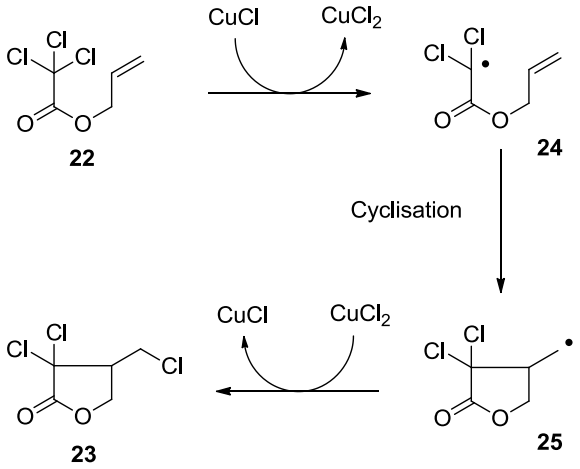
In 1964 Murai *et al* showed that CuCl could catalyse the intermolecular addition of ethyltrichloroacetate across a double bond[51] (Scheme 1.6a). In 1983 Nagashima *et al* then applied similar conditions to achieve the intramolecular addition, resulting in a copper mediated 5-*exo*-trig cyclisation of **22** (Scheme 1.6b).[52]



Scheme 1.6: Inter- and intramolecular addition of trichloroacetates across a double bond.

Reagents and conditions: a) CuCl, EtOH, reflux, b) 30 mol% CuCl, MeCN, 140 ^{o}C.

Nagashima proposed that the reaction proceeded *via* a catalytic redox mechanism where CuCl reacts with the substrate **22** to form the initial tertiary radical **24** and $CuCl_2$. This radical can then cyclise into the double bond to form the more reactive primary radical **25** which then interacts with the $CuCl_2$ generated in the first step to furnish the functionalised lactone **23** and regenerates the CuCl catalyst (Scheme 1.7).



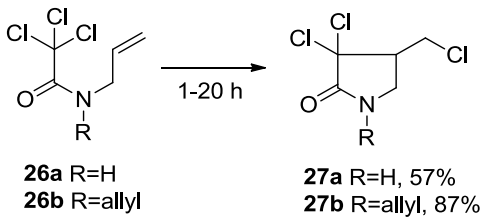
Scheme 1.7: Proposed catalytic redox mechanism.

This CuCl mediated cyclisation has numerous advantages over the traditional tin mediated reaction. The redox mechanism allows for the product to be terminated by a halogen, hence retaining a degree of functionality in the product for further chemistry. The CuCl reagent is significantly cheaper, less toxic, easier to handle, and

easier to remove than the organotin reagents used in the traditional radical cyclisations. In addition to this, the reaction was also shown to proceed with sub-stoichiometric amounts of CuCl making the reaction more industrially viable. As a result of this initial development a large amount of research into copper mediated atom transfer radical cyclisations (ATRC) has focussed upon extending the scope of the reaction to form γ-lactams and other ring sizes as well as γ-lactones. The effect of solvent, temperature and ligands for copper have been examined in order to improve the efficiency of the reactions. The work up until early 2002 has been summarised in a comprehensive review by Clark.[5]

1.2.1 Development of conditions for ATRC

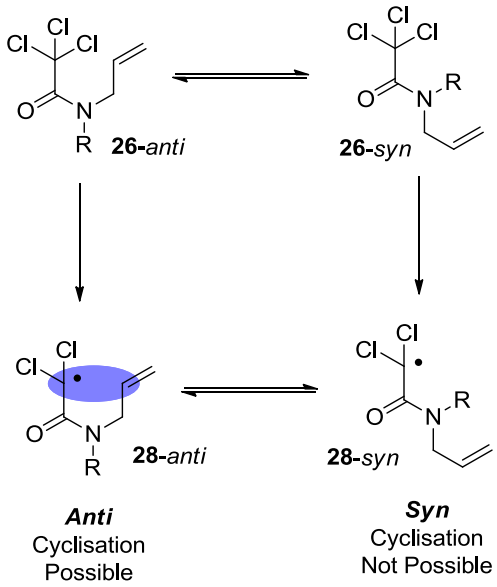
Nagashima was able to apply the conditions used in the synthesis of the γ-lactones to the synthesis of γ-lactams. There was no evidence of products arising from 6-*endo* cyclisation which might be expected in these reactions, with only the 5-*exo* product being observed. However high reaction temperatures and in some cases long reaction times were required in order to achieve synthetically useful yields, (Scheme 1.8).[53,54]



Scheme 1.8: Nagashima's ATRC to produce γ-lactams. *Reagents and conditions:* 30 mol% CuCl, MeCN, 140 ^{o}C.

Cyclisation of both secondary and tertiary amides was possible, although cyclisation of the tertiary amide was more efficient (**26b → 27b**). The greater efficiency for the

cyclisation of the tertiary amide **26b** can be explained by conformational analysis of the precursor. The amide bond characteristically has a high barrier to rotation, in the region of 16-22 kcal/mol,[55] which leads to two possible conformations of the amide precursor, the *anti* conformer and the *syn* conformer, (Scheme 1.9). Only one of these comformers, the *anti*, is predisposed for cyclisation to occur, with the radical and the unsaturated carbon of the radical sink positioned so that orbital overlap is possible. The *N*-protecting group can affect the populations of these two conformers; when unprotected (R=H), the least sterically hindered *syn* conformer is preferred, however bulky or electron withdrawing groups can push the equilibrium towards the *anti* conformer and therefore favour cyclisation.[56]

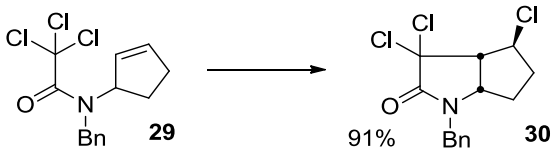


Scheme 1.9: Two conformers of amides arising from amide bond rotation.

The existence of two conformers may also explain why high temperatures and long reaction times are sometimes needed. In these cases high temperatures are required to ensure an appropriate concentration of the *anti* conformer is populated. The importance of the N-CO bond rotation and the population of the two conformers has also been noted by Curran in the cyclisation of *N*-allyl α-polyamides,[17] and by Stork

and Ishibashi in the tin mediated cyclisation of *N*-allyl haloamides.[16,21,57] Newcomb also reported supporting evidence for this using laser flash photolysis kinetic studies of N-CO bond rotation.[58]

Nagashima used the same approach to synthesise bicyclic lactams, providing access to pyrrolidine alkaloid skeletons. Cyclisations of the precursor **29** at 110 ^{o}C in the presence of 30 mol% CuCl in acetonitrile led to the product **30**, as a single diastereomer with a *cis* ring junction, in 91% yield (Scheme 1.10).[54]

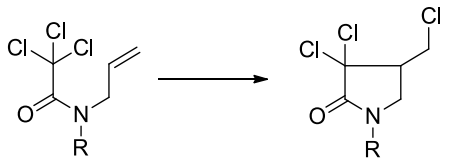


Scheme 1.10: CuCl mediated cyclisation to form a bicyclic ring system. *Reagents and conditions:* 30 mol% CuCl, MeCN, 110 ^{o}C, 1 h.

In order to try and lower reaction temperatures and improve the efficiency of the reaction different copper salts were screened and Cu_2O, $Cu(NO_3)_2.5H_2O$ and Cu(CCPh) all were effective in mediating the cyclisation of the trichloroacetate **22**, although CuCl still remained the most effective.[59] Different solvents were also screened in the reaction of **22**, however only MeCN and alcohols proved to be effective in mediating this cyclisation, and alcohols only gave low yields. The concentration of the reaction was also found to be crucial, with dilute conditions (4-8 mL per 1 mmol of substrate) required for the efficient cyclisation; higher concentrations resulted in a decreasing yield due to intermolecular polymerisation.[59]

1.2.1.1 The effect of ligands on ATRC

The use of copper ligands has been investigated and has proven to accelerate the rate of reactions and allow the cyclisation of less reactive substrates. The addition of 2,2'-bipyridine (bipy) in a 1:1 ratio with CuCl to the reaction of **22** was found to accelerate the rate of reaction fourfold.[59] The Cu(bipy)Cl system was most active in DCM, however other solvents such as DCE and THF were also successful.[60] The more active catalyst system now allowed for cyclisations to be carried out at room temperature, with much shorter reaction times in comparison to the CuCl/MeCN system (Table 1.2).



26c-e **27c-e**

R group	Conditions	Temp	Time / h	Yield / %
Bn (**26c**)	30 mol % CuCl / MeCN	80 ^{o}C	18	68
Bn (**26c**)	30 mol % Cu(bipy)Cl / DCM	r.t.	1	98
Ts (**26d**)	30 mol % CuCl / MeCN	r.t.	24	97
Ts (**26d**)	5 mol % Cu(bipy)Cl / DCM	r.t.	0.2	91
Boc (**26e**)	30 mol % CuCl / MeCN	80 ^{o}C	4	80
Boc (**26e**)	30 mol % Cu(bipy)Cl / DCM	r.t.	2	78

Table 1.2: The effect of bipy on copper catalysed ATRC.

Quayle has applied the Cu(bipy)Cl catalyst system to the target-orientated synthesis of γ-butyrolactones such as **31.**[61] This group of compounds have been shown to be useful intermediates in the synthesis of lignans such as lactol **32** (Figure 1.2).

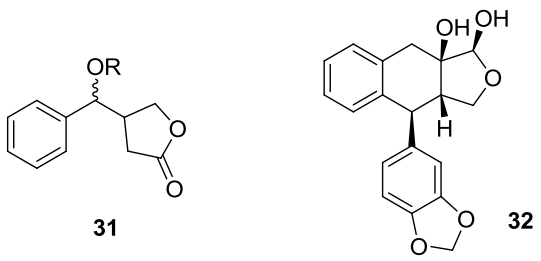
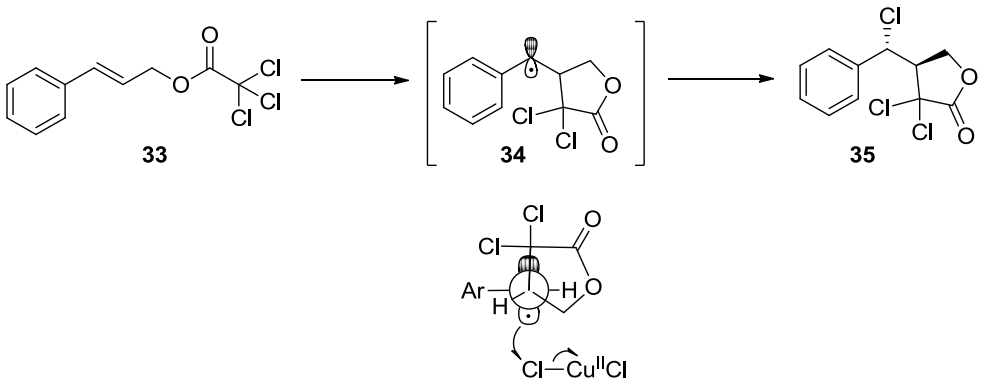


Figure 1.2: Structures from Quayle's target orientated synthesis.

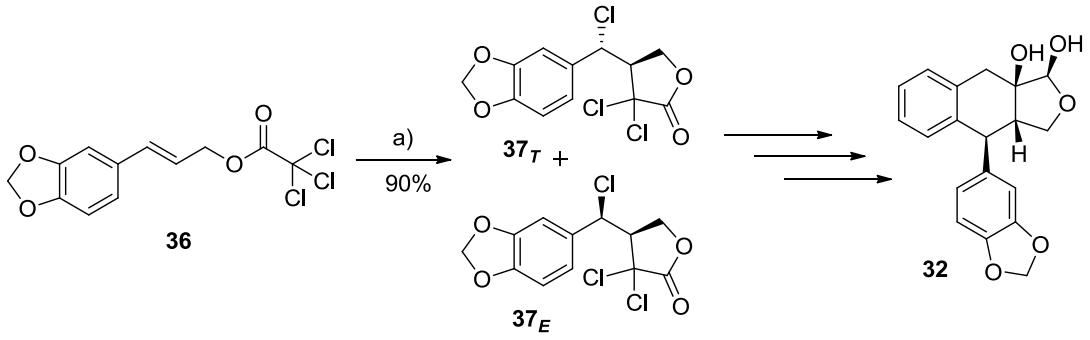
The cyclisation of **33** with CuCl and bipy proceeds to give the γ-butyrolactam **35** in 89% yield with high levels of diastereoselectivity (dr > 95:5) in favour of the *threo*-isomer.[61] The stereochemical result may be rationalised in terms of an 'allylic strain model' shown below (Scheme 1.11). Cyclisation initially generates the planar benzylic radical **34** which adopts a conformation where the bulky aromatic group takes up an 'outside' orientation with respect to the lactone ring, minimising unfavourable steric interactions. Halogen abstraction from the Cu^{II} complex genereated in the first step then proceeds *anti*- to the bulky geminal dichloromethylene group, leading to the high level of stereoselectivity.



Scheme 1.11: Stereo-control in Cu(bipy)Cl mediated cyclisation of 33. *Reagents and Conditions:* CuCl 5 mol%, bipy 5 mol%, DCE, 80 ^{o}C.

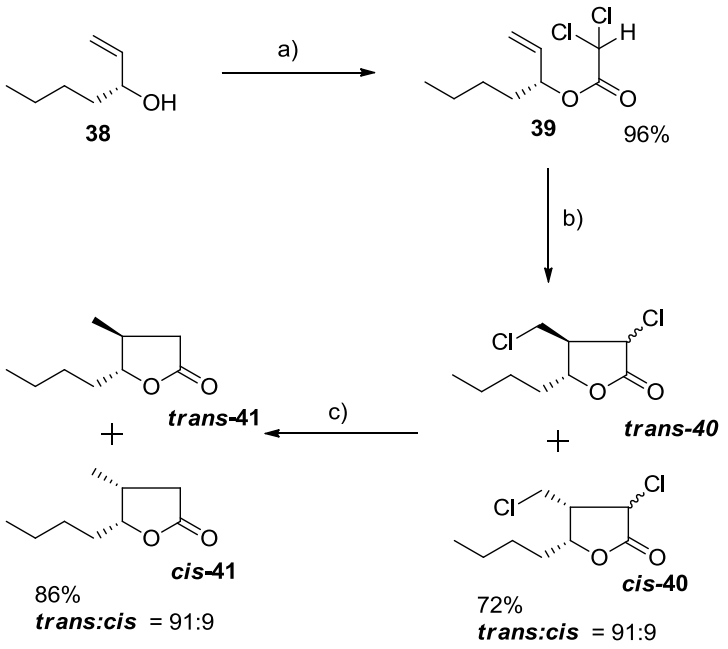
In contrast, when ester **36** (3 mmol) was treated with Cu(bipy)Cl in DCE at reflux for 3.5 h the reaction was almost stereo-random, resulting in lactones $\mathbf{37}_{\boldsymbol{T}}$ and $\mathbf{37}_{\boldsymbol{E}}$ in

a 3:2 ratio and 90% isolated yield (Scheme 1.12).[61] On scaling up the reaction (46 mmol) the *thero*-isomer $\mathbf{37}_{\boldsymbol{T}}$ was the major product, suggesting that it is the initial product and that in the earlier experiments equilibration had occurred following cyclisation. This was confirmed when either isomer $\mathbf{37}_{\boldsymbol{T}}$ or $\mathbf{37}_{\boldsymbol{E}}$ were subjected separately to mild thermolysis in DCE at 80 ˚C giving rise to a 3:2 equilibrium mixture of $\mathbf{37}_{\boldsymbol{T}}$ and $\mathbf{37}_{\boldsymbol{E}}$. The two isomers $\mathbf{37}_{\boldsymbol{T}}$ and $\mathbf{37}_{\boldsymbol{E}}$ were then used in the synthesis of lactol **32**.



Scheme 1.12: Cu(bipy)Cl mediated cyclisation in the synthesis of lactol 32. *Reagents and Conditions:* a) CuCl 5 mol%, bipy 5 mol%, DCE, 80 ^{o}C.

Ghelfi used the Cu(bipy)Cl catalyst system in the synthesis of optically active *Quercus* lactones *e.g*. whisky lactone **41.**[62] These lactones are fragrant compounds found in different types of wood and responsible for the sensory characteristics of many alcoholic beverages.[63] Ester **39** was synthesised from enantiomerically pure alcohol **38**, and then treated with Cu(bipy)Cl to give the cyclised lactones ***trans*-40** and ***cis*-40**, which were dehalogenated to give the target compounds ***trans*-41** and ***cis*-41** with the *trans* isomer as the major product (Scheme 1.13).[62]



Scheme 1.13: ATRC in the synthesis of *Quercus* lactones. *Reagents and Conditions:* a) $Cl_2CHCOCl$, DMAP, DCM, r.t., 2 h. b) Cu(bipy)Cl, 145 ^oC, MeCN. c) Bu_3SnH, AIBN, 80 ^oC, toluene.

Following the discovery of bipy as a ligand to accelerate ATRC reactions, a number of other nitrogen containing ligands were investigated and shown to improve the efficiency of the copper mediated reactions further. It is thought that ligands either help to solubilise the CuCl, alter the redox potential of the catalyst system, or both.[5]

Pyridine imine ligands (NMPI's) (Figure 1.3) are easily prepared by the reaction of commercially available amines with pyridine carboxaldehydes in the presence of $MgSO_4$, and as a result a wide range of catalysts with different solubilities and steric and electronic properties have been synthesised.[64,65]

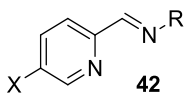
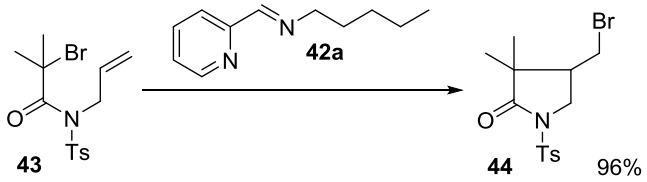


Figure 1.3 General structure for NMPI ligands.

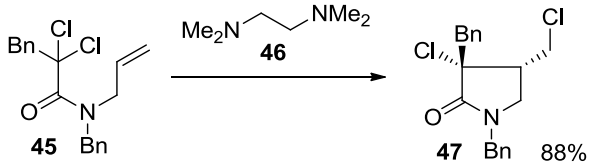
It was found that bulky *N*-alkyl substituents (R) retarded the rate of cyclisation, whereas **42a** (R= *n*-pentyl) with the less bulky substituent proved to be active enough to catalyse the cyclisation of mono-halosubstrates such as **43** at room temperature.



Scheme 1.14: Cyclisation of mono-holosubstrate with NMPI ligand. *Reagents and conditions:* 30 mol% CuBr, 30mol % **42a**, DCM, r.t., 24 h.

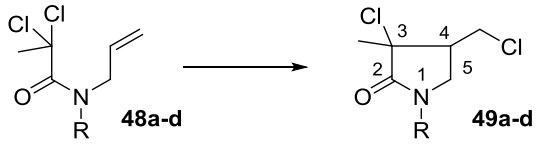
A range of electronically modified ligands, changing X in structure **42**, were also screened and it was found that an electron withdrawing group (X= NO_2) caused a decrease in the rate of cyclisation, whereas a mildly inductive electron donating group (X= Me) showed a slight increase in the rate of cyclisation.[65]

Another bidentate ligand that was shown to be useful in catalysing cyclisation reactions is *N,N,N',N'*-tetramethylethylenediamine (TMEDA) **46** which proved to give a more reactive catalyst system ($Cu(TMEDA)_2Cl$) than either the bipy or NMPI ligands, improving yields as well as allowing for lower catalyst loadings in the reactions to give γ-lactams (e.g. **47**).[66] TMEDA also has the advantage of being commercially available and relatively inexpensive compared to the bipy ligand (TMEDA - 100 mL for £15.30, bipy - 100 g for £85.20, Sigma Aldrich, 25/07/13). The TMEDA complex was found to mediate the cyclisation of **45** to **47** as a single diastereomer in an 88% yield (Scheme 1.15), whereas the CuCl-bipy system failed to achieve any cyclisation product.[66]



Scheme 1.15: Cu(TMEDA)$_2$Cl mediated cyclisation. *Reagents and conditions:* 10 mol% CuCl, 10 mol% TMEDA, MeCN, 60 ^{o}C, 20 h.

Ghelfi and Parsons investigated what effect the nitrogen protecting group had on the Cu(TMEDA)Cl mediated cyclisations.[67] Benzyl protecting groups proved to be the most effective with yields of 99%, however bulkier naphthyl or benzhydril protecting groups resulted in lower yields (Table 1.3, entry 1-6). The *N*-dimethylamino group has also been used giving the desired product in 91% yield (Table 1.3, entry 7) with an excellent yield being achieved when EtOAc was used as an alternative solvent (Table 1.3, entry 8).[68] This protecting group has the advantage over the benzyl group of being easier to remove due to the weaker N-N bond compared to the N-C bond.



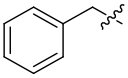
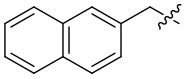
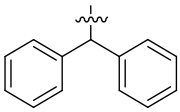
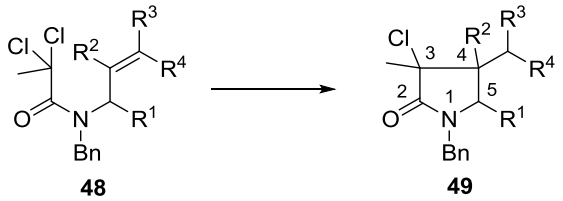
Entry	R group	Solvent	Temp / °C	Conversion / %	Yield / %
1 (**48a**)		MeCN	25	100	99
2 (**48a**)		MeCN	60	100	99
3 (**48b**)		MeCN	25	31	24
4 (**48b**)		MeCN	60	68	58
5 (**48c**)		MeCN	25	83	74
6 (**48c**)		MeCN	60	94	78
7 (**48d**)		MeCN	60	94	91
8 (**48d**)		EtOAc	60	99	97

Table 1.3: The effect of the *N*-protecting group on Cu(TMEDA)Cl mediated cyclisation.

Reagents and Conditions: CuCl 10 mol%, TMEDA 20 mol%, 20h.

Ghelfi also showed the cyclisation to be successful with a range of substitution on the allylic group (Table 1.4). In general the reaction proceeded with excellent yields, the poor yield upon cyclisation of **48g** was attributed to the poor stability of **49g** under the reaction conditions. The C-4 substituent was found to have similar steric interactions with the Me and the Cl at the C-3 position, resulting in limited preference for the *cis* or *trans* product. It was also found that a C-5 substituent forces the C-4 substituent onto the opposite face of the ring (Table 1.4, entries 6 and 7).



Entry	R^1	R^2	R^3	R^4	Conversion / %	Yield / %	*Cis:Trans*
1 (**48a**)	H	H	H	H	100	99	66:34
2 (**48e**)	H	H	Me	Me	100	99	50:50
3 (**48f**)	H	Me	H	H	100	99	31:69
4 (**48g**)	H	Cl	H	H	22	0	N/A
5 (**48h**)	H	H	H	Cl	100	100	80:20
6 (**48i**)	Me	H	H	H	100	98	1:7:22:70[a]
7 (**48j**)	Ph	H	H	H	100	98	2:5:26:67[a]

Table 1.4: Varying the allylic substitution in Cu(TMEDA)Cl mediated cyclisations. *Reagents and Conditions:* CuCl 10 mol%, TMEDA 20 mol%, 60 ^{o}C, MeCN, 20h. [a]Ratio % *t*-4, *t* -5:*c*-4, *c* -5: *t*-4, c -5: *c*-4, *t* -5 taking r-3-Cl.

Both the NMPI and TMEDA systems were found to have an optimum ratio of ligand to copper of 2:1,[64,66] suggesting two bidentate ligands molecules were required to form the active catalyst complex. As a result alternative polydentate ligands such tridentate *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA) **50**,[69] and tetradentate *N,N,N',N',N'',N''*-hexamethyltriethylenetetramine (Me_6-Tren) **51**,[70–72] and tripyridylamine (TPA) **52**,[73–75] ligands have been explored. All form active complexes with a 1:1 copper/ligand ratio.

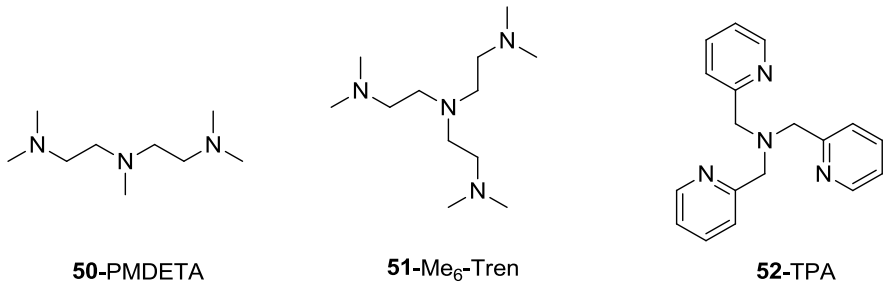
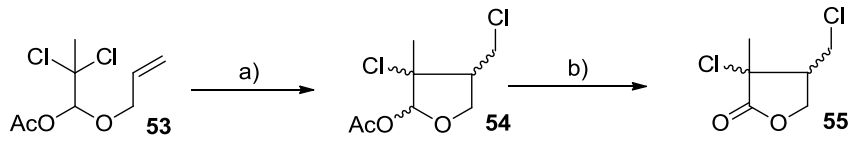


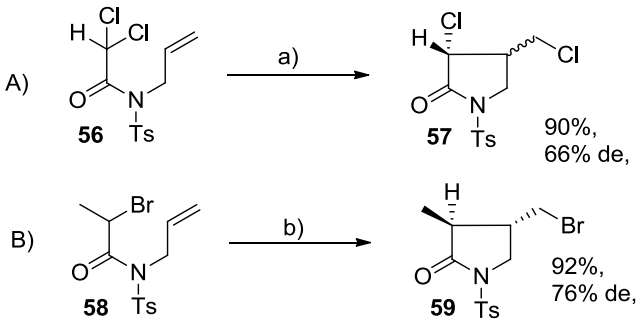
Figure 1.4: Multi-dentate ligands.

Ghelfi used PMDETA to carry out the Ueno-Stork ATRC of dichlorohemiacetal acetate **53** in a one pot, multi-step reaction. The cyclic product **54** was subsequently oxidised to the lactone product **55**.[69]



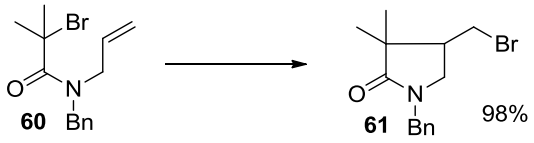
Scheme 1.16: Cu(PMDETA)Cl mediated Ueno-Stork cyclisation. *Reagents and conditions:* a) 10 mol% Cu(PMDETA)Cl, MeCN, 80 ^{o}C, 18 h. b) i) H_2SO_4/H_2O, 80 ^{o}C, 6-24 h, ii) $K_2Cr_2O_7$, H_2SO_4, acetone/H_2O, 25 ^{o}C, 2-4 h.

The tetradenate ligand Me_6-Tren when used as a 1:1 ratio with copper halide was found to be a far more active complex than either bipy or TMEDA in the cyclisation of **56**. When dichloro- compound **56** was treated with 30 mol% Cu(Me_6-Tren)Cl at room temperature the cyclised product **47** was obtained in a 90% yield after 2 h, whereas when NMPI ligand **42a** was used the best conversion obtained was 15 % in 72 h (Scheme 1.17A).[72] The more active nature of the Cu(Me_6-Tren)Cl complex allowed catalyst loadings to be lowered to 5 mol% and the cyclisation was still complete within 24 h.[76] Cyclisation of a number of monohalo-substrates was also possible using the Cu(Me_6-Tren)Cl catalyst system at room temperature (Scheme 1.17B).[76]



Scheme 1.17: Cu(Me6-Tren)CL mediated cyclisations. *Reagents and Conditions: a)* 30 mol% Cu(Me_6-Tren)Cl, DCM (0.12M), r.t., 2h, b) 30 mol% Cu(Me_6-Tren)Cl, DCM (0.12M), r.t.

TPA has also been shown to form a significantly more active catalyst system than the bidentate ligands. As with the Me_6-Tren ligand it effectively catalyses the cyclisation of the relatively deactivated monohalo-substrates (Scheme 1.18).[73]

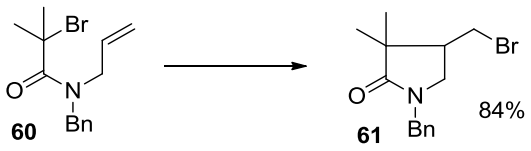


Scheme 1.18: Cu(TPA)Br mediated cyclisation of monobromoacetamide. *Reagents and conditions:* 30 mol% Cu(TPA)Cl, DCM, r.t., 2h.

1.2.1.2 The use of additives in ATRC

Even with these more activated catalysts, in order to achieve high yields in short reaction times high catalyst loadings are still often required, particularly with the less activated substrates. Clark investigated the addition of additives to the reaction to reduce any build-up of inactive $CuBr_2$ back to active CuBr. AIBN was chosen as a potential additive as the by-products should be volatile and therefore facilitate the work-up. It has also been used in combination with Cu(TPA)Br with promising results in intermolecular atom transfer radical addition reactions.[77] It was found that

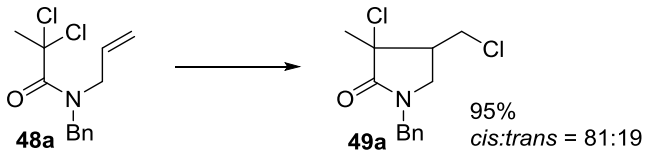
the addition of 10 mol% of AIBN allowed loadings of Cu(TPA)Br to be lowered to 1 mol%, with the cyclisation of **60** proceeding with 100% conversion, and 84% yield at room temperature.[73]



Scheme 1.19: Cu(TPA)Br mediated reaction with AIBN as an additive. *Reagents and conditions:* 1 mol% Cu(TPA)Br, 10 mol% AIBN, DCM, r.t.

When the reaction was trialled with only AIBN and no Cu(TPA)Br, no cyclisation occurred at all showing that the AIBN was not initiating the reaction itself. The reaction was also carried out with $CuBr_2$ as opposed to CuBr and the reaction proceeded with 97% yield showing that under these conditions either CuBr or $CuBr_2$ can be used.[73] This is an example of the 'initiators for continuous activator regeneration' (ICAR) protocol for regenerating the active catalyst species from the deactivated species.[78]

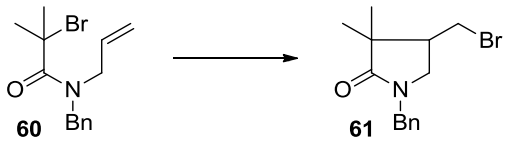
Another common technique employed in atom transfer radical polymerisation (ATRP) and atom transfer radical addition (ATRA) is the 'activators regenerated by electron transfer' (ARGET) process.[78,79] Ghelfi has applied this approach to ATRC, exploiting the reducing nature of ascorbic acid to lower catalyst loading levels to 2-4 mol%.[80] It was found that Na_2CO_3 also had to be added in order to quench the HCl produced in the catalyst regeneration step. Thus, cyclisation of **48** reached 100% conversion in two hours at room temperature when treated with 4 mol% Cu(PMDETA)Cl, 5 mol% ascorbic acid and 5.5 mol% Na_2CO_3 (Scheme 1.20), whereas when a standard redox catalyst was employed in MeCN the reaction took 20 h to reach completion.[66]



Scheme 1.20: ARGET-ATRC. *Reagents and conditions:* 4 mol% Cu(PMDETA)Cl, 5 mol% ascorbic acid, 5.5 mol% Na_2CO_3, EtOH, r.t., 2h.

The reaction also had the advantage that it worked in ethanol, a safe solvent, obtainable from renewable sources, and that only small amounts of solvent were required (2 mmol of substrate/mL ethanol). The reaction was also tested using TMEDA as the ligand however this resulted in only 53% conversion, indicating that the choice of ligand was important.[80]

Whilst the ARGET-ATRC conditions of Ghelfi were shown to be effective for the cyclisation of both dichloro- and trichloroacetamides, they were not applied to the cyclisation of monohalo-substrates. Clark however, screened a number of reagents common in ARGET-ATRP reactions to find conditions to carry out the cyclisation of the monobromo-substrate **60**.[81] The reaction was trialled with phenols,[82] ascorbic acid,[80,83] glucose,[84] hydrazine,[78] as well as the common reductant $NaBH_4$, and these reagents were compared to the ICAR reagent AIBN.

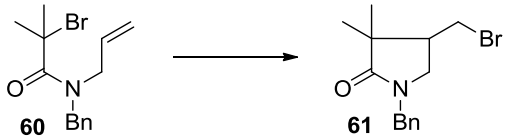


Entry	Additive	Solvent	Conversion	Yield
1	C_6H_5OH	MeOH	10	[a]
2	C_6H_5OH	DCM	91	83
3	Ascorbic acid	MeOH	55	9
4	Ascorbic acid	DCM	19	18
5	AIBN	MeOH	50	43
6	AIBN	DCM	100	84
7	NH_2NH_2	MeOH	10	11
8	Glucose	MeOH	23	17
9	$NaBH_4$	MeOH	100	82[b]
10	$NaBH_4$[c]	MeOH	67	52
11	KBH_4[c]	MeOH	100	74
12	KBH_4	THF	0	0
13	KBH_4[d]	MeOH	0	0

Table 1.5: ARGET reagents for cyclisation of monobromosubsrtate 60. *Regents and Conditions:* 1 mol% Cu(TPA)Br, 10 mol% additive, 50 ^oC, 5h, 0.12M. [a] Not measured as conversion too low. [b] Reaction time 10 mins at r.t. [c] 5 mol% of additive used. [d] No Cu(TPA)Br added.

Of the common ARGET reagents screened in methanol only ascorbic acid proved to be more effective than the ICAR reagent AIBN (Table 1.5, entries 3 and 5) and in DCM only phenol gave comparative results (Table 1.5, entries 2 and 6). However $NaBH_4$ proved to be very effective giving 100% conversion in 10 mins at room temperature (Table 1.5, entry 9). This result led to further borohydride reducing agents being screened, of which KBH_4 was the most effective, with loadings of 5 mol% of borohydride still giving 100% conversion (Table 1.5, entry 11). The solvent choice proved to be important, with no reaction observed in anhydrous THF (Table 1.5, entry 12). Hydride sources have been shown to mediate 5-*exo trig* cyclisations of aryl halides in the presence of an initiator,[85,86] so a control reaction was carried out with the addition of no Cu(TPA)Br to see if the borohydride was mediating the cyclisation itself, however no reaction was observed (Table 1.5, entry 13).

It is known that Cu(TPA)Br disproportionates to give Cu^0 metal and $[Cu^{II}(TPA)Br][Br]$ in polar solvents such as MeOH and DMSO,[87] and therefore Clark investigated the use of Cu^{II} salts as precatalysts for the reaction following an 'activators generated by electron transfer' or AGET method.[81] This approach uses the $[Cu^{II}(L)X]X$ species and a reductant at the start of the reaction, rather than the oxidatively less stable $Cu^{I}(L)X$ species.[88]



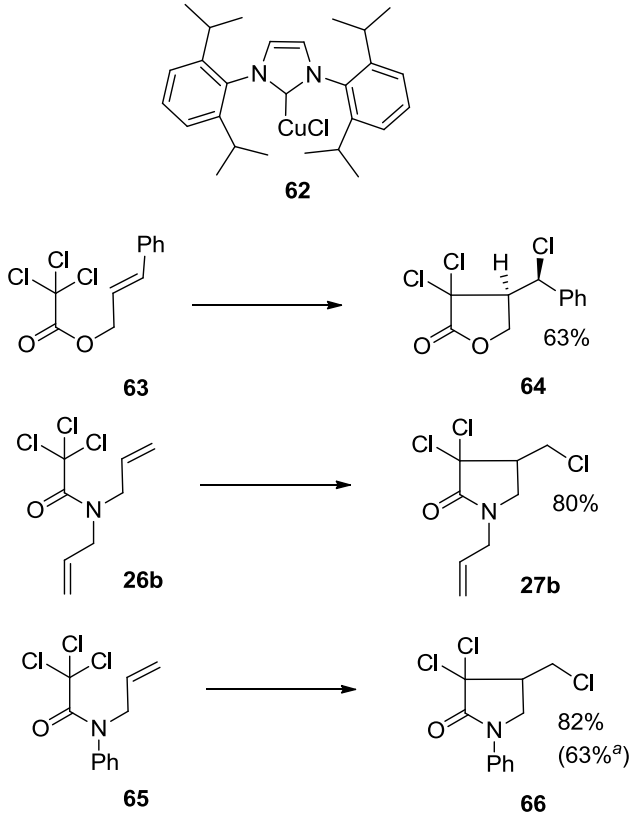
Entry	Cu Source (mol%)	KBH_4 mol%	Conversion	Yield
1	CuBr (1)	10	100	68
2	CuBr (0.1)	5	23	18
3	$CuBr_2$ (1)	10	100	84
4	$CuBr_2$ (0.1)	5	0	0
5	$Cu(OTf)_2$ (0.1)	5	100	85
6	$CuSO_4.5H_2O$ (0.1)	5	100	97
7	$Cu(acac)_2$ (0.1)	5	100	83
8	$Cu(ClO_4)_2.6H_2O$(0.1)	5	100	85
9	$CuSO_4.5H_2O$ (0.05)	2.5	40	35

Table 1.6: AGET cyclisation of monobromosubsrtate 60. *Regents and Conditions:* Copper source, KBH_4, r.t., 10 min, MeOH, 0.12M.

Four Cu^{II} salts, $Cu(OTf)_2$, $CuSO_4.5H_2O$, $Cu(acac)_2$ and $Cu(ClO_4)_2.6H_2O$ were all found to be superior to CuBr and $CuBr_2$, with loadings as low as 0.1 mol% of Cu and 5 mol% of KBH_4 giving 100% conversion within 10 mins (Table 1.6). It was possible to drop the loadings even lower to 0.05 mol% Cu and 2.5 mol% KBH_4 and still obtain reasonable activity (Table 1.6, entry 9).[81] $CuSO_4.5H_2O$ was chosen as the ideal copper source due to its low cost (£36.50 for 500 g, Sigma Aldrich, 25/07/13). These reactions did not require anhydrous salts and it was not necessary to exclude moisture from the reactions.

1.2.1.3 The use of copper-carbene complexes in ATRC

Stable Cu^{I}-NHC complexes have been shown to act as catalysts in hydrosilylation,[89] C-H activation[90] and Huisgen dipolar cycloaddition ('click') reactions[91] and Quayle has investigated their use in ATRC reactions.[92] Exposure of ester **63** and amides **26b** and **65** to ligand **62** in both toluene and DCE resulted in the desired cyclised products **64, 27b** and **66** in low yields, <5%, 22% and 38% respectively. However when the reactions were carried out in a microwave reactor the yields were much improved (Scheme 1.21).[92] Irradiation in DCE at 110 ^{o}C proved to be the optimal conditions for these reactions, with lower temperatures resulting in slower reactions, whilst higher temperatures led to reduced yields. It was possible to lower catalyst loadings to 1 mol% without greatly affecting the yield, although longer reactions times were required; cyclisation of **65** with only 1 mol% of catalyst led to the product **66** in a 63% yield after 17 h compared to 82% in 3 h with 5 mol% of catalyst.[92] Examination of the crude NMR from the reaction of amide **26b** showed that the carbene complex **62** was still present and had not undergone significant decomposition during the reaction suggesting that recycling of the catalyst is a possibility.[92]



Scheme 1.21: Carbene mediated ATRC. *Reagents and conditions:* 5 mol% **62**, DCE, μW, 110 °C, 3 h. [a] 1 mol% **62**, 17 h.

1.2.1.3 The use of solid supported copper catalysts.

A range of solid supported copper catalysts have also been developed[93–95] allowing easy separation of the catalyst from the cyclised product and re-use of the catalyst. Clark immobilized amine and pyridine based ligands on silica, polystyrene and JandaJel, which then formed the active catalyst complex when stirred with the relevant copper salt under an inert atmosphere.[93,94]

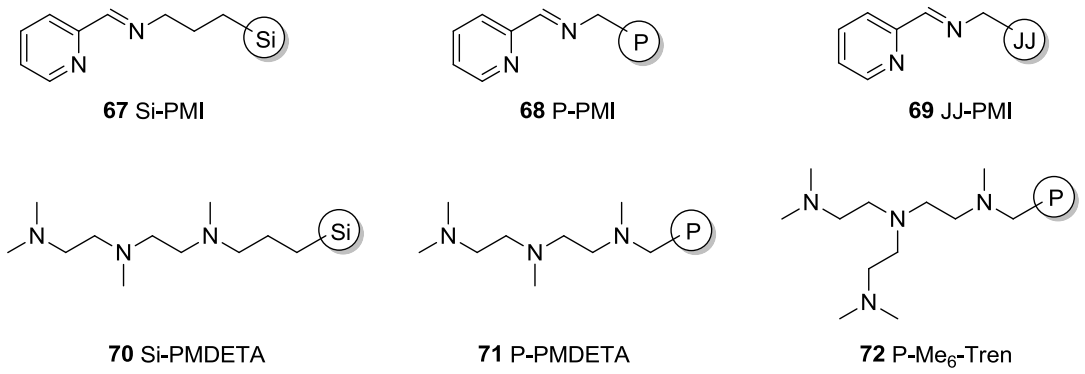
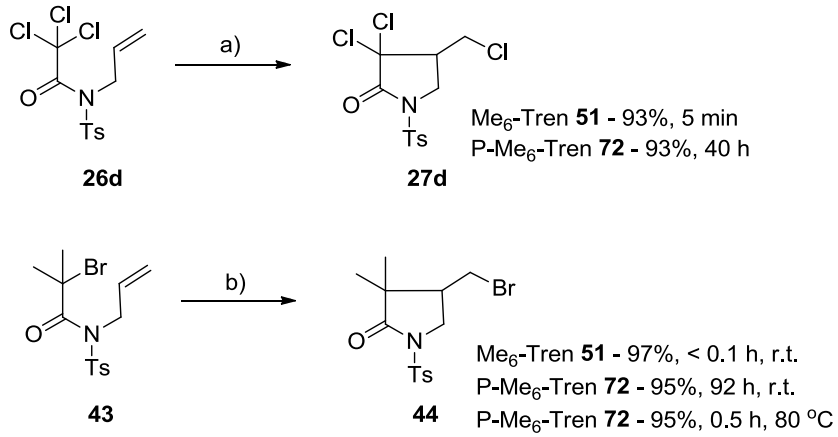


Figure 1.5: Solid supported ligands for ATRC.

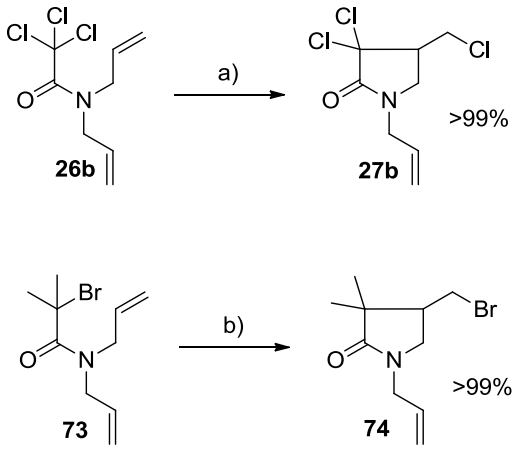
Cyclisations of both activated trichloroacetamides such as **26d** and relatively deactivated monobromoacetamide **43** are both successful with the heterogeneous catalysts although they were found to be slower than the homogenous equivalents.[94] The trichloro- compounds undergo facile cyclisation at room temperature within 1 hour, whereas the less activated monobromo- compounds require higher temperatures (80 ^{o}C) and longer reactions times (24 h) (Scheme 1.22).



Scheme 1.22: Solid-supported ATRC. *Reagents and Conditions:* a) 30 mol% ligand, 30 mol% CuCl, DCE, r.t. b) 30 mol% ligand, 30 mol% CuBr, DCE.

Nagashima has investigated the use of a Cu(bipy)Cl complex immobilised in a polysiloxane gel ([Cu/bipy]@Si) as a reusable catalyst system in ATRC reactions. The gel proved to be more stable than the standard Cu(bipy)Cl complex in solution

and can be stored under nitrogen for over a month and handled under aerobic conditions. Again, cyclisations of both trichloro- and monobromoacetamides were successful giving quantitative yields. Upon recycling of the catalyst the same yield was obtainable, although longer reaction times were required (Scheme 1.23).[95]

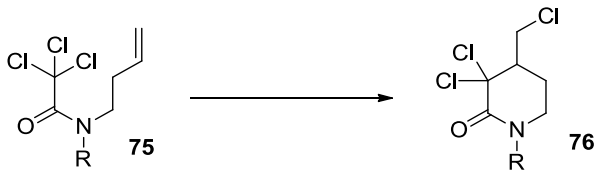


Scheme 1.23: Polysiloxane Gel Encapsulated Cu(bipy)X mediated ATRC. *Reagents and Conditions:* a) [Cu/bipy]@Si 0.45 mol%, DCM, r.t., 4 h. b) [Cu/bipy]@Si 0.45 mol%, DCM, r.t., 16 h.

In summary, these copper mediated 5-*exo trig* ATRC reactions have undergone significant improvements since their first discovery in 1983 and now exhibit a substantial range of advantages over the traditional tin mediated cyclisations. It is now possible to carry out cyclisations on relatively unactivated monohalosubstrates (e.g. **60**) with low catalyst loadings (e.g. 0.05 mol%), achieving high yields at low temperatures (RT) in short reactions times (<20 mins). The reactions can also be mediated by relatively non-toxic and cheap reagents in green solvents such as ethanol, and generally just require filtering through a silica plug to remove the copper residues to work-up the reactions. It is possible to recycle the catalysts if solid supported variants are used.[93–95]

1.2.2 Synthesis of other ring sizes by ATRC

ATRC has also been applied to the synthesis of larger ring sizes. Clark and Verhlac have shown that copper mediated ATRC can be used to synthesise δ-lactams *via* 6-*exo trig* cyclisations.[76] The cyclisation of **75a** (R = Bn) was carried out at both 25 ^{o}C and 80 ^{o}C with three different ligands; bipy, PMDETA and TPA. All three ligands were found to be effective and gave similar results, with only the *exo* product being observed in all cases. Although reasonable yields were achieved at 25 ^{o}C (Table 1.7 entries 1-3), significantly better results were achieved upon heating the reaction to 80 ^{o}C with higher yields in much shorter reaction times (Table 1.7 entries 4-5). It was also found that when a bulky *t*-butyl *N*-protecting group (**75b**) was used the reaction was not impeded and still gave high yields in reasonable reaction times (Table 1.7 entries 6-8).

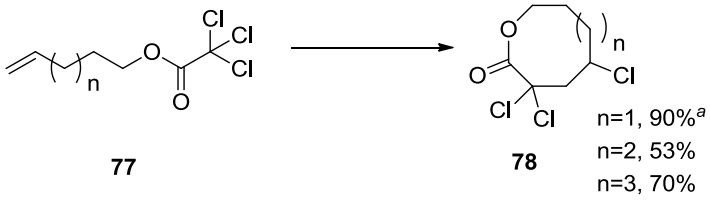


Entry	R Group	Ligand	Time / h	Temp / ^{o}C	Yield
1	Bn (**75a**)	Bipy	72	25	60
2	Bn (**75a**)	PMDETA	72	25	30
3	Bn (**75a**)	TPA	72	25	40
4	Bn (**75a**)	PMDETA	2	80	92
5	Bn (**75a**)	TPA	2	80	90
6	*t*-Bu (**75b**)	Bipy	18	80	99
7	*t*-Bu (**75b**)	PMDETA	18	80	98
8	*t*-Bu (**75b**)	TPA	18	80	96

Table 1.7: Synthesis of δ-lactams *via* 6-*exo* cyclisation. *Regents and Conditions:* CuCl 30 mol%, ligand (30 mol%), DCE.

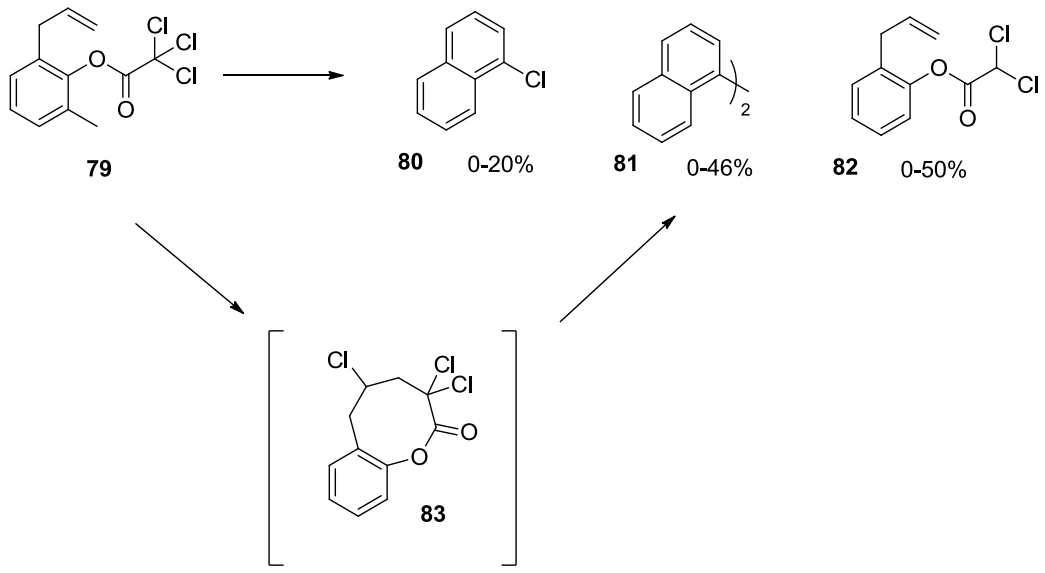
Verlhac has also used ATRC to carry out macrolactonisation of trichloroacetates *via* 8-, 9- and 10-*endo trig* cyclisations.[75,96] The use of the highly active Cu(TPA)Br

complex allowed for the cyclisations of trichloroacetates with 3-10 mol% of catalyst, in DCE at reflux giving yields between 53 and 90% (Scheme 1.24).



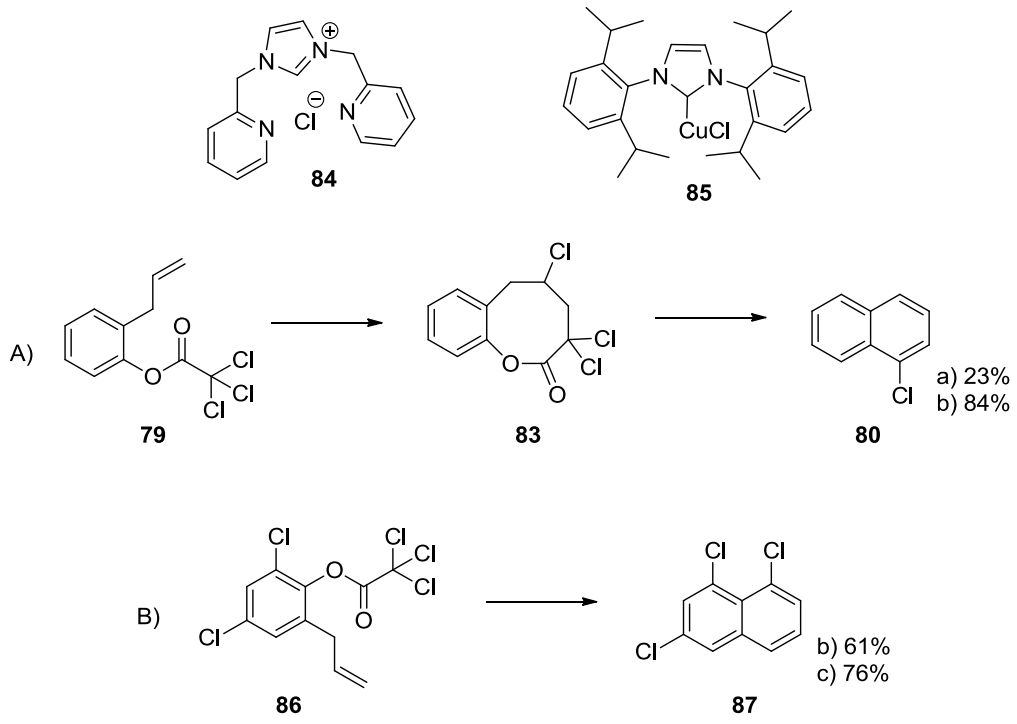
Scheme 1.24: Macrocyclisation using copper mediated ATRC. *Reagents and conditions:* Cu(TPA)Br 10mol%, DCE, 0.1M, reflux. [a]3 mol% of Cu(TPA)Br used.

Investigations into the synthesis of medium-sized benzene ring fused lactones have been carried out by both Ram[97] and Quayle[98] and both have observed the production of a benzannulated product *via* a lactone intermediate formed in an 8-*endo trig* cyclisation. Ram treated trichloroacetate **79** with 1 equivalent of the Cu(bipy)Cl catalyst system resulting in the benzannulated compound **80**, however the yields were poor and the reaction was complicated by the formation of the biaryl compounds **81** and the reduced compounds **82** (Scheme 1.25).[97]



Scheme 1.25: Cu(bipy)Cl mediated benzannulation reaction. *Reagents and Conditions:* Cu(bipy)Cl (1 eq.), benzene, reflux.

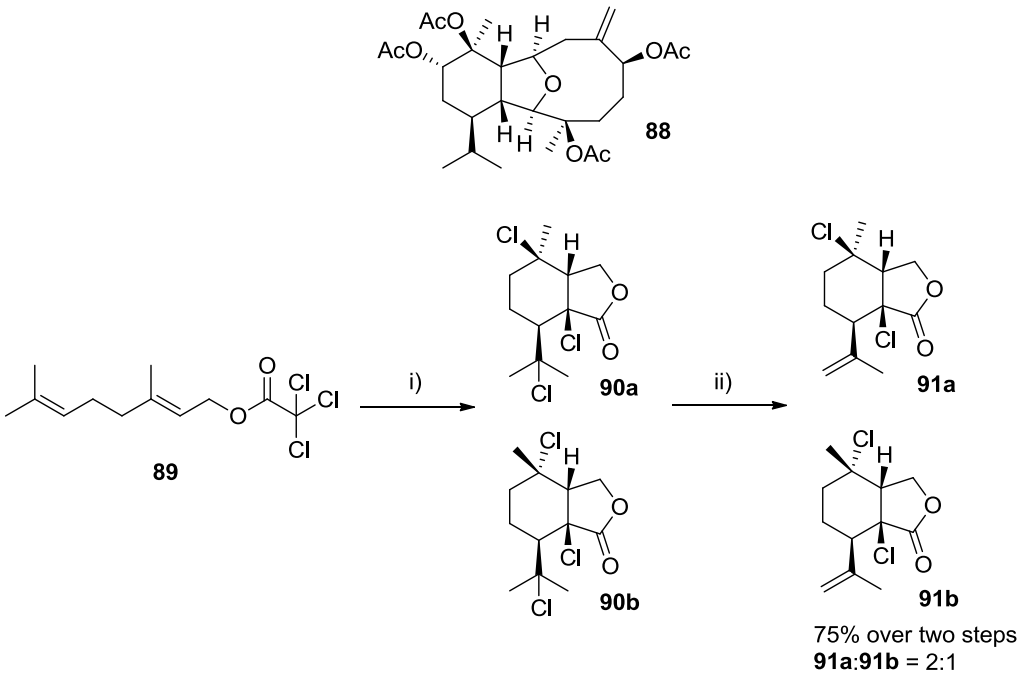
Quayle has successfully synthesised of a number of benzannulated products using copper complexes of ligands **84** and **85**.[92,98] Initially the cyclisation of ester **79** with 5 mol% Cu(**85**)Cl in toluene afforded lactone **83** in 95% conversion in 48 h *via* an 8-*endo trig* cyclisation along with the benzannulated **80** as a minor by-product. Repeating the reaction for 120 h led to complete consumption of the ester **79** and lactone **83** with the benzannulated product **80** as the major product, however after column chromatography this was only obtained in a 23% yield. When ester **79** was treated with the same catalyst system in DCE under microwave irradiation at 200 ^{o}C the benzannulated product **80** was obtained in a greatly improved 84% yield in a much reduced reaction time of only two hours (Scheme 1.26A).[98] The copper-carbene complex **84** was also shown to mediate the benzannulation reaction, providing similar, if not better, yields (Scheme 1.26B).[92]



Scheme 1.26: Quayle's Benzannulation *via* an 8-*endo trig* ATRC intermediate. *Reagents and Conditions:* a) Cu(**85**)Cl 5 mol%, toluene, reflux, 120 h. b) Cu(**85**)Cl 5mol%, DCE, 200 ^{o}C, μW, 2 h. c) Cu(**84**)Cl 5 mol%, DCE, 200 ^{o}C, μW, 2 h.

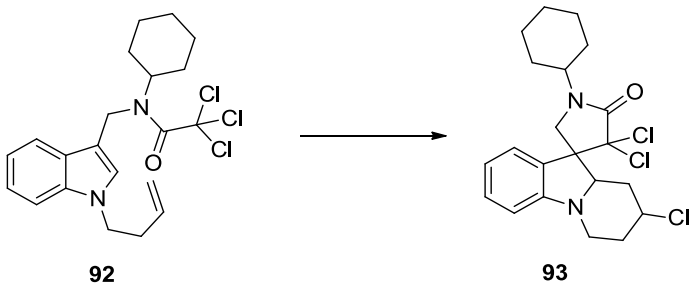
1.2.3 Tandem ATRC

Tandem atom transfer cyclisations have also been shown be useful in the synthesis of polycyclic systems. Quayle has applied a 5-*exo* cyclisation followed by a 6-*exo* cyclisation to the synthesis of a 6,5-bicyclic ring system **91**[99] as the core for the Eunicellin **88** series of natural products.[100,101] The addition of **89** to a preformed solution of Cu(bipy)Cl 5 mol% in DCE followed by heating to 90 ^{o}C for 3.5 hours led to the unstable trichloroacetates **90a** and **90b**, which upon purification by column chromatography led to **91a** and **91b** in a 2:1 ratio after elimination of HCl (Scheme 1.27).[99] The stereostructure was assigned based upon a single crystal X-ray that was obtained of **90a**. The X-ray structure showed that the cyclohexane ring adopts a chair conformation with the C4-Cl substituent axially disposed and the bulky chloroisopropyl group at C7 in an equatorial position. The lactone was shown to be *cis*-fused with the C7a-Cl axially disposed with respect to the cyclohexane ring. NOE measurements were carried out on both **91a** and **91b** which suggest that this is also the conformation of the eliminated products in solution.



Scheme 1.27: Tandem ARTC in the synthesis towards Eunicellins. *Reagents and Conditions:* i) CuCl 5 mol%, bipy 5 mol%, DCE, 90 ^{o}C, 3.5 h. ii) SiO_2.

Stevens has also applied a tandem cyclisation approach to the synthesis benzospiro-indolizidinepyrrollidione **93**, as a racemic mixture, *via* sequential 5-*exo* and 6-*endo* cyclisations.[102] TMEDA was used as the ligand and it was found that a 2:1 ratio of ligand to CuCl was required in order to obtain the best yield.

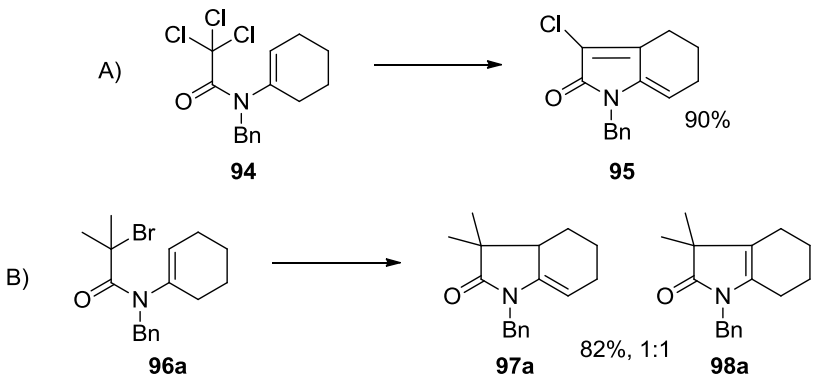


Scheme 1.28 Tandem cyclisation in the synthesis of benzospiro-indolizidinepyrrollidones.
Reagents and Conditions: CuCl 40 mol%, TMEDA 80 mol%, MeCN, reflux, 21 h.

1.2.4 5-*Endo* Cyclisations

The ligand accelerated conditions have been shown to facilitate 4-*exo and* the traditionally disfavoured[22] 5-*endo* cyclisations of enamides.[71,103,104] For enamides there are generally two competing reaction pathways; the 4-*exo* pathway is generally quicker, but reversible, and results in the kinetic product, whereas the 5-*endo* pathway leads to the less strained thermodynamic product.

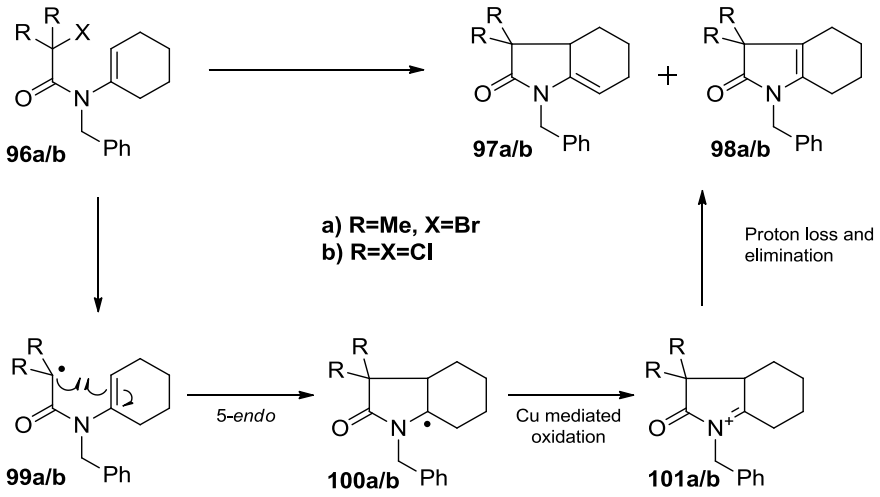
Interestingly, when cyclising enamides under normal ATRC conditions, the expected atom transfer products were not obtained, instead unsaturated cyclisation products were formed. Treatment of trichloroacetate **94** with Cu(bipy)Cl (50 mol%) in refluxing toluene resulted in the diene **95** in 90% yield.[104] (Scheme 1.29A) while cyclisation of the monobromo-substrate **96** with Cu(Me_6-Tren)Br (30 mol%) in DCM furnished two alkene products **97** and **98** in a 1:1 ratio in 82% combined yield (Scheme 1.29B).[71]



Scheme 1.29: Copper Mediated 5-*endo* Cyclisations. *Reagents and Conditions:* a) 50 mol% Cu(bipy)Cl, toluene, reflux. b) 30 mol% Cu(Me_6-Tren)Br, DCM, r.t.

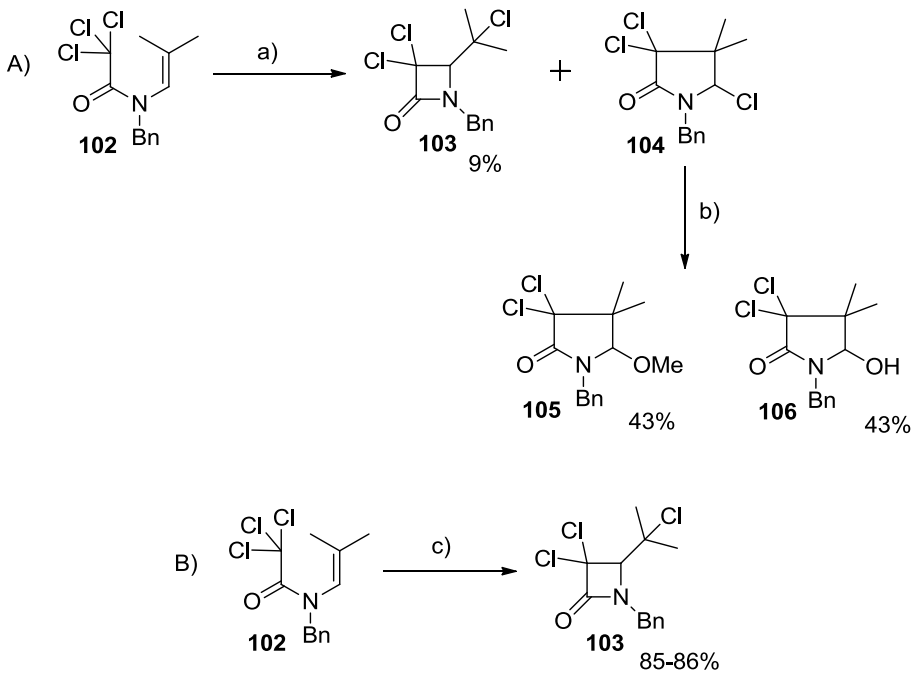
Mechanistically it has been postulated that the reactions proceed *via* an initial 5-*endo* cyclisation to give the tertiary radical **100**, which then undergoes a Cu(II) mediated oxidation *via* a radical-polar crossover reaction to give the corresponding *N*-

acyliminium ion **101**, which, upon elimination of a proton furnishes the alkene products **97** and **98**. Further elimination of HCl from **97b** or **98b** can lead to the diene **95** (Scheme 1.30).



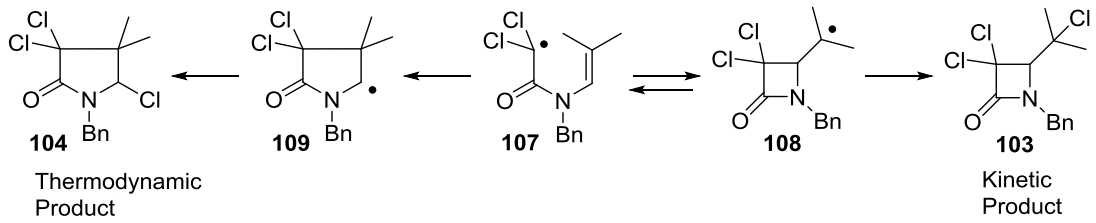
Scheme 1.30: 5-*endo* Radical Cyclisation *via* an *N*-Acyliminium Ion.

Ghelfi has used both Cu(TMEDA)Cl and Cu(bipy)Cl to catalyse 5-*endo* cyclisations but did not observe the eliminated products that Clark observed, instead the 5-*endo* and 4-*exo* atom transfer products were observed.[105] Treatment of trichloroenamide **102** with Cu(bipy)Cl in toluene at reflux led to complete conversion to the β-lactam **103** and γ-lactam **104**, (Scheme 1.31A). The crude ratio of 4-*exo* to 5-*endo* products varied (**103** : **104** = 1 : 2.6-9.6), but the 5-*endo* product was always found to be the major component in the crude mixture. Upon purification on silica gel the hydroxy-γ-lactam **106** and methoxy-γ-lactam **105** were formed from the 5-*endo* product **104**. In contrast when the reaction was carried out in acetonitrile rather than toluene only the β-lactam product **103** was observed with no evidence for the γ-lactam product **104**, (Scheme 1.31B).[105]



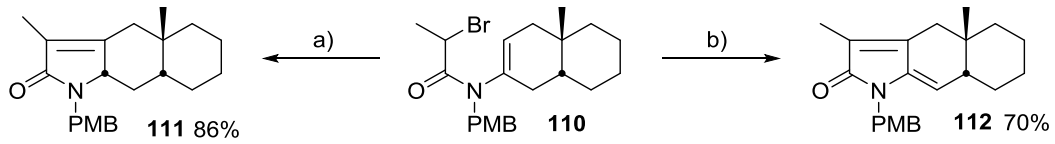
Scheme 1.31: 5-endo vs. 4-exo cyclisations. *Reagents and Conditions:* a) Cu(bipy)Cl 50 mol%, toluene, reflux. b) MeOH, SiO_2. c) Cu(bipy)Cl or Cu(TMEDA)Cl 50 mol%, acetonitrile, reflux.

This change in regioselectivity is thought to be due to a reversible mechanism where the β-lactam **103** is the kinetic product and γ-lactam **104** is the thermodynamic product, (Scheme 1.32).[105] 4-*Exo* cyclisation of **107** to give **108** is therefore expected to be quicker than 5-*endo* cyclisation to give **109**. The Cu complexes used are readily soluble in acetonitrile, hence formation of radical **108** is expected to be rapidly followed by atom transfer from the $CuCl_2$ species to give β-lactam **103**. However, solubility of $CuCl_2$ species in toluene is low resulting in a much slower rate of trapping of the radical **108** and providing it with a longer 'life time', allowing for equilibration to the more stable stable radical **109** to occur. Trapping of this radical resulted in the γ-lactam **104** as the major product.



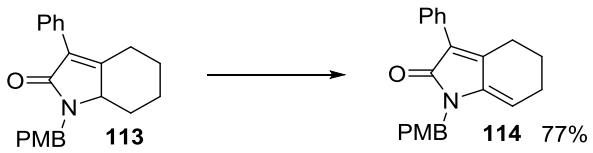
Scheme 1.32: Kinetic and thermodynamic pathways in cyclisation of enamides.

The more active Cu(TPA)Cl complex has been shown to mediate the cyclisation of the less reactive secondary monohalosubstrates.[106] The reaction of enamide **110** with 1 equivalent of Cu(TPA)Br in refluxing toluene gave the α,β-unsaturated lactam **111** in 86% yield (Scheme 1.33). Interestingly if DCE was used as the solvent the diene **112** was formed exclusively in a 70% yield.



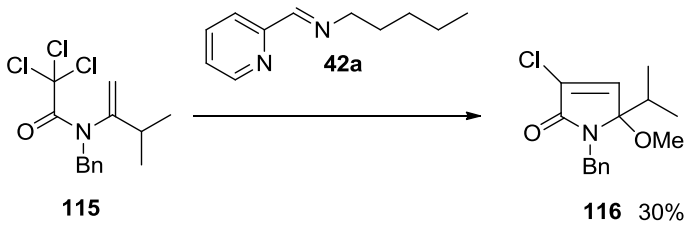
Scheme 1.33: Copper mediated 5-*endo* cyclisations of secondary monohalosubstrates. *Reagents and Conditions:* a) 1 eq. Cu(TPA)Br, toluene, 110 °C, 2h. b) 1 eq. Cu(TPA)Br, DCE, 80 °C, 2h.

It is postulated that the diene **112** is formed by further oxidation of the monoene **111**, as occurs when **113** is transformed to **114** by heating with 1 eq. of Cu(TPA)Br (Scheme 1.34).



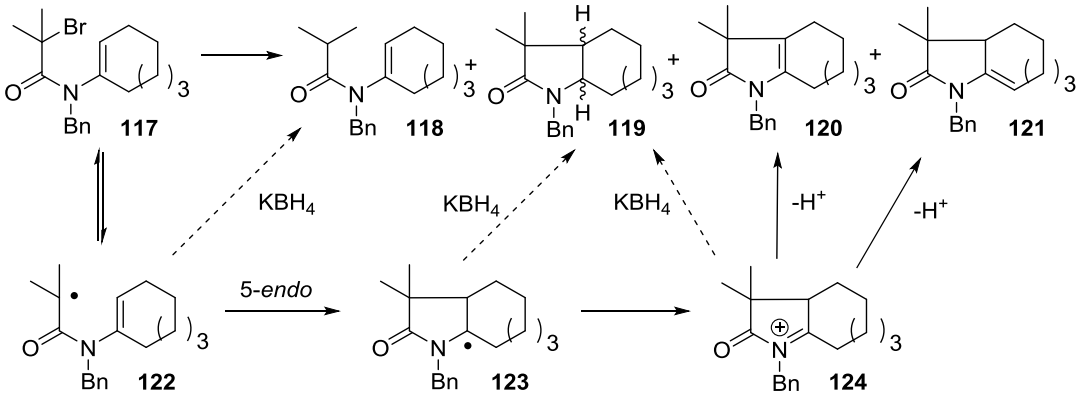
Scheme 1.34: Conversion of monoene 113 into diene 114 by Cu(TPA)Br. *Reagents and Conditions:* 1eq. Cu(TPA)Br, DCE, 80 °C, 2h.

Attempts have been made to trap out the postulated *N*-acyliminium ion, however there has only been limited success. The cyclisation of enamide **115** in the presence of MeOH led to the formation of lactam **116**, albeit in a low 30% yield.[5]



Scheme 1.35: Trapping acyliminium ion with methanol. *Reagents and Conditions:* 30 mol% CuBr, 30 mol% **42a**, 10 eq. MeOH, DCM.

Clark has applied his $CuSO_4/KBH_4$ conditions to the 5-*endo* cyclisations of enamides and has investigated the possibility of reductively trapping the acyliminium ion *in situ* with the borohydride reagent, or by the nucleophilic solvent.[81] As with the 5-*exo* cyclisations, the 5-*endo* cyclisations were effective with low catalyst loadings. Cyclisation of **117** led to four different products; the reduced compound **119**, the two oxidatively terminated products **120** and **121**, and the precyclised reduced product **118**. The reduced compound **119** may be formed by either trapping of the acyliminium ion **124** by the borohydride, or *via* direct reduction of the intermediate radical **123**.



Scheme 1.36: $CuSO_4$/KBH_4 mediated 5-*endo* cyclisation. *Reagents and Condition:* $CuSO_4.5H_2O$, KBH_4, MeOH, r.t., 30 min.

Cyclisation of **117** with 1 mol% $CuSO_4$ and 100 mol% KBH_4 in MeOH led to the reduced cyclised product **119** in 11% yield, and the oxidatively terminated products **120** and **121** in 6% and 69% yields respectively. Increasing the amount of KBH_4 to 10 equivalents in a hope to competitively trap the acyliminium ion reductively to give **119** was only partially successful with an increased yield of 32%, however a significant amount (30%) of the precyclised reduced product **118** was then observed. Unfortunately it was not possible to find conditions that led to the reduced cyclised product **119** in high yield.[81]

1.2.5 ATRC mediated by other metals.

As many transition metals have multiple easily accessible oxidation states they make ideal candidates for mediating redox initiated ATRC reactions. In recent years notable methods using metals other than copper, such as ruthenium,[48–50,107] zinc[108] and titanium[109] have been developed.

1.3 Atropisomersism

Enamides such as **96a** have been shown to exhibit atropisomerism.[110,111] Atropisomerism is a phenomenon where chirality occurs due to restricted rotation about a single bond.[112] Atropisomers do not necessarily contain a stereogenic centre, instead chirality arises due to two possible spatial arrangements about the given bond axis, leading to the two enantiomers. Figure 6 shows an atropisomeric biaryl compound which has a chiral axis about the aryl-aryl bond, and the corresponding space-filling model which illustrates how rotation about the bond is hindered due to steric clashing of the bulky R^1 and R^2 groups with the R^3 and R^4 groups.

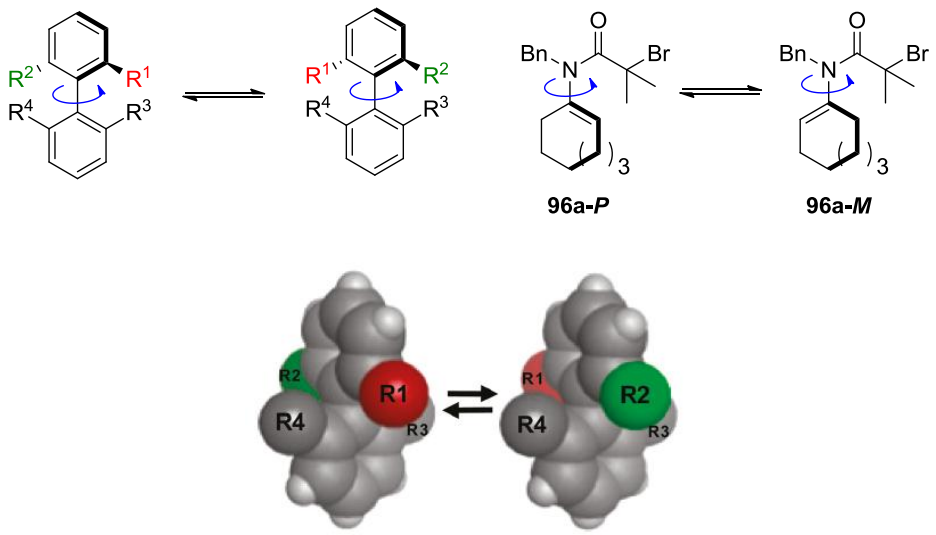


Figure 6: Depiction of Atropisomerism showing space-filling models.[113]

Atropisomers are identified by the Cahn-Ingold-Prelog using *M* and *P* descriptors rather than the *R* and *S* used for stereoisomers.[114] Racemisation of atropisomers occurs thermally with no need for breaking and forming any bonds. The only energy required for racemisation to occur is that to overcome the barrier to rotation and rotate a single bond through 180 °. As racemisation occurs through bond rotation, which is time dependent, half-lives for atropisomers can vary greatly from a matter of minutes to years, depending on the degree of steric hindrance, temperature, and

solvent. In favourable cases, where the barrier to rotation is high enough the two atropisomers can be separated at room temperature.

The first stable atropisomers **125** were isolated in 1922 by Christie and Kenner,[115] and were resolved by co-crystallisation with brucine **126**, a chiral amine alkaloid. The two salts were obtained in approximately equal yields through fractional crystallisation and had distinctly different solubilities, crystalline forms, melting points and $[\alpha]_D^{20}$.

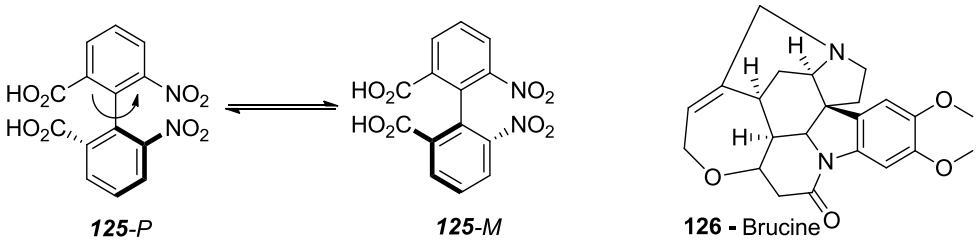


Figure 1.7: First isolated atropisomers.

Following the discovery of atropisomerism, it has been identified in a large variety of molecules, both natural and synthetic.

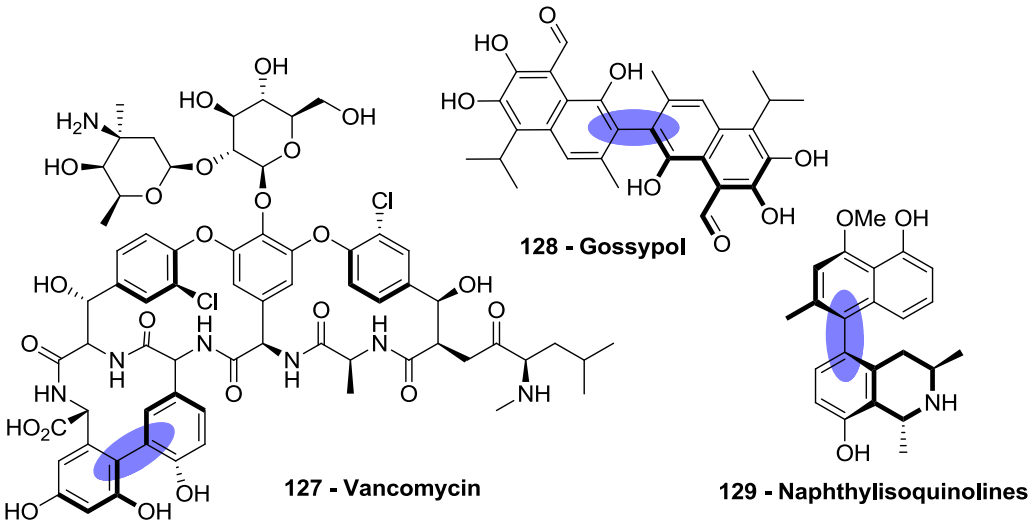


Figure 1.8: Atropisomeric natural products.

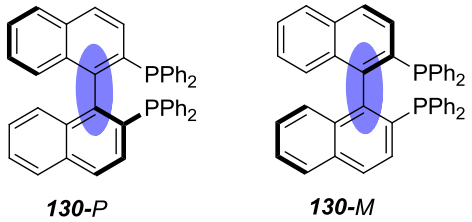
1.3.1 Atropisomerism in natural products

The natural products vancomycin **127,**[116] gossypol **128**[117] and naphthylisoquinolines **129**[118] all exhibit atropisomerism. Vancomycin **127**,[116] often referred to as one of our 'last defence' antibiotics, is a very interesting molecule with many naturally occurring points of chirality in both the sugars and the heptapeptide chain. It also has two atropisomeric chiral planes formed from the bisaryl ethers with a chiral axis about the aryl-aryl bond. Gossypol **128** is a toxic yellow pigment from cotton plants which exhibits anti-cancer properties with the two different atropisomers showing different mechanisms for anti-cancer activity.[117] The two atropisomers naturally occur in a range of ratios from 30% ee (-) to 90% ee (+).[117] Naphthylisoquinolines **129** are part of some plants self-defence mechanism and exhibit anti-malarial properties.[118] They have a chiral axis about the bond between the naphthyl and the tetrahydroisoquinoline component.

These three natural products all have the chiral axis occurring about an aryl-aryl bond and this type of atropisomerism has been the most widely exploited synthetically. The factors controlling the rate of racemisation of biaryls have been extensively studied and are summarized in a review by Adams.[119] It was evident from these studies that in order for a biaryl compound to exist as two stable enantiomers 3 of the 4 *ortho* substituents had to be bigger than a hydrogen atom.[119] Even with this condition satisfied compounds with small substituents such as a fluorine or a methoxy group might still not be resolvable and Sternhell has quantified these rules in terms of steric interference vaules.[120]

1.3.2 Atropisomerism in synthetic compounds

Many axially chiral biaryl compounds have been synthesised and are used as ligands in asymmetric synthesis,[121–123] one of the most notable being 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl **130** (BINAP).[124] BINAP has two diphenylphosphinonaphthyl groups linked at the 1- and 1'- positions and it is about this bond where the restricted rotation occurs giving rise to the chiral axis.



130-P *130-M*

Figure 1.9: BINAP

It is commonly complexed with ruthenium,[125,126] rhodium[127,128] or palladium[129,130] for use in enantioselective synthesis, such as the synthesis of menthol where BINAP is used to synthesis one of the chiral intermediates on an industrial scale in 96-99% *ee*.[131] BINAP itself is synthesised from 1,1-binaphthol another chiral ligand which is prepared from an asymmetric coupling of 2-naphthol using copper (II) chloride and amphetamine.

A number of methods have been developed for the asymmetric synthesis of binaphthyl compounds. These involve both the synthesis of a racemic mixture followed by resolution of that mixture,[132] or the preparation of single atropisomers *via* an asymmetric synthesis.[133,134]

More recently this phenomenon has been recognised in alternative synthetic systems such as benzamides **131**,[135,136] benzanilides **132**,[137] anilides **133**[136,138] and enamides **134**.[110]

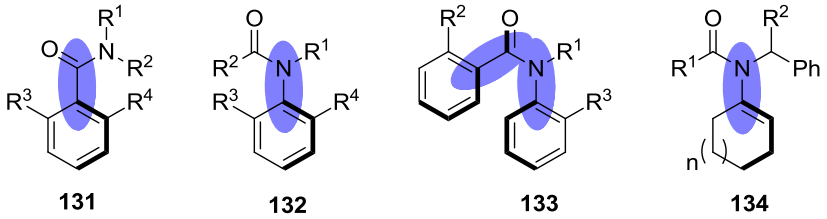


Figure 1.10: Atropisomerism in alternative synthetic systems

1.3.3 Measuring the barrier to rotation in atropisomers

The half-life of atropisomers can be calculated based upon the barrier to rotation about the bond with restricted rotation and can range from milliseconds to years. A number of different methods can be used to investigate the barrier to rotation in atropisomers. Clayden applied three different methods to analyse the barrier to rotation in tertiary amides **135**; variable temperature NMR spectroscopy, resolution by chiral HPLC followed by analysis of subsequent racemisation and chromatographic separation of diastereomers on silica followed by analysis of subsequent epimerisation.[139]

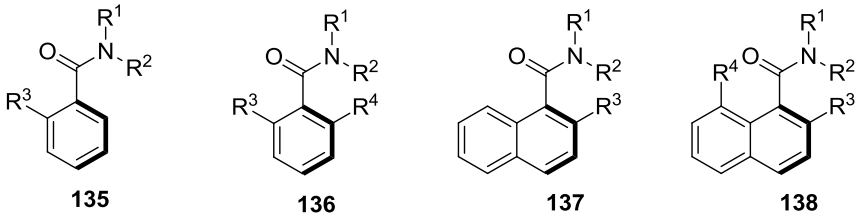


Figure 1.11: General structures of tertiary amides investigated by Clayden.

VT NMR analysis proved to be most effective for calculating the barriers to rotation of amides with only one *ortho* substituent (**135**, **136a** R^3 = H) as the barrier to rotation in these compounds was significantly lower than the 2,6-disubstituent compounds **136** where the chromatography methods were more applicable.[139]

Tertiary aromatic amides with only one *ortho* substituent, **135** and **136a,** were found to be chiral on the NMR timescale, but racemised quickly with a half life of <2s at 20 ^{o}C. Those with two *ortho* substituents, **136**, can in general be separated into the two atropisomers unless either R^3 or R^4 is a freely rotating trigonal substituent or silyl group. For the 2-substituted tertiary 1-naphthamides **137** the barrier to rotation is largely influenced by the size of the R^3 substituent. With the *peri*-substituent naphthamides **138** even when the R^3 substituent was a hydrogen atom or the trigonal CHO group the atropisomers could be separated. [139]

Similar techniques have also been employed by Lunazzi in the analysis of highly hindered naphthyl phenyls,[140] naphthyl sulfones,[141] naphthyl sulfoxides,[142] naphthyl imines[143] and naphthyl ketones.[144] Dynamic NMR has also been used to calculate the barrier to rotation in enamides.[110,111] NMR analysis of *N*-benzylated enamides such as **96a** show the benzyl protons to be diastereotopic at low temperatures, appearing as two mutually coupled doublets due to slow rotation about the *N*-alkenyl bond. Upon heating the doublets coalesce to form one singlet as the rate of rotation about the *N*-alkenyl increases (Figure 1.12). Use of the WINDNMR 7.1 line shape analysis programme[145] allowed the rotational rate constant, $k_{rot,}$ to be calculated for each temperature, and an Eyring plot then allowed rate of rotation at 298 K, k_{298}, to be calculated, which when factored into the Arrhenius equation allowed the barrier to rotation about the *N*-alkenyl bond to be calculated.

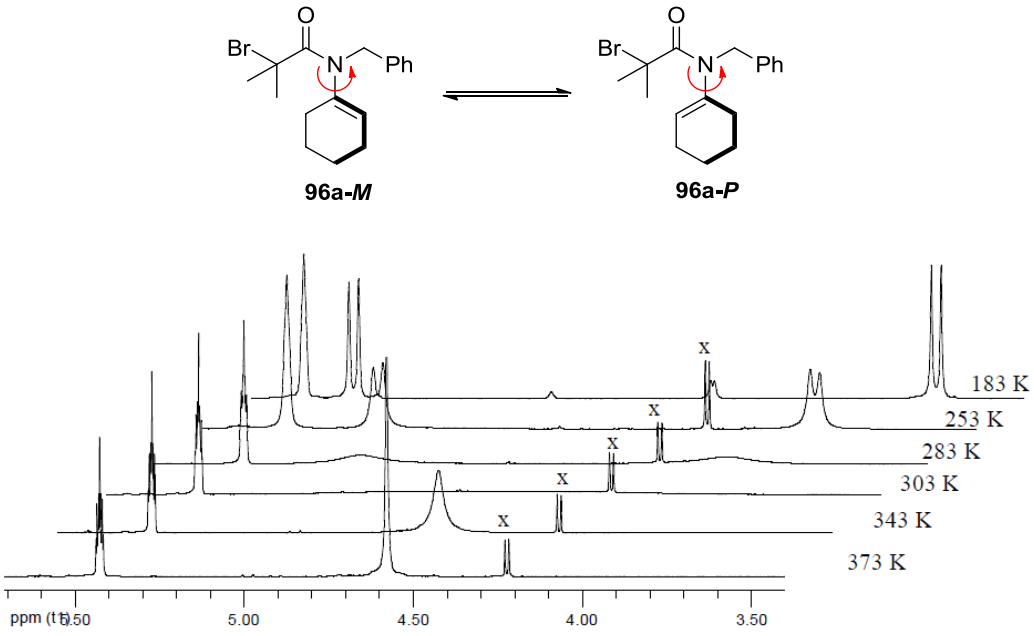


Figure 1.12: VT NMR of Enamide 96a (x = impurity)

1.4 Atropisomerism in Radical Cyclisations

Atropisomerism can have important consequences in the cyclisation of anilides. Work by Curran has looked at the atropisomerism of anilides where there are two rotational elements that must be considered. (*E*)-**89** and (*Z*)-**89** rotamers occur due to the amide rotation about the N-CO bond as well as (*M*)-**89** and (*P*)-**89** isomers due to the restricted rotation around the *N*-aryl bond.[146,147]

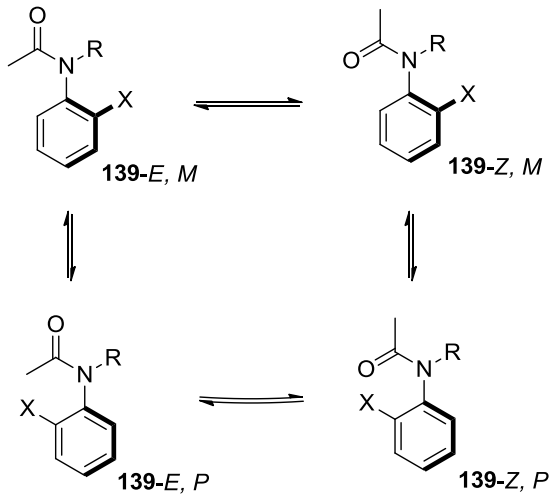
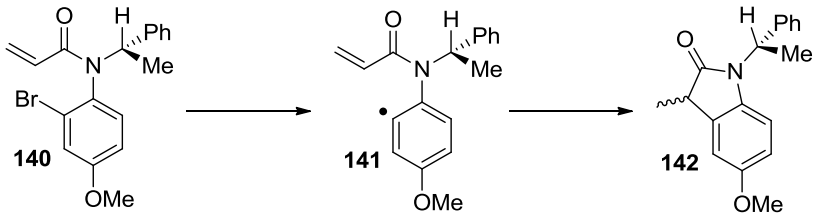


Figure 1.13: Rotamers of radical precursors

Curran has shown that *ortho* substitution of the anilide (X ≠ H) is necessary in order to increase the barrier to rotation around the *N*-aryl bond to a level where atropisomerism can be observed in variable temperature proton NMR, and if the substituent at this position is sufficiently bulky (e.g. X = I) the atropisomers can be resolved by methods such as chiral HPLC.[148,149] The magnitude of the barrier to rotation was found to vary depending on the level of substitution in the anilides around the aromatic ring, at X, and at the α- position of the carbonyl. Curran found that when X = I a barrier to rotation large enough to allow resolution at room temperature could be achieved.

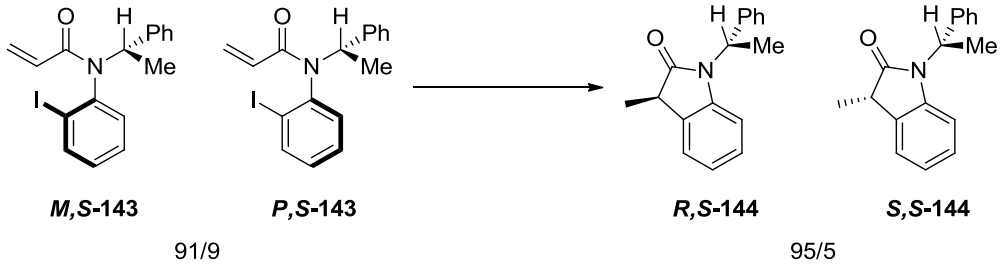
1.4.1 Chirality Transfer in Radical Cyclisations

Curran then investigated whether chirality transfer was possible during the radical cyclisation of acrylanilides designed for 5-*exo trig* cyclisations.[150] Chirality transfer in 5-*exo trig* cyclisations had previously been attempted by having a chiral inducing group elsewhere in the molecule (Scheme 1.37).[151]



Scheme 1.37: Attempted chirality transfer using a chiral inducing group. *Reagents and Conditions:* Bu_3SnH, AIBN, toluene, reflux.

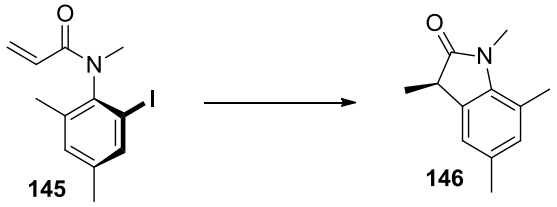
When cyclisation of (*S*)-acrylanilide **140** was attempted a 1:1 mixture of diastereomers **142** was obtained and it was unclear why the reaction was so unselective. Curran noticed that acrylanilide **140** contained an axis of chirality, caused by slow rotation about the *N*-aryl bond, as well as the chiral group and was consequently a 1:1 mixture of diastereomers itself, leading to a 1:1 mixture of diastereomeric radical intermediates and hence the unselective cyclised diastereomeric products **142**. He then synthesised acrylanilide **143** and the diastereomers were resolved by chiral HPLC giving a 91/9 mixture of ***M,S*-143** / ***P,S*-143** which under the cyclisation conditions showed chirality transfer giving a 95/5 mixture of diastereomers ***R,S*-144** / ***S,S*-144**.[150]



Scheme 1.38: Cyclisation of resolved diastereotopic acryanilides showing chirality transfer.

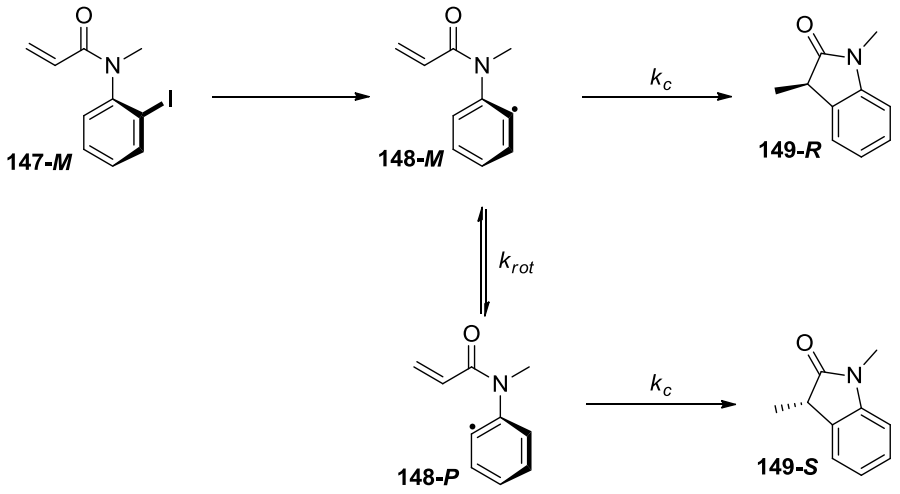
Reagents and Conditions: Bu_3SnH, Et_3B/O_2, DCM, -78 ^oC.

Curran then looked at whether chirality transfer from acrylanilides could be achieved without the need for a chiral auxiliary group elsewhere in the molecule. Anilide **145** was synthesised and found to have a barrier to rotation of ~29 kcal mol^{-1}, allowing for the separation of atropisomers by chiral HPLC. Radical cyclisation of one atropisomer using Bu_3SnH then afforded the cyclised product **146** with ~90% chirality transfer (Scheme 1.39).[150]



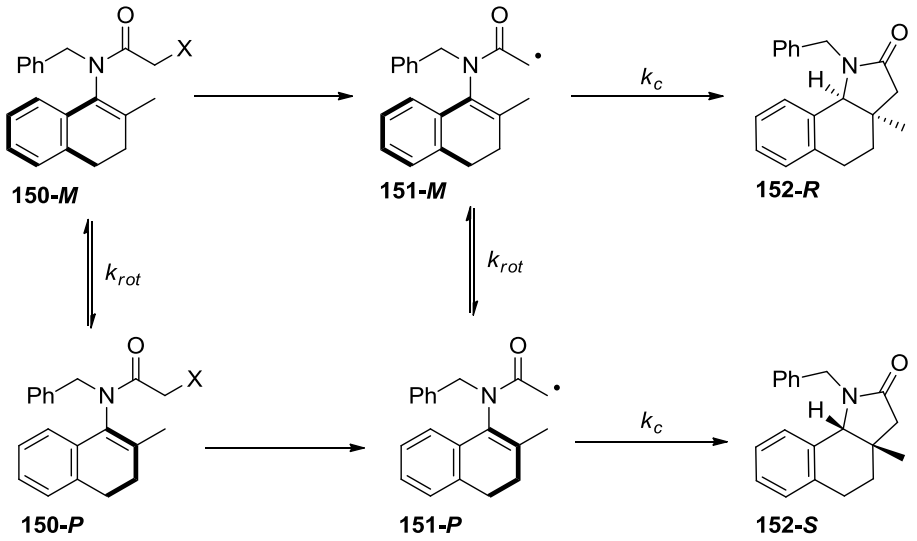
Scheme 1.39: Chirality transfer in the 5-*exo* cyclisation of acrylanilides. *Reagents and conditions:* Bu_3SnH, Et_3B, O_2, 20 ^oC, benzene.

One important consideration when investigating chirality transfer during cyclisation reactions of molecules such as **147** is to keep in mind that the radical intermediate **148** formed is much more configurationally labile around the *N*-aryl bond than the starting material **147** as the loss of the bulky iodine atom from **147** will lead to a much lower barrier to rotation. In order for the chirality of the starting material to be transferred to the product the rate of cyclisation k_c must be greater than the rate of rotation k_{rot} of the radical intermediate under the reaction conditions (Scheme 1.40).



Scheme 1.40: Competing bond rotation and cyclisation of the radical.

This success in chirality transfer with atropisomeric anilides **145** and the presence of atropisomerism in related enamides such as **96a** suggests that chirality transfer may be possible in the cyclisation of enamides. Comprehensive mechanistic studies by Newcomb[58] and Chatgilialoglu[152] have shown that rates of cyclisation can be measured for enamides and their 5-*endo* cyclisations. Whereas the rates of 5-*exo* cyclisations of aryl radicals **148** have been calculated to be ~ 3×10^9 s^{-1},[148] studies show the rate of 5-*endo* cyclisations of enamide radicals e.g. **151** derived from enamide **150** to be in the order of 10^4 slower.[153] This suggests chirality transfer in 5-*endo trig* cyclisations of enamides **150** would be more difficult to achieve than in the related 5-*exo trig* cyclisations of **148** as the barrier to rotation **(*M*)-151** → **(*P*)-151** will have to be significantly higher in order to prevent racemisation of the radical intermediate prior to cyclisation (Scheme 1.41).



Scheme 1.41: Competing bond rotation and cyclisation of enamides.

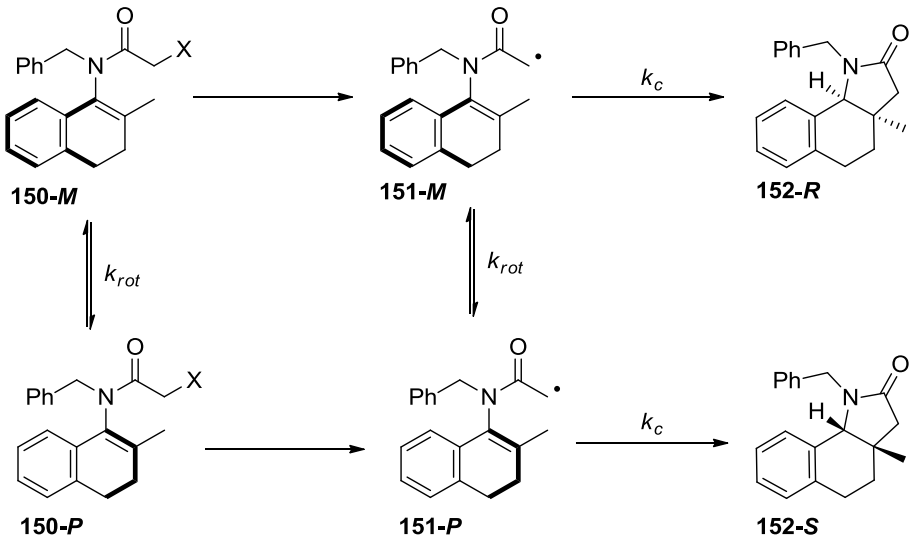
1.5 Summary

Over the past couple of decades there have been significant improvements in the conditions for radical cyclisations. The development of copper mediated atom transfer radical cyclisation as a less toxic, non-reductive alternative to the traditional tin mediated cyclisations has grown in importance. The use of ligands for copper (see section 1.2.1.1) has allowed catalyst loadings to be reduced as low as 1 mol% and has facilitated the cyclisation of less activated substrates, notably the 5-*endo* cyclisations of enamides (see section 1.2.4). These enamide substrates exhibit atropisomerism, a phenomenon exploited in anilides to achieve chirality transfer upon cyclisation (Scheme 1.48). Herein we report investigations into the effect of the substitution at the alkene on the barrier to rotation in enamides and the results of cyclisations of atropisomeric enamides with high barriers to rotations. We also report the results when copper mediated cyclisation conditions were applied to the synthesis of oxindoles *via* the cyclisation of anilides.

2.0 Investigations into the Barrier to Rotation in Enamides.

2.1 Introduction

Atropisomerism in enamides has been observed due to restricted rotation about the *N*-alkenyl bond and can result in the existence of two distinct isomers.[110,111] Anilides, which also exhibit atropisomerism, can be separated by chiral HPLC when the barrier to rotation is high enough, and have been shown to undergo 5-*exo* cyclisation of a single atropisomer with 90% chirality transfer.[150] Thus if enamides **150** with a high enough barrier to rotation could be synthesised, the atropisomers could be separated, and chirality transfer may be possible in the cyclisation of enamides **150** → **152**.

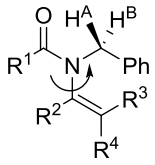


Scheme 2.1: Possible chirality transfer in the cyclisation of enamides.

The possibility of chirality transfer depends on the rate of cyclisation **151-*M*→152-*R*** being faster than the rate of rotation of the radical **151-*M*→151-*P***. Therefore in order to better contemplate the prospect of chirality transfer in enamides, a better understanding of the rotation dynamics about the *N*-alkenyl bond was required.

2.1.1 Investigations into the Barriers to Rotation in Enamides

N-benzyl enamides **153** have proven to be ideal compounds for calculating barriers to rotation using variable temperature (VT) NMR.[110,111,154] When the *N*-alkenyl bond is rotating freely the two methylene protons H^A and H^B are equivalent and appear in the proton NMR as a singlet, however when the rotation about the C-N is slow the protons become diastereotopic and appear as two mutually coupled doublets in the proton NMR due to the orthogonal nature of the amide and alkene functional groups.



153

Figure 2.1: *N*-benzyl enamides.

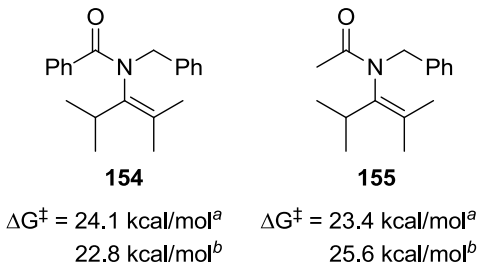
Ahlbrecht and co-workers measured the barrier to rotation of simple *N*-benzyl enamides.[154] $\Delta\upsilon$, the shift distance in Hz between H^A and H^B, which is dependent on temperature, was measured and extrapolated to the coalescence temperature, T_c, by linear regression, and $\Delta G^{\ddagger}$ was calculated for T_c using Equation 2.1.

$$k = \pi(\Delta\upsilon^2 + 6J_{AB}{}^2)^{0.5} / \sqrt{2}$$

Equation 2.1

It was found that the effect of the R^1 substituent was mainly electronic in nature, however the effects of the R^2, R^3, and R^4 substituents were rationalised by non-bonding interactions between the substituents. The barriers of rotation were found to vary from <7.4 kcal/mol to >24.1 kcal/mol and compounds **154** and **155** were found to have high enough barriers to rotation to allow separation of the atropisomers.[154]

Separation *via* diastereotopic salts was not successful due to the basicity of the compounds, instead low pressure liquid chromatography on microcrystalline, swollen triacetylcellulose with ethanol/H_2O as the eluent yielded enriched samples of the atropisomers. More precise barriers to rotation were then obtained monitoring thermal racemisations by polarimetry, giving results in good agreement with those obtained by NMR analysis.[154]



154 $\Delta G^{\ddagger}$ = 24.1 kcal/mol[a] 22.8 kcal/mol[b]

155 $\Delta G^{\ddagger}$ = 23.4 kcal/mol[a] 25.6 kcal/mol[b]

Figure 2.2: Atropisomeric enamides separated by Ahlbrecht. [a]Calculated from NMR. [b]Calculated by thermal racemisation.

Curran examined halo-enamides **156** – **158** as 5-*endo*-*trig* radical cyclisation precursors and found that they existed as a single amide rotamer in solution and exhibited atropisomerism.[153] The ^{1}H NMR showed only a single resonance for each different proton or group of protons, suggesting either the existence of one single amide rotamer or two amides rotamers in rapid equilibrium on the NMR timescale. α-Haloamides have amide rotation barriers typical of other amides,[155] therefore the barriers to rotation about the N-CO bond in **156 - 158** are likely to be in the range of 15-17 kcal/mol,[156] meaning the latter explanation is unlikely as processes with barriers of that height are typically slow on the NMR timescale. The diastereotopic methylene protons exhibited sharp, well resolved doublets suggesting that the compounds where axially chiral in solution. X-ray crystal structures of **157** and **158** showed the existence of the *E*-amide rotamer in the crystal and showed the

compounds to be non-planar. In compound **157** the plane of the amide and the alkene were found to be almost orthogonal with a dihedral angle of 74°.[153]

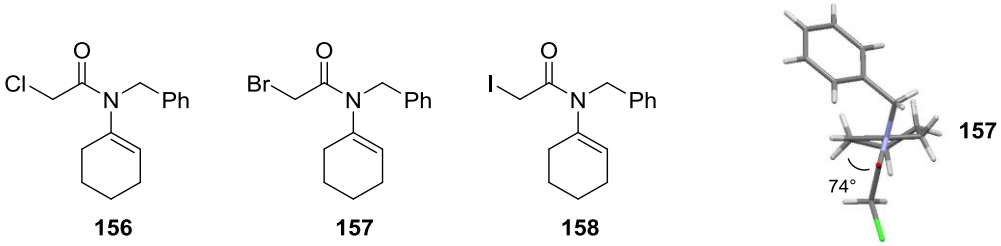


Figure 2.3: Atropisomeric enamides studied by Curran.

2.1.1.1 Previous Investigations within the Clark Group

To gain further understanding of the rotation dynamics of enamides the Clark group have synthesised a series of compounds to further investigate what effect the acyl group and a cycloalkene group have on the magnitude of the barrier to rotation. As with Alhbrecht, Clark also synthesised *N*-benzyl enamides to allow the barrier to rotation to be calculated *via* VT NMR, however instead of using the method employed by Ahlbrecht, Clark used line shape analysis to calculate the barrier to rotation. Line shape analysis of the VT NMR spectra using the WINDNMR[145] software allowed values for k_{rot} to be determined at each temperature, which when factored into the Arrhenius equation (Equation 2.2) allowed determination of $\Delta G^{\ddagger}$ at each temperature. Eyring plots of 1/T against ln(k/T) where then produced allowing access to values for $k_{\text{rot } 298}$, $\Delta G_{298}^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta H^{\ddagger}$, for the bond rotation using equations 2.3 - 2.6.

$$\Delta G = RT\ln\left(\frac{k.h}{k_B T}\right)$$

Equation 2.2

$$k_{rot\,298} = 298K \cdot e^{(\frac{slope}{298K} + intercept)}$$

Equation 2.3

$$\Delta \boldsymbol{G^{\ddagger}_{298}} = -\boldsymbol{R} \cdot \boldsymbol{298K} \cdot \boldsymbol{ln}(\frac{\boldsymbol{k_{298} \cdot h}}{\boldsymbol{k_B} \cdot \boldsymbol{298K}})$$

Equation 2.4

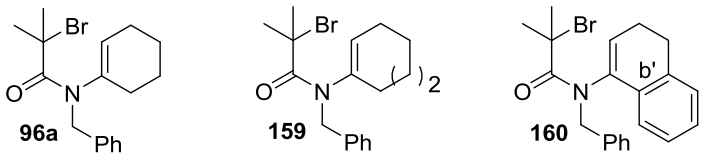
$$\Delta \mathrm{H} = -R \cdot slope$$

Equation 2.5

$$\Delta S = R \cdot \left(\text{int.} - \ln\left(\frac{k_B}{h}\right)\right)$$

Equation 2.6

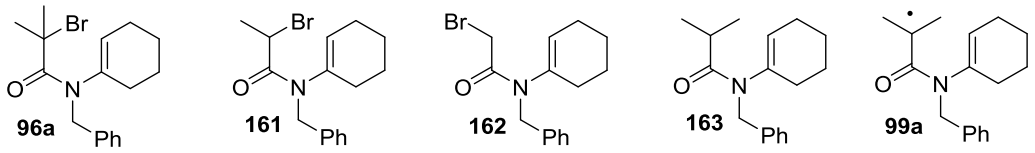
Clark first investigated the nature of the cycloalkenyl group and a range of cyclic enamides with varying sized rings were synthesised. The size of the cycloalkenyl group was found to have little effect on the barrier to rotation (compare **96a** and **159**, $\delta\Delta G^{\ddagger}_{298}$ = 0.2 kcal mol^{-1}). When the enamide was substituted at the β'- position, particularly if it is sp^2 hybridised (resembling an anilide), the barrier to rotation was seen to increase significantly (compare **96a** and **160**, $\delta\Delta G^{\ddagger}_{298}$ = 4.7 kcal mol^{-1}).[110]



$\Delta G^{\ddagger}_{298}$ 13.3 kcal mol-1 13.5 kcal mol-1 18.0 kcal mol-1

Figure 2.4: Enamides synthesised while investigating the nature of the alkenyl group (barriers measured in toluene).

Clark then investigated the effect of the acyl group on the barrier to rotation.[111] Sequential addition of a methyl group to the acyl group was also found to increase the barrier to rotation by 0.8-1.3 kcal mol^{-1} (compare **96a**, **161** and **162**). In order to estimate barriers to rotation for radicals derived from these bromides, radical models were synthesised with the halogen replaced by a hydrogen atom (*e.g.* enamide **163** as a model for radical **96a)**. Using these 'radical models' the barrier to rotation was found to decrease by 1-2 kcal mol^{-1} compared to the bromo derived radical precursors (compare **99a** and **163**), equating to a 5-26 fold increase in the rate of rotation around the *N*-alkenyl bond.[111]



$\Delta G^{\ddagger}_{298}$ 13.3 kcal mol-1 12.0 kcal mol-1 11.1 kcal mol-1 11.7 kcal mol-1

Figure 2.5. The effect of the acyl group on the barrier to rotation (barriers measured in toluene).

Clark also calculated the barriers to rotation for enamides **156** – **158** to investigate the effect of the halogen atom itself.[110] The enamides were found to have similar rotation dynamics with barriers to rotation varying between 11.7-12.1 kcal mol^{-1}.

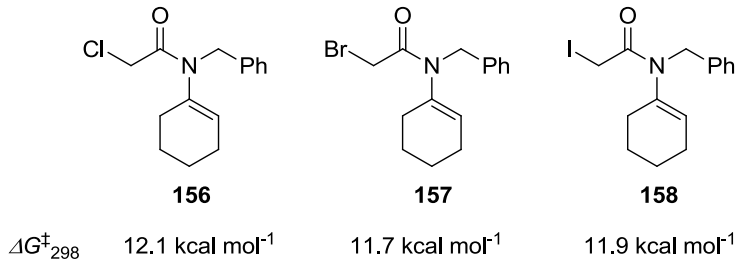


Figure 2.6: The effect of the halogen atom on the barrier to rotation (barriers measured in chloroform).

The barrier to rotation of enamide **157** was measured in different solvents to assess any solvent effects.[110] Only minor differences in the barrier to rotation were observed; in d_4-methanol the barrier was measured at 11.6 kcal mol^{-1}, and in d_8-toluene the barrier was calculated to be 11.1 kcal mol^{-1}. d_8-Toluene was considered the best choice of solvent as it allowed for the VT NMR to be run over a larger temperature range.

Finally tetrasubstitued enamides, substituted at both the *β* and *β*"-positions were prepared. These compounds had barrier to rotations too high to calculate *via* VT NMR, however the compounds were resolvable by chiral HPLC, allowing the barrier to rotation to be calculated by monitoring the rate of racemisation at 80 ˚C (>25 kcal mol^{-1}).[157]

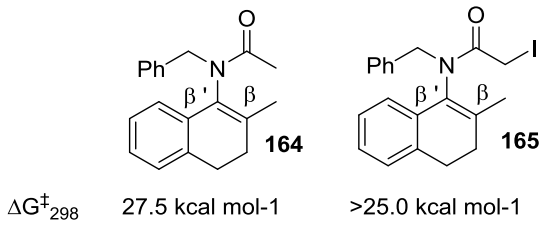
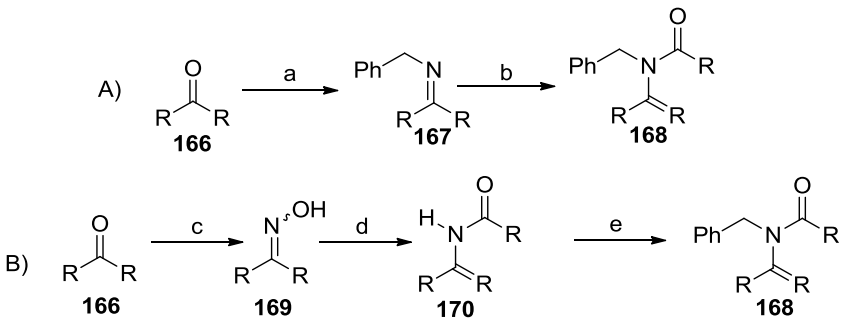


Figure 2.8. Tetrasubstitued enamides.

2.1.2 Previous Routes for Synthesis of Enamides.

There were two main methods employed by Clark for the synthesis of enamides **156**-**165**. The first route (route A) starts with a ketone **166**, which is reacted with benzylamine under Dean-Stark conditions to give an imine **167**, before treatment with a base and acid halide to give the desired enamide **168**. The second route (route B) starts with the same ketone **166**, but instead involves reacting it with hydroxylamine in the presence of sodium acetate to give the oxime **169**, which then undergoes an iron mediated acylation reaction to give the enamide **170**, before benzylation with benzyl bromide in the presence of sodium hydride to give the final enamide **168**. The oxime route proved to be more successful with the more substituted enamides where the imine route failed to give any of the desired product.[157]

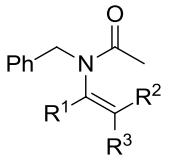


Scheme 2.2: The two routes previously used to synthesis enamides. *Reagents and conditions:* a) 1 eq. benzylamine, toluene, reflux.; b) 1 eq. 2-chloroacetylchloride, 1 eq. *N,N*-diethylaniline, toluene, 0 ^{o}C.; c) 1.2 eq. NaOAc, 1.2 eq. $NH_2OH.HCl$, MeOH, reflux.; d) 3 eq. 2-chloroacetic acid, 3 eq. 2-chloroacetic anhydride, 2 eq. Fe(O), toluene, 70 ^{o}C.; e) 5 eq. NaH, 1.05 eq. BnBr, THF, reflux.

2.2 Results and Discussion

2.2.1 Investigations into the Substitution Level at the Alkene

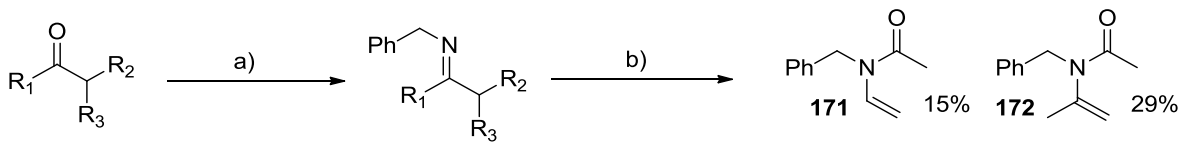
Previous investigations had shown that enamides with tetrasubstituted alkenyl groups **164-165** had significantly higher barriers to rotation than related enamides with lower substitution at the alkene. However we did not have a complete picture of the effect of the substitution level at the alkene on the barrier to rotation. Therefore initial investigations looked at the synthesis of a series of compounds (**171** - **176)** with varying levels of substitution at the alkene.



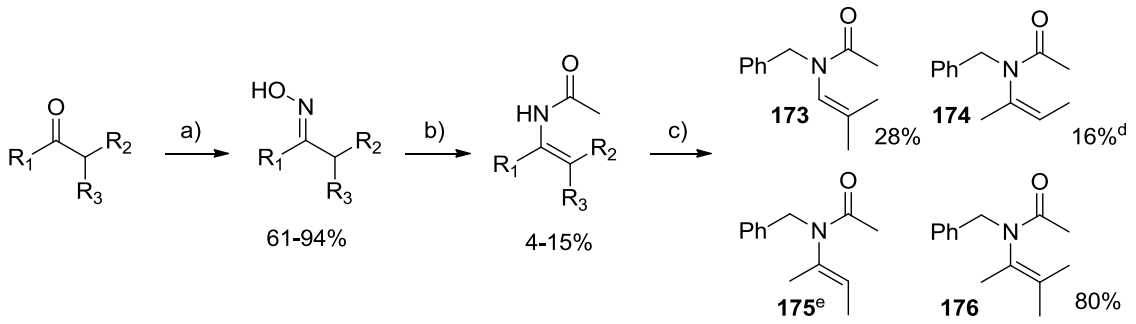
171, $R^1 = R^2 = R^3 = H$ **174,** $R^1 = R^2$ = Me, R^3 = H
172, R^1 = Me, $R^2 = R^3 = H$ **175,** $R^1 = R^3$ = Me, R^2 = H
173, R^1 = H, $R^2 = R^3$ = Me **176,** $R^1 = R^2 = R^3$ = Me

Figure 2.9. Compounds synthesised to investigate the effect of substitution at the alkene.

Compounds **171** and **172** were synthesied *via* the imine route (A, Scheme 2.2) where the appropriate ketone was reacted with benzylamine followed by acylation with acetyl chloride with Et_3N as a base (Scheme 2.3). Whereas compounds **173-176** were synthesised *via* the oxime route (B, Scheme 2.2) which was then subjected to an Fe(0) mediated rearrangement to give the secondary enamide, followed by anion formation with NaH and alkylation with benzyl bromide (Scheme 2.4).



Scheme 2.3. Synthesis of compounds 171 and 172 *via* the imine. *Reagents and conditions:* a) 1.0 eq. benzylamine, toluene, reflux, b) 1.1 eq. acetyl chloride, 1.2 eq. Et_3N, toluene, 0 ^oC – r.t.



Scheme 2.4. Synthesis of compounds 173 - 176 *via* the oxime. *Reagents and conditions:* a) 1.2 eq. $NH_2OH.HCl$, 1.2 eq. NaOAc, MeOH, reflux, b) 2eq. Fe(0), 3eq. AcOH, 3eq. Ac_2O, toluene, 85 ^oC, c) 5eq. NaH, 1.1 eq benzyl bromide, THF, 0 ^oC – reflux. ^{d} Further compound was obtained as a mixture with **175**. ^{e} Only obtained as a mixture with **174**, (2:1 ratio of **175** : **174**).

These compounds were all analysed by 500 MHz ^1H VT NMR and from the data it is clear that mono- and disubstituted enamides **171** and **172** have relatively low barriers to rotation. On cooling **171** the benzylic CH_2 singlet begins to broaden as expected, but even at -94 ^oC decoalescence is not observed and therefore the barrier to rotation can not be calculated. Based on other results (see Table 2.1) we can say that these barriers to rotation are <7.6 kcal mol^{-1}. Two amide rotamers of enamide **171** were observed at room temperature, whereas normally *N*-alkyl enamides exhibit only a single *E*-amide rotamer in solution.

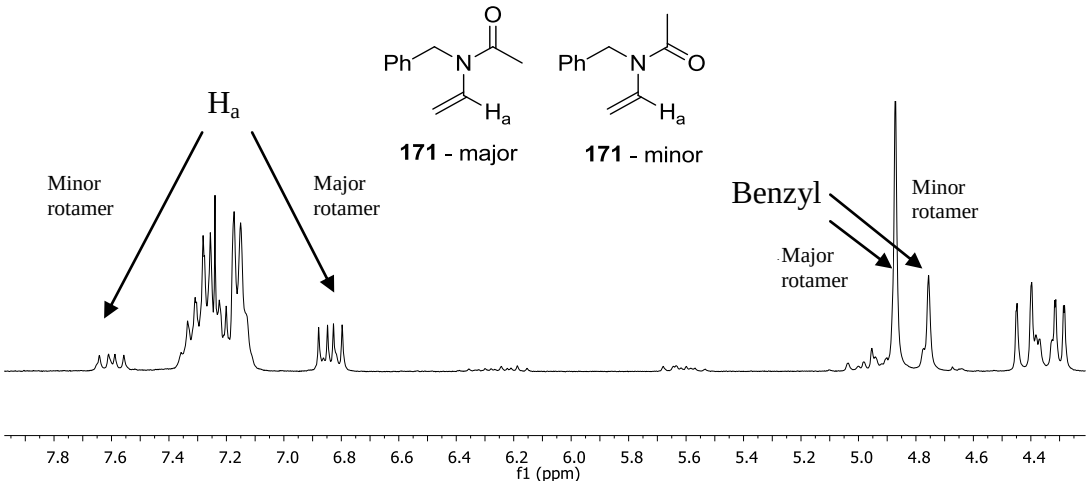


Figure 2.10. 400 MHz ^1H NMR of enamide 171 showing the two different rotamers.

The ^{1}H NMR showed two sets of peaks which upon heating (298K→373K) broadened and coalescenced to give a single set of peaks. This is consistent with a slow rotation around the amide bond and a fast rotation around the *N*-alkenyl bond at 298K, with rapid rotation around the amide bond and the *N*-alkenyl bond at 373K.

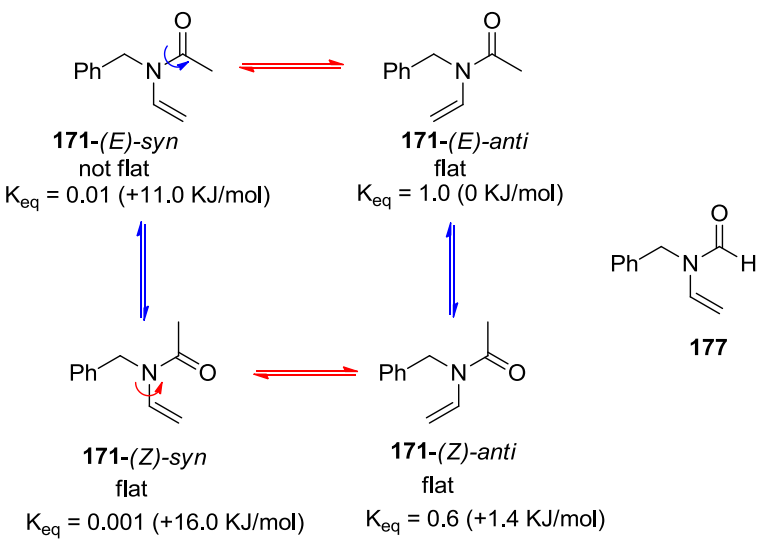


Figure 2.11. Theoretical analysis of enamide 171 showing the four different possible conformations.

Theoretical analysis of enamide **171** using B3LYP 6-31(G)d indicated that three out of the four possible conformations were planar, with the *(E)-anti* and *(Z)-anti* conformations predominating at equilibrium. Experimentally two conformations were seen in the ^{1}H NMR at 298K in a 2:1 ratio: in good agreement with theory. The major isomer was assigned as *(E)-anti*-**171** and the minor isomer as *(Z)-anti*-**171** based upon the ^{1}H NMR chemical shift and NOE data. The α-enamide proton resonates at 6.80 ppm in the major conformer and 7.50 ppm in the minor conformer. This data is in good agreement with that reported for related compound **177**.[73]

Enamides **174** and **175** were both synthesised simultaneously from the same starting material, 2-butanone oxime. Purification after the final step yielded pure enamide **174**, however enamide **175** could not be obtained free of **174** and remained a mixture of the two isomers (2:1 ratio of **175** : **174**). The ^{1}H NMR of the mixture clearly showed the compounds had distinctly different barriers to rotation (Figure 2.12), with the benzyl protons for one compound appearing as a singlet and for the other compound as two doublets.

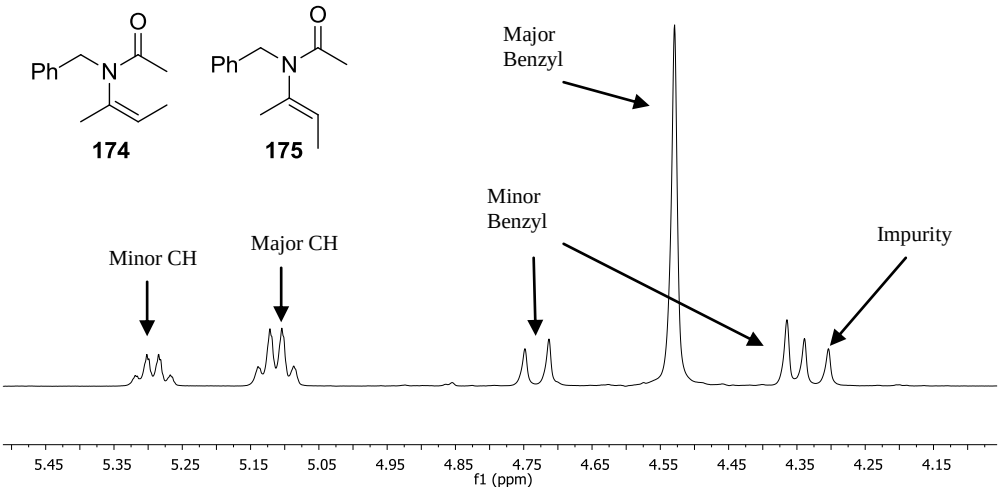


Figure 2.12. 400 MHz ^{1}H NMR of enamide 174 and 175 showing the two different isomers.

NOe experiments were used to assign the two isomers. The compound with the highest barrier to rotation was identified as enamide **174** and the lowest barrier to rotation was identified as enamide **175** (Figure 2.13) as expected. In compound **174** the β–methyl group is pointing towards the acyl group and therefore is likely to increase the barrier to rotation, whereas in **175** the methyl group is pointing away from the acyl group and less likely to result in an increase in the barrier to rotation.

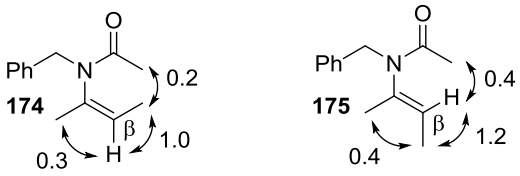


Figure 2.13. NOE results of enamide 174 and 175 showing % enhancement.

Unlike the mono **171** and disubstituted **172** enamides it was possible to use 400 MHz ^{1}H VT NMR and line shape analysis to calculate the barriers to rotation for the tri-substituted enamides **174** and **175** and they were determined to be 16.3 kcal mol^{-1} and 9.4 kcal mol^{-1} respectively (Table 2.1). However for enamide **174** coalesence was only just observed at 368K, close to the maximum temperature obtainable of 373K for the solvent used (d_8-toluene) and as a result this value may be less accurate than that for **175**.

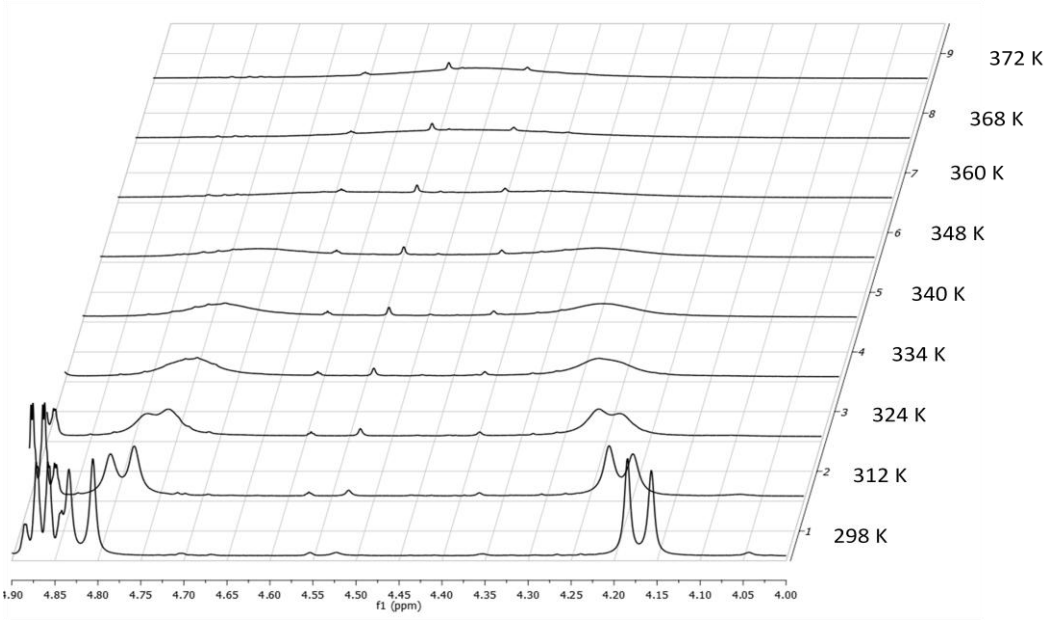


Figure 2.14: 500 MHz ^{1}H NMR VT NMR of 174 between 298K and 372K

Line shape analysis of the NMR's allowed k_{rot} to be calculated for each temperature. These values were then factored into the Arrhenius equation (Equation 2.2) allowing

the calculation of $\Delta G^{\ddagger}$ at each temperature. Eyring plots where then produced allowing access to values for $k_{rot\ 298}$ and $\Delta G_{298}^{\ddagger}$ for the bond rotation using equations 2.3 and 2.4, (see Table 2.1).

The tetrasubstituted enamide **176** showed two clearly resolved doublets for the benzyl protons at room temperature which upon heating to 373K broadened but did not reach the point of coalescence. This meant the barrier to rotation was too high to be calculated by 500 MHz ^{1}H VT NMR. As enamide **160** had previously had its barrier to rotation calculated by 500 MHz ^{1}H VT NMR as 18.0 kcalmol^{-1} we know the barrier to rotation of enamide **176** must be >18.0 kcalmol^{-1}.

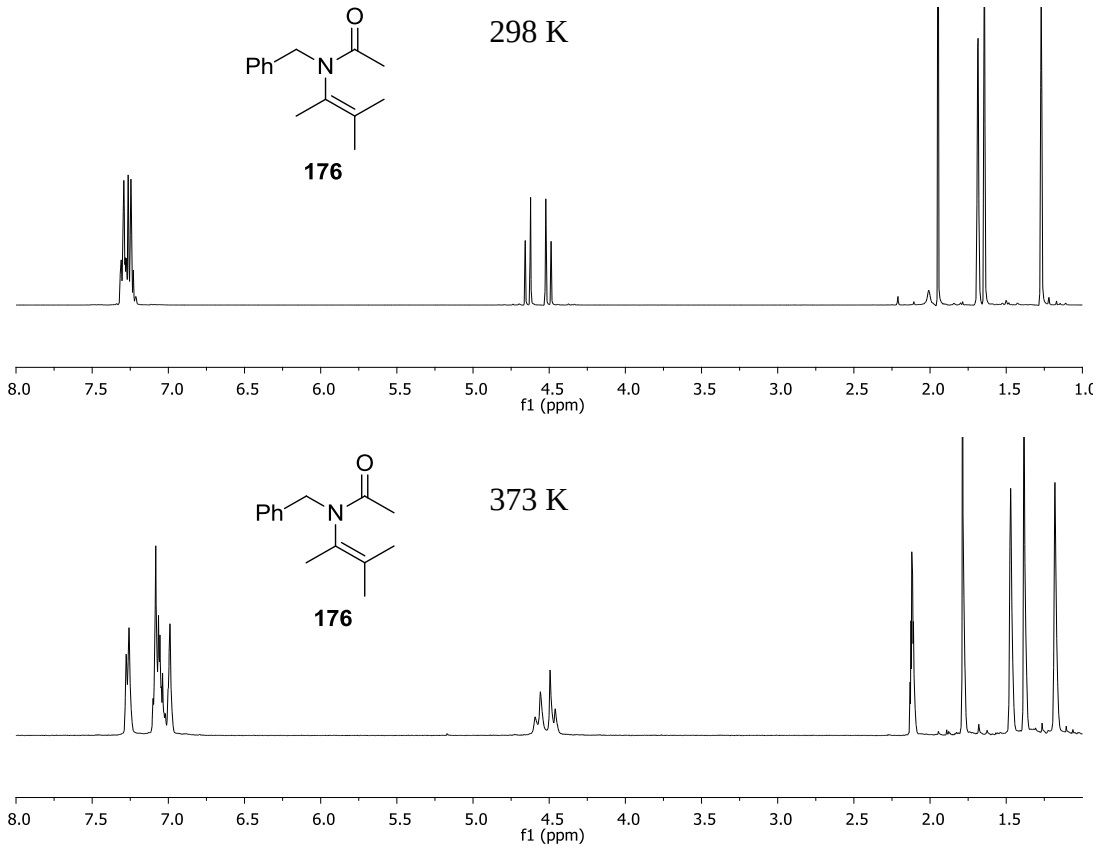


Figure 2.15: 400 MHz ^{1}H VT NMR of 176 at 298K (CDCl3) and 373K (toluene).

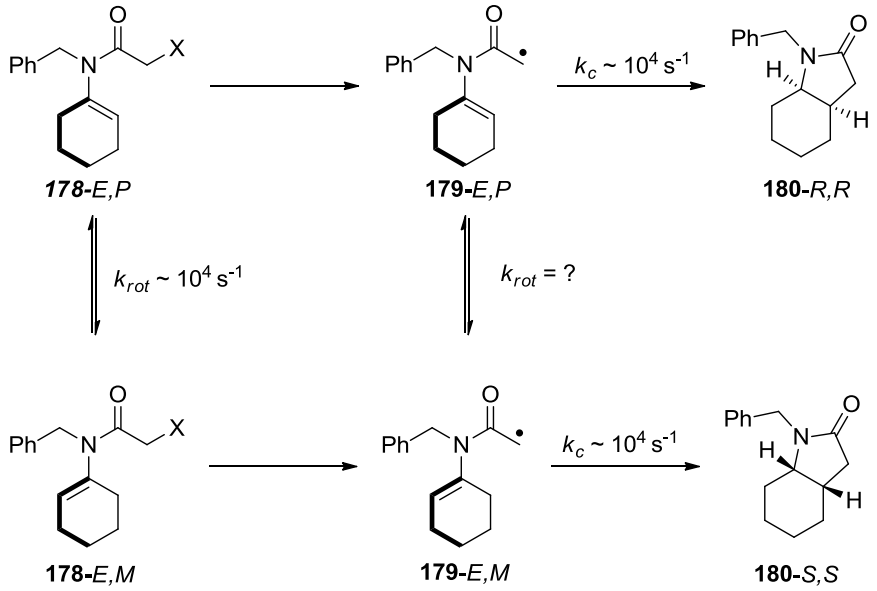
Substrate	Level of substitution	$\Delta G^{\ddagger}_{298}$ (kcal mol^{-1})
171	Mono-	<7.6[a]
172	Di-	<7.6[a]
173	Tri-	<7.6[a]
174	Tri-	16.3
175	Tri-	9.4
176	Tetra-	>18.6[b]

Table 2.1. Barriers of rotation for enamides 171-176. [a] Too low to measure by 500 MHz ^{1}H VT NMR, [b] Too high to measure by 500 MHz ^{1}H VT NMR,.

These results show not only that the level of substitution at the alkene is important but also that the stereochemistry at the alkene can greatly affect the barrier to rotation. This can been seen particularly well when comparing **174** and **175**; when the methyl group is *cis* to the nitrogen (**174**) the barrier to rotation is ~7 kcal mol^{-1} higher than when it is *trans* to the nitrogen (compound **175**). As we were particularly interested in atropisomeric enamides that could be resolved and potentially used in asymmetric radical reactions (Scheme 2.5) we next focussed our efforts on the synthesis of radical models of tetrasubstituted enamides.

2.2.2 Synthesis of Radical Models for Tetra-Substituted Enamides.

In order for chirality transfer to occur in a 5-*endo trig* radical cyclisation (**179** → **180**) the barrier to rotation of the radical **179** (produced from homolysis of halide **178**) must also be high so that k_{rot} is slower than k_c otherwise the single atropisomer of the enamide radical **179** could racemise prior to cyclisation.

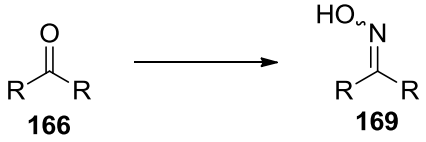


Scheme 2.5: Potential chirality transfer in enamides.

Therefore we prepared a range of *N*-acetyl tetrasubstituted enamides where the halogen atom had been replaced with hydrogen atom as models for the radical intermediates **(195** – **201**), Figure 2.18. These enamides were all synthesised *via* the 'oxime route'.

2.2.2.1 Synthesis of Oximes

Firstly the oximes were all synthesised from the corresponding ketone. In the majority of cases a mixture of *E* and *Z* isomers were produced.



Scheme 2.6: Synthesis of oximes from ketones. *Reagents and conditions:* a) 1.2 eq. NaOAc, 1.2 eq. $NH_2OH.HCl$, MeOH, reflux.

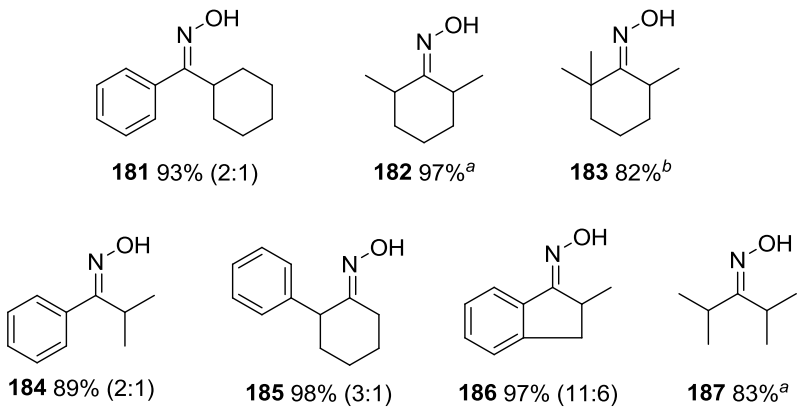
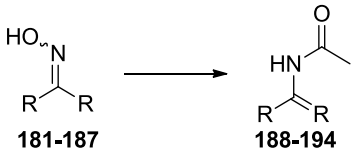


Figure 2.16: Oximes synthesised, showing yield and ratio of isomers. [a]Only one isomer possible. [b]Only one isomer observed.

Roberts *et. al.* studied the formation and conformation of oximes.[158] They found those with a quaternary α-carbon gave only a single isomer with the OH group *anti* to the quaternary carbon. This was rationalised due to steric reasons. Similar results were found in our work as oxime **183** was isolated as only a single isomer, that was assigned as the *anti* isomer, based upon the literature precedent. Oximes **181**, **184** and **186** containing an sp^2 hybridised carbon at the α-position gave rise to a mixture of isomers due to the lower steric demand of the carbon atom. Roberts determined that for mixtures the major isomer was that where the OH group was *anti* to the most substituted carbon. We have therefore tentatively assigned the major isomers of our oximes as the *anti* isomers, however as the conformation of this bond does not affect our subsequent synthesis and is lost in the following reaction this has not been confirmed.

2.2.2.2 Acylation of the Oximes

Oximes **181-187** were then all subjected to acylation by acetic anhydride and acetic acid in the presence of iron powder to give the enamides **188 - 194**.



Scheme 2.7: Synthesis of enamides from oximes. *Reagents and conditions:* 3 eq. acetic anhydride, 3 eq. acetic acid, 2 eq. Fe(O), toluene, 70 ^{o}C.

In all cases the desired enamide **188-194** was isolated in low to moderate yields (14-69%). Enough material was gained for the purpose of our subsequent investigations and so the reactions were not optimised further. Acylation of oxime **186** resulted in two products, the desired enamide **193** (50%) and the diacylated product **193a** (10%). This minor diacylated by-product was not detected in the acylation of any of the other oximes.

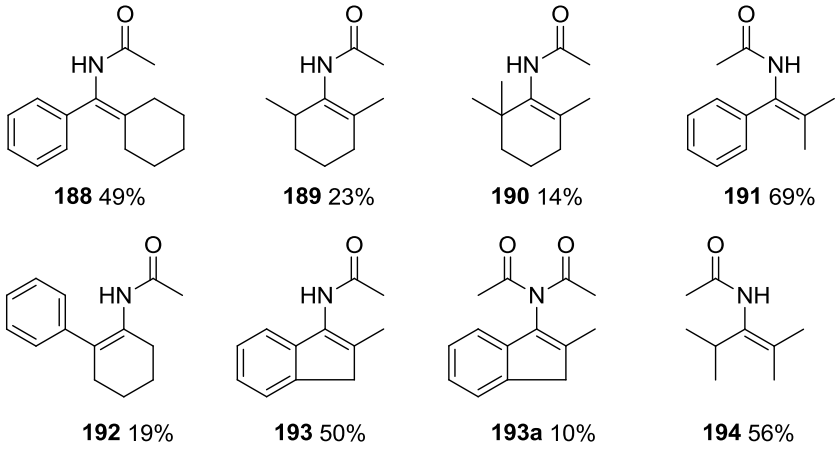
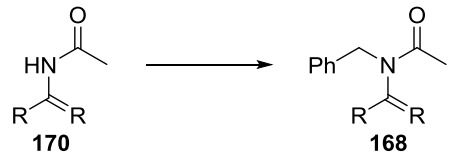


Figure 2.17: Enamides synthesised from oximes.

2.2.2.3 Benzylation of Enamides to give Radical Models

The enamides **188 - 194** were then deprotonated using sodium hydride before the addition of benzyl bromide to give the desired enamides **195 - 201** in 61 – 86% with one unexpected result (compound **198**).



Scheme 2.8: Benzylation of enamides. *Reagents and conditions:* 1.05 eq BnBr, 5 eq. NaH, THF, reflux.

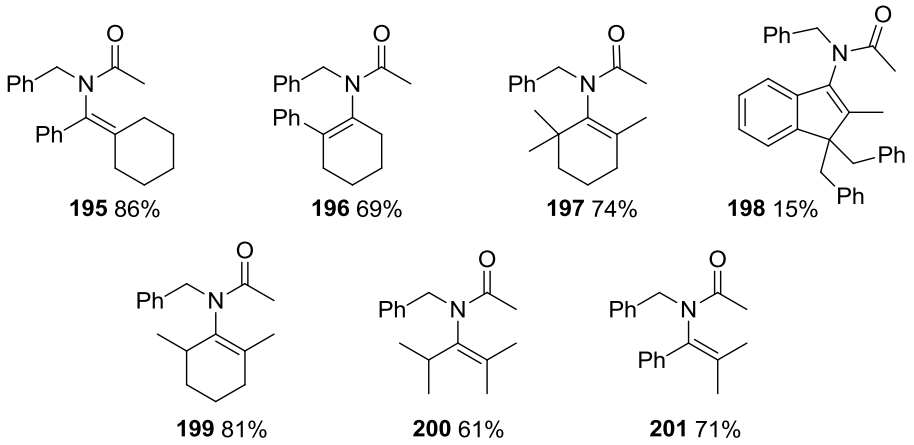
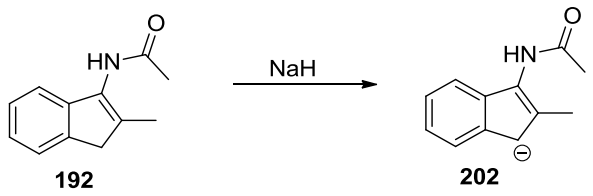


Figure 2.18: Enamides synthesised as radical models.

Enamide **192** formed a tri-benzylated product **198** with two benzyl groups adding on to the benzylic position of the indene ring. These protons, like those in cyclopentadiene, have an unusually high acidity as the loss of one of these protons would lead to a stable aromatic anion, which can then react further with the benzyl bromide to give the per-benzylated product.



Scheme 2.9: Deprotonation of enamide 192.

2.2.3 Analysis of Barriers to Rotation in Enamides 195 - 201

In the 400 MHz ^{1}H NMR of all the enamides **195** - **201** the benzyl protons appear as two clearly resolved doublets showing their diastereotopicity, indicating the chiral environment resulting from an axis of chirality around the N-C=C bond with a high barrier to rotation.

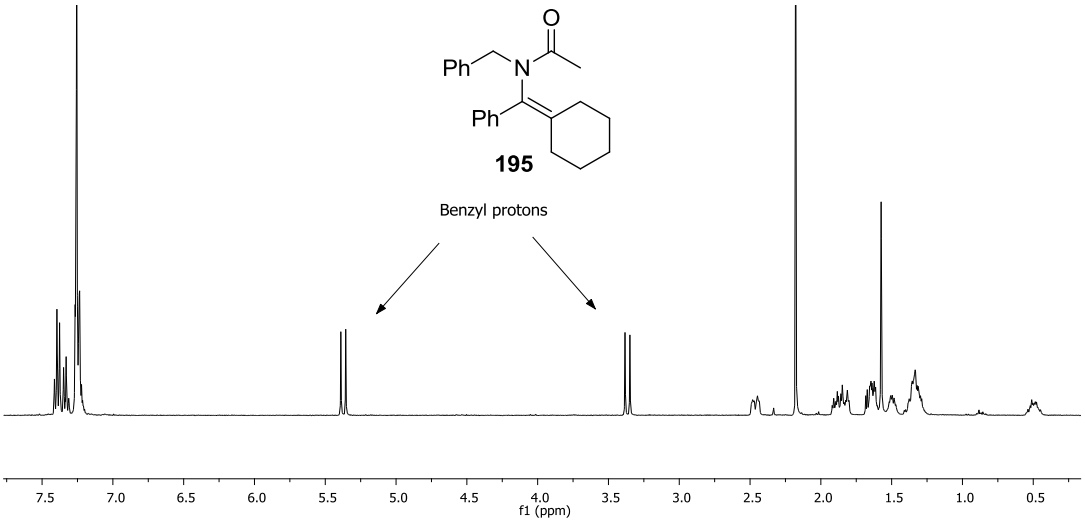


Figure 2.19: 400 MHz ^{1}H NMR of enamide 195.

It was not possible to measure the barrier to rotation using VT NMR as coalescence of the benzyl doublets was not observed within the temperature ranges possible on the NMR machine (183 K – 373 K). This high barrier to rotation observed for enamides **195** – **201** suggests that the analogous radical intermediates (with the radical at the acyl methyl carbon) would also have a high barrier to rotation and could lead to chirality transfer during cyclisation.

2.2.3.1 Barrier to Rotation Calculation by Chiral HPLC

Chiral HPLC is another method which can be used to measure the barrier to rotation of atropisomers by separating the two atropisomers and then measuring the rate of racemisation. This method has been used to calculate the barrier to rotation in other tetrasubstituted enamides (**164** and **165**).[157]

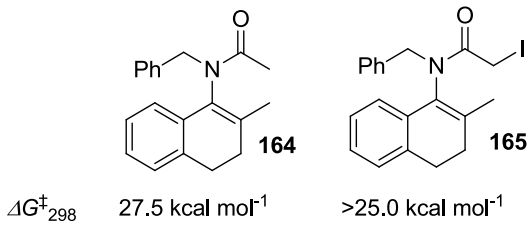


Figure 2.20. Compounds separated on chiral HPLC.

Separation of the synthesised enamides **195** – **201** was attempted on a number of in house chiral columns (Chiralcel OD, OD-H, AD, AD-H, OB, IA) with limited success. Separation was only achieved with enamide **198** where the two atropisomers were almost fully resolved (Figure 2.21), however separation was not observed with the other enamides.

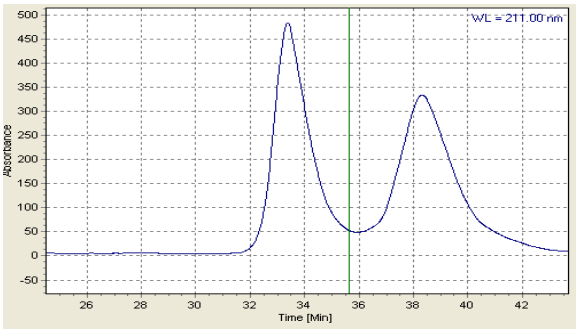


Figure 2.21. Chiral HPLC trace of compound 198.

A selection of the enamides (Figure 2.22) were then sent to our collaborators, Curran and co-workers, in Pittsburg, America for attempted separation on a Whelk-O

column, the type used previously for the separation of enamide atropisomers such as enamide **164** and **165**.

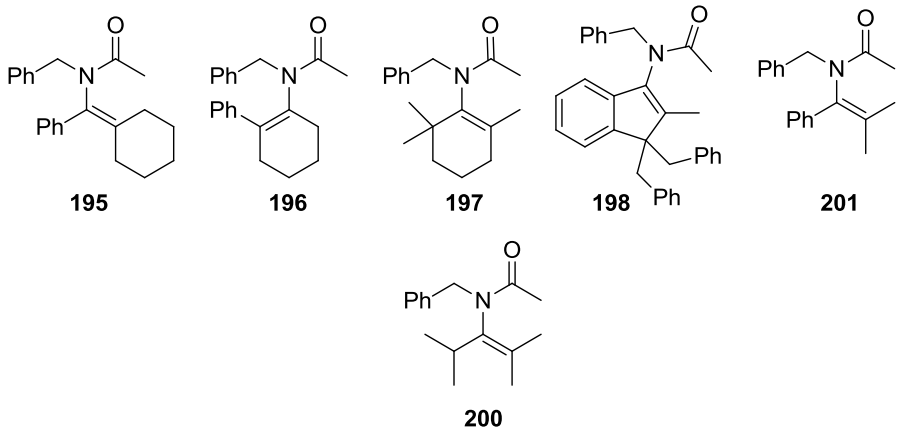


Figure 2.22: Enamides sent to Curran for attempted Separation by Chiral HPLC.

Enamide **200** had been synthesised previously in the group and separated by Curran allowing calculation of the barrier to rotation, 25.7 kcal mol^{-1}, by monitoring the rate of racemisation.[157] Unfortunately separation of compounds **195**, **196** and **201** on the Whelk-O was unsuccessful; it was not clear whether this was due to equilibration due to a low barrier to rotation (atropisomers interconverting too quickly) or a poor resolution on the column for these structures.

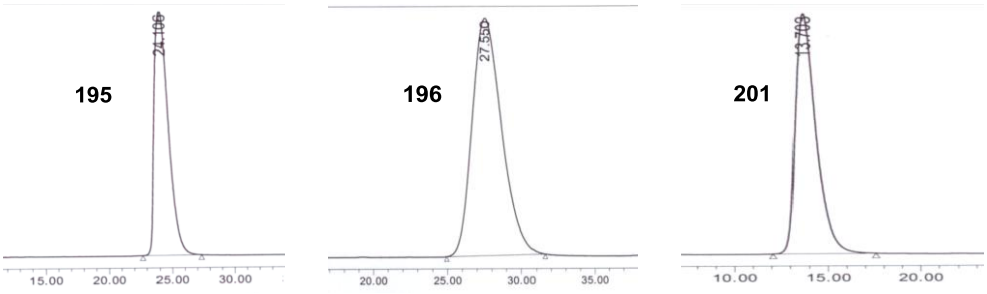


Figure 2.23: HPLC chromatograms of enamides showing no separation.

However separation was achieved with enamides **197** and **198**. Enamide **198** gave similar results to those achieved on in-house columns giving partial separation of the

two atropisomers. As complete separation was not a achieved an, accurate barrier to rotation was not calculated, however enriched fractions took several hours to racemise in *i*PrOH at room temperature suggesting a barrier to rotation >24 kcal mol^{-1}. Better separation was possible with enamide **197**. Separation yielded one atropisomer with >97:3 er which underwent racemisation at 82 ^{o}C in *i*PrOH. From this data the barrier to rotation was calculated to be 31 kcal mol^{-1} resulting in a half life of 128 years at 298K or 10.6 days at 353K (a typical temperature to mediate a radical cyclisation reaction).

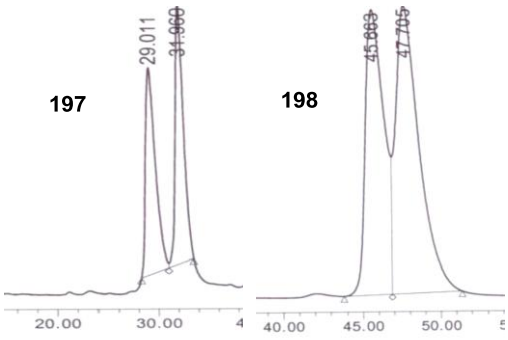
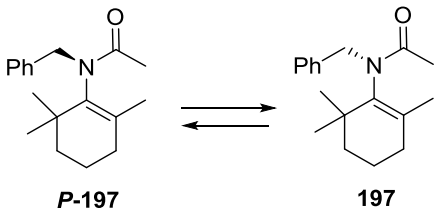


Figure 2.24: HPLC chromatograms of enamides 197 and 198.



***P*-197** **197**

Scheme 2.10: Racemisation of enamide 197. *Reagents and Conditions: i*PrOH, 82 ^{o}C.

2.2.3.2 Comparison of Barriers to Rotation in 'Radical Models'.

Comparing the results for the barriers to rotation calculated for the radical models **195-200**, as well as values previously reported provides some interesting

observations. Although we did not observe coalescence in the 400 MHz ^{1}H VT NMR of enamide **201**, and were therefore unable to obtain a value for the barrier to rotation, Ahlbrecht had previously calculated the barrier using his extrapolation method to be 21.3 kcalmol^{-1}. This is 6.2 kcalmol^{-1} lower than the value obtained for the restricted conformational analogue **164** (Figure 2.25). This relatively low value for **201** suggests a co-operative gearing of the phenyl substituent in the β position during the key rotation around the *N*-alkenyl bond in **201**. This could also explain why we were unable to calculate the barrier to rotation for **195** as again the phenyl substituent can undergo a co-operative gearing process during the rotation about the *N*-alkenyl bond. The higher value obtained for enamide **200** compared to **201** suggests that the isopropyl group is less able to partake in this process. A increase of almost 10 kcal mol^{-1} occurs due to the addition of a β'-methyl substituent between enamides **203** and **164,** therefore it is not surprising that we were unable to calculate a barrier to rotation for enamide **196** which only has substitution in the β'-position. However enamide **197**, which gave the highest barrier to rotation of 31 kcalmol^{-1}, has substituents at both the β'- and β''-positions that are conformationally restricted and unable to undergo any co-operative gearing to aid rotation about the *N*-alkenyl bond.

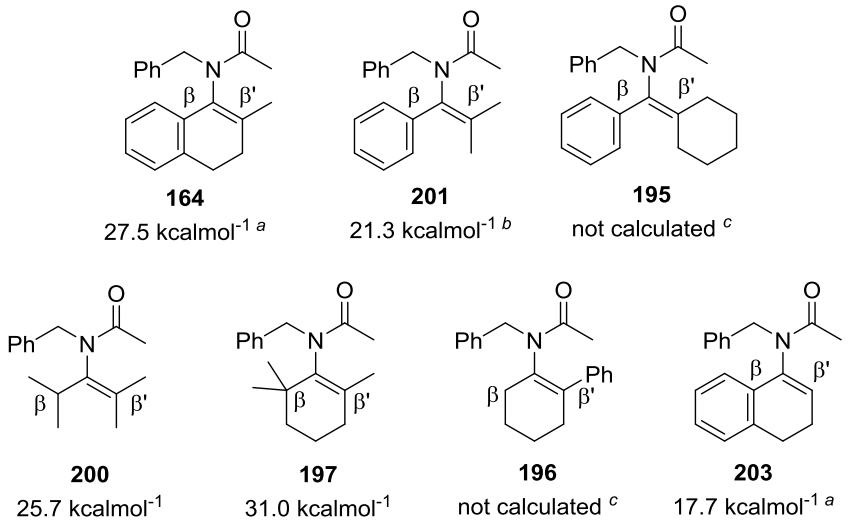


Figure 2.25: Comparsion of barriers to rotation. [a]Calculated previously within the group,[157] [b]Calculated by Ahlbrecht.[154] [c]Unable to calculate barrier to rotation by either ^{1}H VT NMR or chiral HPLC.

2.2.4 Synthesis of halogenated analogues for cyclisations.

From the work on 'radical models' we knew we could achieve high barriers to rotation so we next began synthesising halogenated analogues of the 'radical models' which could then undergo 5-*endo* cyclisation. We looked at compounds with a tertiary halogen on the α-carbonyl carbon (**204** X = CCl_3, **205** X = $C(Me)_2Br$) as these should undergo copper mediated cyclisations, and those with a primary halogen on the α-carbon (**206** X = Cl, **207** X = Br) that could undergo tin mediated cyclisations (Figure 2.26).

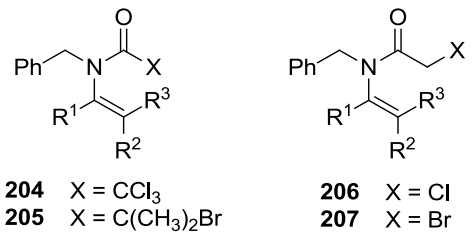
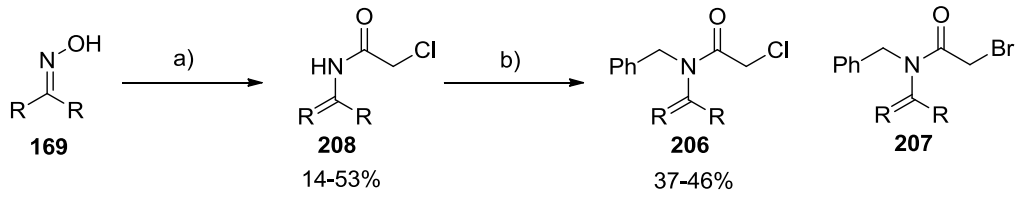


Figure 2.26. General structures of halogenated enamides.

2.2.4.1 α-Haloenamides

A number of chlorinated analogues of the tetrasubstituted enamides **206-207** were prepared from the corresponding oximes **169** using chloroacetic anhydride (Scheme 2.11). Upon carrying out the alkylation reaction with benzyl bromide some of the bromoenamide product **207** is obtained alongside the desired chlorinated product **206** due to displacement of the chlorine with bromide.



Scheme 2.11: Synthesis of tetrasubstituted chloroenamides. *Reagents and conditions:* a) 2 eq. Fe(0), 3 eq. chloroacetic anhydride, 3 eq. chloroacetic acid, toluene, 85 ^{o}C, b) 5 eq. NaH, 1.1 eq benzyl bromide, THF, 0 ^{o}C – reflux.

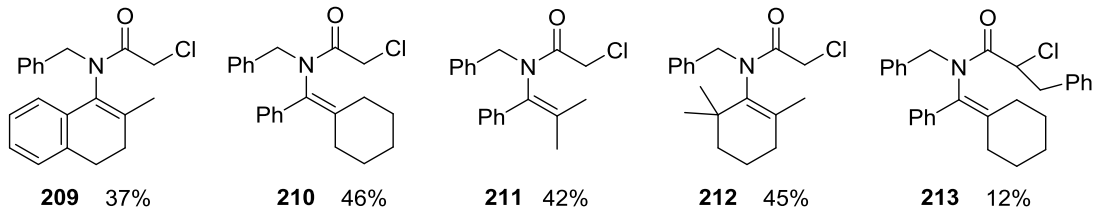


Figure 2.27: Tetrasubstituted chloroenamides.

Figure 2.27 shows the chloroenamides that were synthesised. When preparing **210**, a side product **213** was formed in 12% yield by the sequential addition of second benzyl group on the *α*-carbon to the carbonyl. As with the non-halogenated 'radical analogues' these enamides all had barriers of rotation that were too high to be calculated using 400 MHz ^{1}H VT NMR with the benzyl protons appearing as two mutally coupled doublets that did not coalesce at 373K. Based upon the results from the chiral HPLC of the 'radical analogues' we did not expect separation of enamides

210 – **211** to be successful. We sent enamides **209** and **210** to Curran and co-workers for separation and analysis by chiral HPLC.

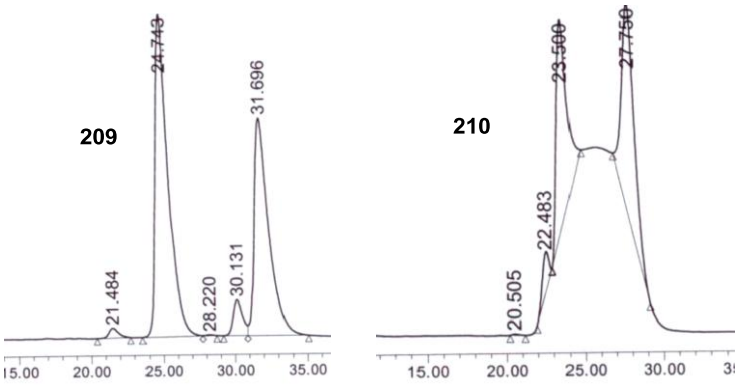
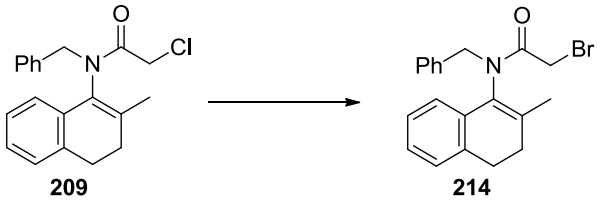


Figure 2.28: HPLC chromatograms of enamides 209 and 210 on a Whelk-O column.

Enamide **209** gave excellent separation (24.7 min and 31.7 min) and allowed isolation of a single atropisomer in >99:1 er which slowly underwent racemisation in *i*PrOH at 82 ^{o}C allowing the barrier to rotation to be calculated as 27.8 kcalmol^{-1} giving a half life of 173 days at 298 K. This value is very similar to that for the 'radical analogue' **164** (27.5 kcalmol^{-1}) and is relatively high suggesting that chirality transfer may be possible in the tin mediated cyclisation of enamide **209**. Enamide **210** gave an interesting result indicative of two atropisomers that were interconverting on the HPLC timescale. Based on a half life of mins at 298 K the barrier to rotation was estimated to be in the range 20 – 23 kcalmol^{-1}. As the values for the barrier to rotation of enamides **164** and **209** are very similar it suggests that the addition of the chlorine atom on the α-carbon to the carbonyl has minimal effect on the barrier to rotation. Therefore, based upon the results of the 'radical analogues' enamides **211** is likely to be inseparable by chiral HPLC with a barrier similar to that of **210** in the range of 20 – 23 kcalmol^{-1}. However enamide **212** should have a high barrier to rotation, similar to its radical analogue **197** (31.0 kcal mol-1) and is

therefore a good candidate for investigating chirality transfer in tin mediated 5-*endo* cyclisations.

As **209** showed promise for the possibility of chirality transfer, this compound was chosen to make the brominated analogue **214**. Although enamide **214** was also formed during the synthesis of **209**, it was only a minor component. In order to obtain more of enamide **214**, the Finklestein reaction was used to convert chloro-enamide **209** into bromo-enamide **214**. Hence, treatment of **209** with LiBr at room temperature for 60 hours yielded **214** in 84% yield.



Scheme 2.12: Conversion of chloro-enamide 209 into bromo-enamide 214. *Reagents and conditions:* 10 eq. LiBr, acetone, r.t.

As expected the 400 MHz ^{1}H NMR of **214** showed two clearly resolved doublets for the benzyl protons at room temperature and coalescence was not observed at 373K. As with enamide **209**, excellent separation was achieved on the Whelk-O column (28.6 min and 35.1 min) which allowed isolation of a single atropisomer in >98:2 er which slowly underwent racemisation in *i*PrOH at 82 ^{o}C allowing the barrier to rotation to be calculated as 29.3 kcalmol^{-1} giving a half life of 5.6 years at 298 K. This barrier is ~1.5 kcal mol^{-1} higher than that for the 'radical analogue' **164** and the chlorinated analogue **209**, showing that the large size of the bromine atom increases tha barrier to rotation about the *N*-alkenyl bond. As with the chlorinated analogue, the high barrier to rotation and long half life suggest that chirality transfer may be possible upon cyclisation of enamide **214** even at elevated temperatures.

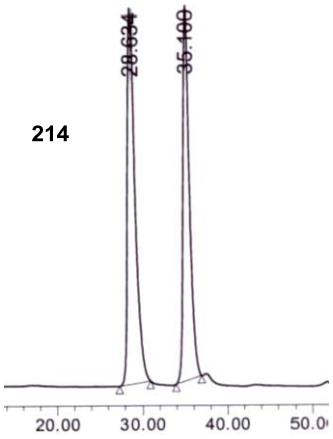


Figure 2.29: HPLC chromatogram of enamide 214.

2.2.4.2 Enamides for copper mediated cyclisations.

The α-haloenamides in section 2.2.4.1 can be subjected to tin cyclisation conditions, however we also wanted to investigate the possibility of chirality transfer in copper mediated ATRC reactions. For this we needed to synthesise enamides with tertiary halides *e.g.* **204** and **205**, however preparing such substrates proved more challenging than with the 'radical analogues' and the α-haloenamides.

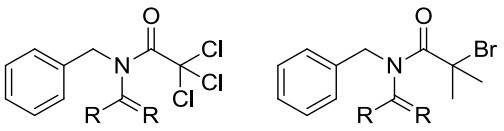


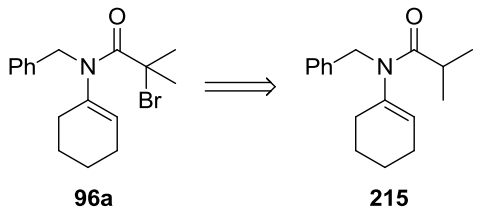
Figure 2.30: Enamides that can undergo copper mediated ATRC reactions.

We had prepared *N*-acetyl **195-200** and *N*-chloroacetyl **209-213** enamides by submitting them to the iron mediated acylation of oximes (method B, Scheme 2.2) with acetic anhydride and chloroacetic anhydride respectively. Trichloroacetyl anhydride can be used in this approach to prepare structures **204** but the yields were

low. Previous work had shown that a bromine atom could not withstand these harsh conditions so it was not possible to prepare the tertiary bromide enamides **205** by this protocol. In addition the preparation of hindered enamides by the imine route (method A, Schmeme 2.2) is normally unsuccessful.[157] Due to this, we investigated an alternative approach involving bromination of an isopropyl acetate group to introduce the halogen.

2.2.4.2.1 Attempted Synthesis of 205 by Bromination

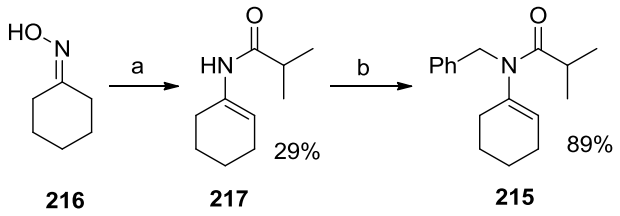
In order to develop a protocol we initially investigated this approach for the synthesis of known enamide **96a**. This was for two reasons. Firstly, cyclohexanone oxime was commercially available and secondly, we already had authentic samples of **96a** which would help us identify any trace amounts produced during the investigation.



96a **215**

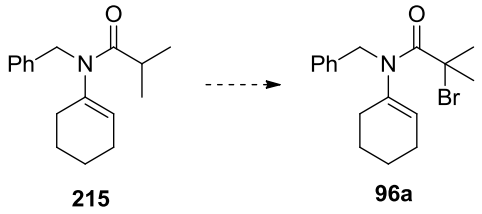
Scheme 2.13: Retrosynthetic analysis of enamide 96a.

Enamide **215** was synthesised by acylation of cyclohexanone oxime **216** with isobutyric anhydride, followed by benzylation of **217** using benzyl bromide and sodium hydride.



Scheme 2.14: Synthesis of *N*-benzyl-*N*-(cyclohexene-1-yl)isobutryamide. *Reagents and conditions;* a) Fe(0), isobutyric anhydride, isobutyric acid, toluene, reflux.; b) NaH, BnBr, THF, reflux.

A range of literature conditions for bromination were then attempted with varying bromine sources and conditions, all of which were unsuccessful (Table 2.1).



Scheme 2.15. The attempted bromination reactions.

While two approaches (Table 2.2, entries 6 and 7) showed the correct mass for the product in the mass spectrum of the crude reaction mixtures, the 400 MHz ^{1}H NMRs were very messy and there was no sign of the desired product following column chromatography. A peak at 256.1 suggestive of the eliminated product **218** was identified in both reaction mixtures. This peak was also seen in the crude mass spectra for entries 1, 2, 4, 6, 7, 8, 9, 10 and 11. A further peak at 274.2 (Table 2.2, entries 1, 2, 6, 7, 8, 9, and 10) which could correspond to the hydroxyl products **219** or **220** was also observed. All the reactions gave very messy crude NMR spectra and none of these postulated products could be identified or isolated by column chromatography.

Entry	Bromine Source	Conditions
1[159]	Br_2	s-BuLi, -78 ^oC, THF, forward addition
2[159]	Br_2	s-BuLi, -78 ^oC, THF, reverse addition
3[160]	Br_2	n-BuLi, -78 ^oC, THF, forward addition
4[161]	Br_2	AcOH, reflux
5[162]	Br_2	LDA, -78 ^oC, THF
6[163]	Br_2	DCM, r.t.
7[164]	NBS	p-TsOH, MeCN, reflux
8[165]	NBS	TMSOTf, MeCN, r.t.
9[166]	NBS	NH_4OAc, CCl_4, reflux
10[167]	NBS	1,1-Azobis(cyclohexylcarbonitrile), CCl_4, reflux
11[168]	$Cu(II)Br_2$	EtOAc, $CHCl_3$, reflux

Table 2.2: Bromine sources and conditions used in the attempted bromination reactions.

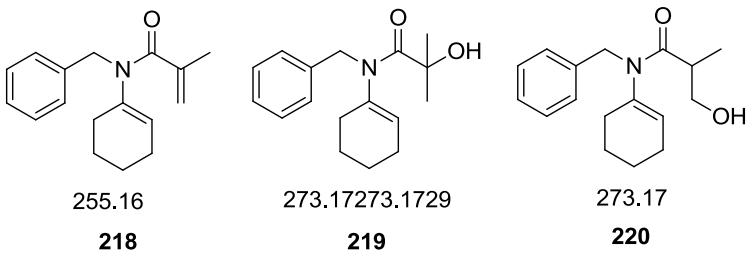
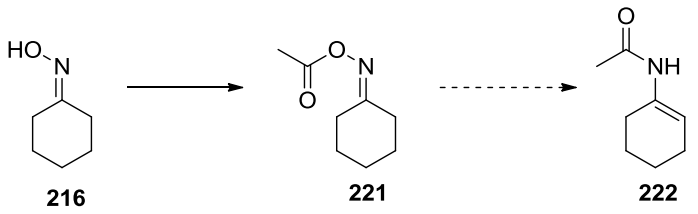


Figure 2.31: Possible products in the attempted bromination reactions.

2.2.4.2.2 Attempted Modifications of Acylation Reaction.

As we had no success with brominating enamide **215** we next tried modifying the conditions of the iron mediated acylation so that the bromine atom could be tolerated. Tang *et. al.* have shown that iron acetate can be used as a direct replacement to iron,[169] however in our hands, heating cyclohexanone oxime **216** as a

model with iron acetate, acetic acid and acetic anhydride failed to produce the desired **222** instead the only product isolated was **221** which is thought to be an intermediate in the reaction to give the acylated product **222**.[170]



216 **221** **222**

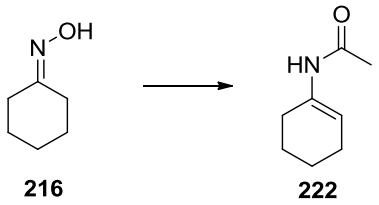
Scheme 2.16: Attempted acylation of cyclohexanone. *Reagents and conditions:* 3 eq. Ac_2O, 3 eq. AcOH, 2 eq. $Fe(OAc)_2$, toluene.

The reaction was attempted first at room temperature, then at 70 ^oC and then at reflux in order to try and push the reaction past this intermediate, however **221** was the only product obtained in all cases. We therefore concluded that iron acetate was not a strong enough mediator of the rearrangment reaction.

Barton *et. al.* have reported that a similar transformation can be carried out using just the anhydride in pyridine.[171] Hence we tried heating cyclohexanone oxime in pyridine with acetic acid, however, in our hands this again just gave us the intermediate **221**. Barton also reported that metals such as chromium(II), and titanium(II) acetate have been used to mediate this rearrangement.[171] We chose not to test these metals as we felt that they too were unlikely to tolerate halogen substituents.

Singh *et. al.* have reported a phosphine mediated reductive acylation of oximes **216** to **222**).[170] They have shown that a range of phosphines can be used (Ph_3P, DPPE, and Et_3P) to mediate the reaction with numerous substrates. In addition they have

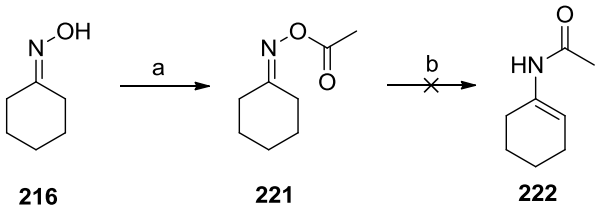
shown that transformation of an oxime acetate **221** to the enamide **222** directly is possible by reacting with the Et_3P in the absence of an anhydride.



216 **222**

Scheme 2.17: Singh's acylation of cyclohexanone: *Reagents and conditions:* R_3P, Ac_2O, toluene, reflux.

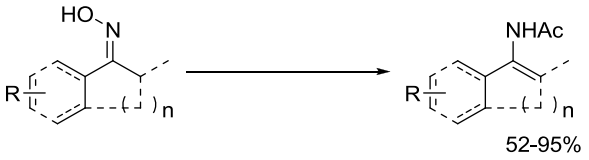
These conditions were tried with both cyclohexanone **216** and tetralone oximes however only the intermediate oxime acetate **221** was evident. Heating **221** with Ph_3P under the conditions of Singh *et. al.* for 90 hours did not facilitate the reaction to **222.**



216 **221** **222**

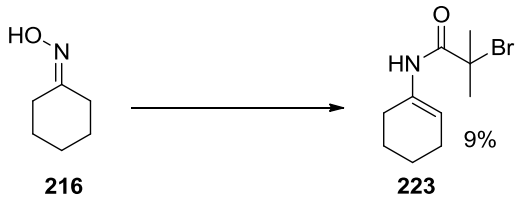
Scheme 2.18: Attempted phosphine mediated acylation of cyclohexanone. *Reagents and conditions;* a) Ph_3P, Ac_2O, toluene, reflux.; b) Ph_3P, toluene, reflux.

In 2011 Guan and co-workers published a copper mediated acylation of oximes, primarily using acetic anhydride to give the acetate enamide (Scheme 2.19) but also using propionic anhydride to give the propionate derivative.[172] Although they have reported the reaction was unsuccessful using the halogenated trifluoroacetic anhydride we attempted the reaction with 2-bromoisobutyric anhydride to see if we could obtain any of the desired bromoenamide **223** (Scheme 2.20).



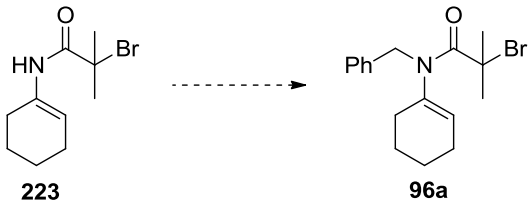
Scheme 2.19. Guan's copper mediated acylation of oximes.[172] *Reagents and conditions:* 0.1 eq. CuI, 3 eq. $NaHSO_3$, 2 eq. Ac_2O.

We initially tried the reaction on cyclohexanone oxime **216**. Pleasingly a low yield of the desired bromide **223** was obtained (9%). Other compounds were produced from the reaction but were not identified at this point. We next focussed on whether we could carry out the *N*-benzylation step to give **96a** (Scheme 2.21) on this material **223**, before any attempts at optimising the reaction.



Scheme 2.20. Copper mediated acylation of oximes. *Reagents and conditions:* 0.1 eq. CuI, 3 eq. $NaHSO_3$, 2 eq. 2-bromoisobutyryic anhydride.

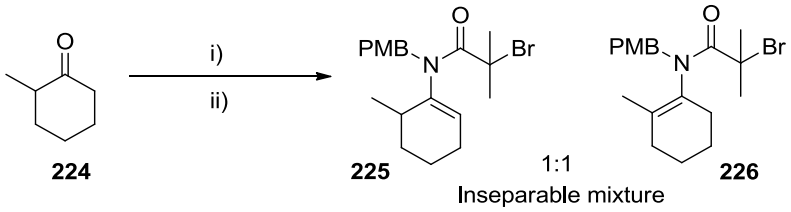
Unfortunately we were unsuccessful with alkylating enamide **223**. Using the normal method of deprotonation with sodium hydride, followed by the addition of benzyl bromide there was no sign of the desired product **96a**.



Scheme 2.21: Desired alkylation of enamide 223.

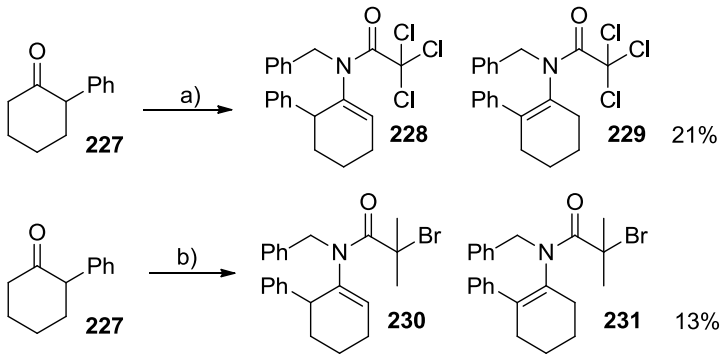
2.2.4.2.3 Synthesis of Tetrasubstituted Enamides *via* the Imine Route

As we were having no success trying to modify the conditions of the acylation reaction, we decided to further investigate the synthesis of these compounds *via* the imine route after coming across the preparation of one tetrasubstituted enamide this way by McDonagh.[173] In this instance a mixture of the regioisomers **225** and **226** was obtained, which could not be separated.



Scheme 2.22: Synthesis of tetrasubstituted enamides *via* an imine intermediate. *Reagents and conditions:* i) 1.0 eq. *p-methoxy*benzylamine, toluene, reflux, ii) 1.0 eq. 2-bromoisobutryl bromide, 1.0 eq. *N,N*-diethylaniline, toluene, 0 ^{o}C – r.t.[173]

Pleasingly, we found it was possible to synthesise enamides **229** and **231** by this route and have been able to go on to cyclise these (see chapter 3). As McDonagh found, we got a mixture of the two regioisomers which proved very difficult to separate, however after multiple attempts compounds **229** and **231** were obtained pure in yields of 21% and 13% respectively.



Scheme 2.23: Synthesis of tetrasubstituted enamides *via* an imine intermediate. *Reagents and conditions:* a) i) 1.0 eq. benzylamine, toluene, reflux, ii) 1.1 eq. trichloroacetyl chloride, 1.2 eq. Et_3N, toluene, 0 ^oC – r.t. b) i) 1.0 eq. benzylamine, toluene, reflux, ii) 1.1 eq. 2-bromoisobutyryl bromide, 1.2 eq. Et_3N, toluene, 0 ^oC – r.t.

Having had success with synthesising enamides **229** and **231** *via* the imine route, we applied the same conditions to the synthesis of enamides **232 – 236**. The desired products were obtained in better yields (38-74%) as there was only one possible regioisomer, which also meant purification was easier.

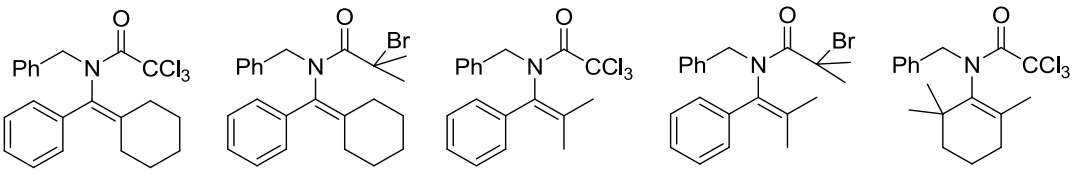


Figure 2.32: Tetrasubstituted enamides synthesised *via* the imine route showing yields and the ratio of amide rotamers.

These compounds all provided unusual 400 MHz ^1H NMR results; whereas all tetrasubstituted enamides synthesised previously showed one set of peaks consistent of largely a single *E*-amide rotamer in solution, the ^1H NMR of enamides **232** – **236** at 298 K showed two sets of peaks (Figure 2.33), however at 373 K there was just a single set of peaks (Figure 2.34). This is indicative of the presence of both *E*-**235** and

Z-**235** amide rotamers in solution. The population of the two rotamers seems to be independent of the alkene group, and dictacted by the acyl substitutent, with **233** and **235** showing similar ratios of rotamers and **232**, **234** and **236** showing similar ratios. Heating a sample of **232** to reflux in toluene for 24h followed by cooling did not change the ratio of rotamers showing that they are at equilibrium in solution. Thus as the enamides become more hindered at the acyl position the *E*-amide rotamer becomes less favourable. Unfortunately, as the *Z* rotamer is not predisposed for cyclisation this means heating may be required to cause an appropriate population of the reactive *E*-conformer. This in turn will increase the rate of rotation around the *N*-alkenyl bond and may reduce the chance of chirality transfer in these substrates.

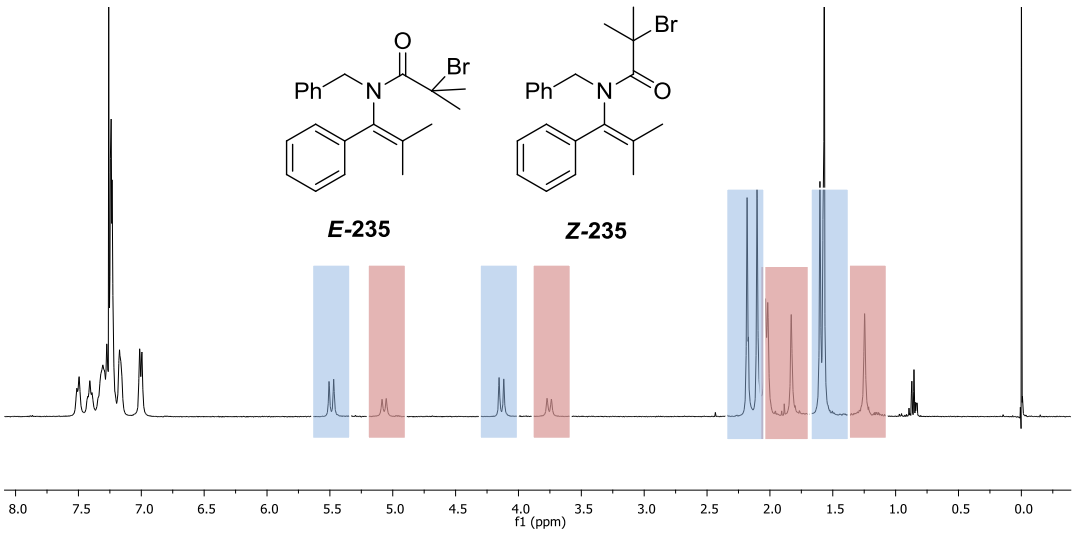


Figure 2.33: 400 MHz ^{1}H NMR of enamide 235 at 298 K showing slow rotation around both the NC=O and NC=C bonds.

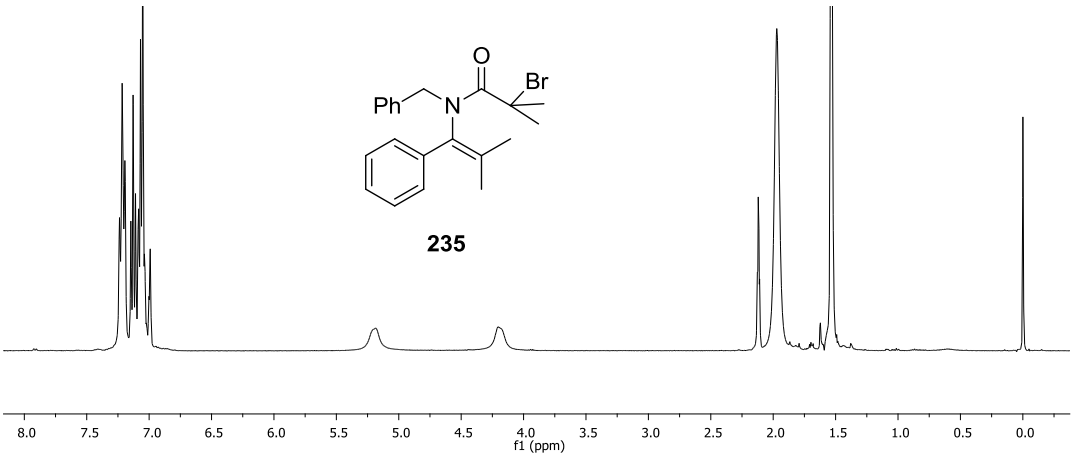


Figure 2.34: 400 MHz ^{1}H NMR of enamide 235 at 373 K.

Based upon the failure to separate the atropisomers of the related acetate analogues **195 – 196**, we did not expect separation of enamides **232 – 235** by chiral HPLC. However, increased substitution at the α-carbonyl has been shown to increase this barrier to rotation so we sent enamides **232** and **233** to Curran to attempt separation by chiral HPLC, although unfortunately no separation was achieved.

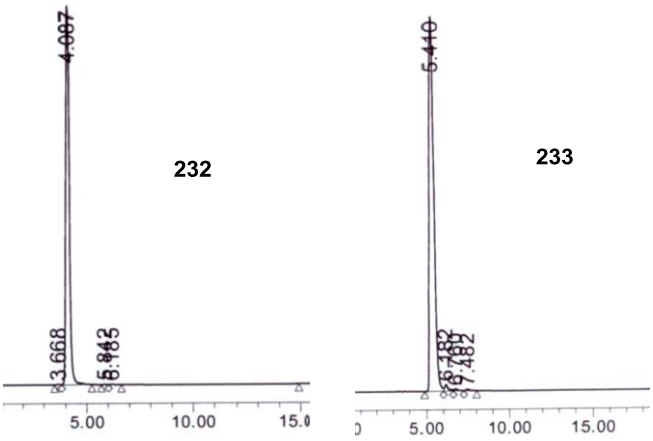


Figure 2.35: HPLC chromatograms of enamides 232 and 233

The barrier to rotation calculated for enamide **197** was calculated as 31.0 kcalmol^{-1}, we therefore expect the trichloroacetate analogue **236** to also have a high barrier to rotation, as previous results have shown that increased substitution at the acetate

increases the barrier to rotation.[111] Enamide **236** is therefore a suitable compound to attempt chirality transfer in a copper mediated ATRC reaction.

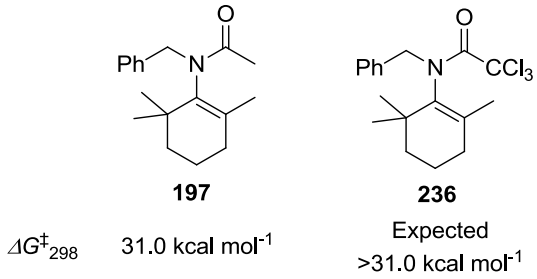


Figure 2.36: Enamide 236 and the acetate analogue 197.

2.2.4.2.4 Synthesising the Methyltetralone Analogue 237

As enamides **164**, **209**, and **214** all gave barriers to rotation high enough to make them suitable to be separated at room temperature, we were also particularly interested in synthesising enamide **237**.

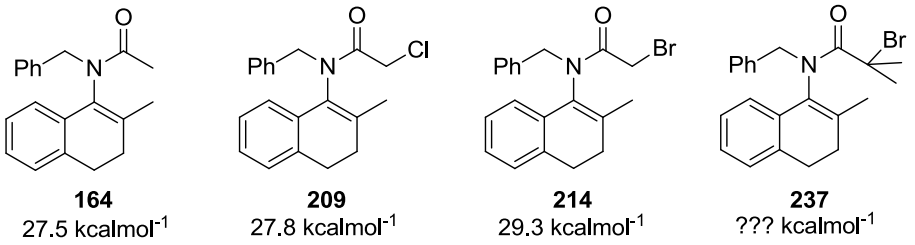


Figure 2.36: Methyltetralone based enamides

Attempts at preparing the imine derived from benzylamine and methyltetralone using TsOH catalysis failed. Instead we prepared the imine *in situ* by reaction with titanium isopropoxide at 80 ^{o}C. After addition of triethylamine and bromoisobutyryl bromide it was possible to prepare the desired **237**, albeit in a 9% yield. As before for **232-236,** the 600 MHz ^{1}H NMR of **237** indicated that both the *E*- and *Z*- amide rotamers were present in solution in a 1:0.17 ratio. Based on the barriers to rotation of enamides **164**, **209** and **214** and results showing increased substitution at the α-

carbon increases the barrier to rotation we expect enamide **237** to have a high barrier to rotation and be separable by chiral HPLC, therefore a suitable compound to attempt chirality transfer in copper mediated ATRC reactions.

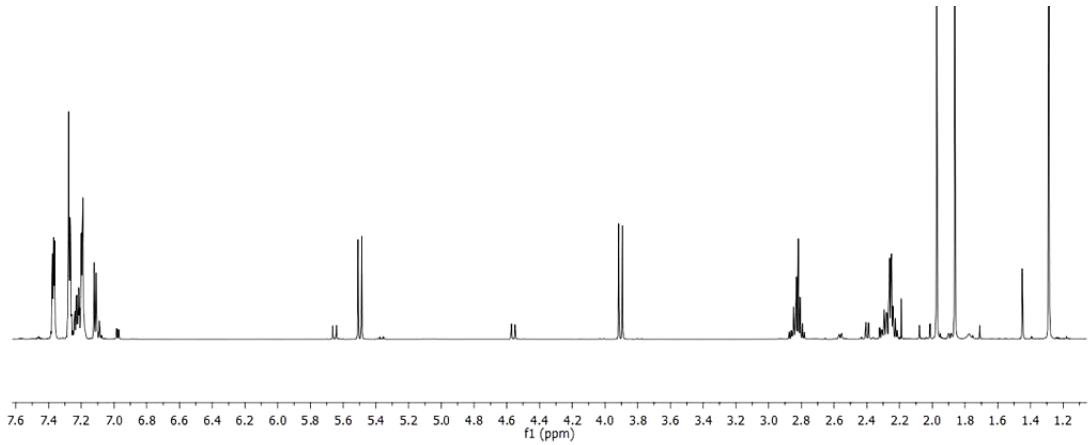


Figure 2.37: 600 MHz ^{1}H NMR of enamide 237.

2.2.4 Structural Analysis by Crystallography

Crystallography also provides some interesting insight into the conformation of the prepared enamides. Crystals structures of enamides **161**, **164** and **238**, made previously within the group, had been obtained and show that the *N*-alkenyl bond prefers to lie orthogonal to the plane of the N-CO bond with torsion angles ranging from 53^{o} to 85^{o} (Table 2.3, entries 1-3).[157] We obtained crystal structures of the synthesised enamides **195**, **229** and **235** and these also followed this trend with the torsion angles between the alkene bond and the N-CO bond between 65^{o} and 95^{o} (Table 2.3, entries 4-6). This indicates there is restricted rotation about the *N*-alkenyl bond as the two planes are not lying flat as expected if the bond was freely rotating.

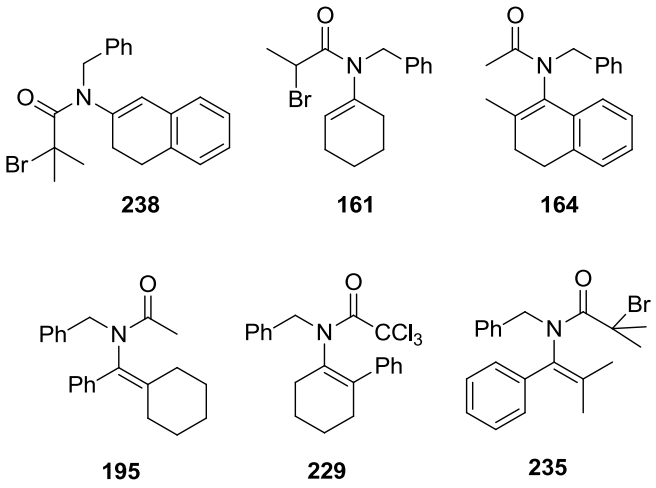


Figure 2.38: Compounds with structures elucidated by crystallography.

Entry	Compound	Torsion Angle[a]	Amide conformation
1	**238**	53°	*E*
2	**161**	85 °	*E*
3	**164**	74 °	*E*
4	**195**	65 °	*E*
5	**229**	95 °	*Z*
6	**235**	69 °	*Z*

Table 2.3: Torsion angles and amide conformations deduced from crystal structures. [a]Torsion angle between N-CO bond and alkene bond.

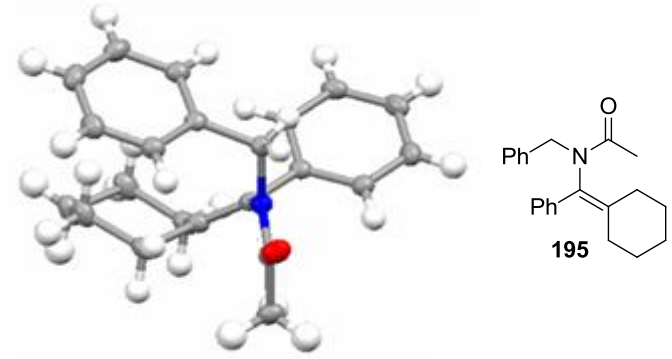
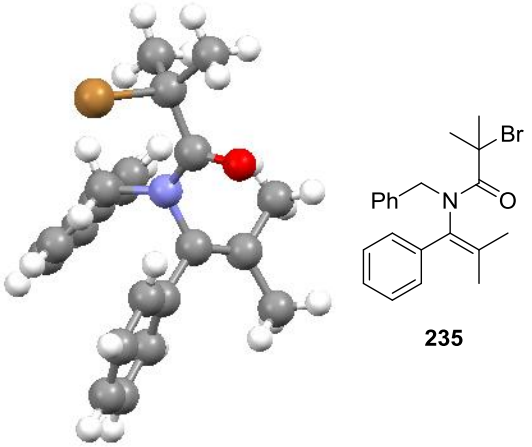


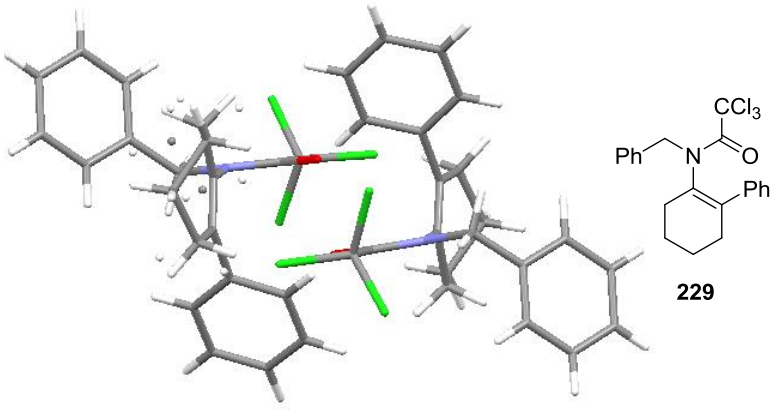
Figure 2.39. X-ray crystal structure of enamide 195 occupying the *E*-amide rotamer.

It is also interesting to observe the conformation of the amide bond in the crystal structures obtained. Whereas enamides **161**, **164**, **238** and **195** showed a preference for the *E*-amide rotamer in the solid state, the more hindered tetrasubstituted enamides with the larger acyl groups, **229** and **235** show a preference for the less common *Z*-amide rotamer in the solid state. This is in agreement with the ^{1}H NMR where both amides rotamers were observed.



235

Figure 2.40: X-ray crystal structure of enamide 235.



229

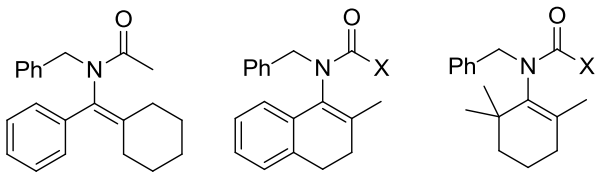
Figure 2.41: X-ray crystal structure of enamide 229.

In the crystal structure of **229** both atropisomers can be seen co-crystallising but interestingly, whereas one atropisomer shows only one conformation for the cyclohexenyl ring, the other has a degree of disorder here with two observed conformations in a 54:46 ratio.

Based upon these results, an interesting question arises, as to whether it is possible that molecules with exceptionally high barriers to rotation, e.g. **209** and **237**, will prove difficult to cyclise as significant steric crowding from the alkenyl substituents will occur on moving to planarity.

2.2.5 Summary

A range of different enamides (**171 - 176, 195 - 201, 209 - 214, 229, 231 and 232 - 237**) have been synthesised of which the majority exhibited slow rotation about the *N*-alkenyl bond, with barriers to rotation varying between <9.4 and 31 kcal mol^{-1}. The level of substitution at the alkene was found to be a key factor in controlling the rate of rotation about the *N*-alkenyl bond, with tetrasubstituted enamides e.g. **209**, **214** and **236,** giving the highest barriers to rotation. However tetrasubstituted enamides with freely rotating β-substituents, *e.g.* **195**, appear to have a co-operative gearing leading to lower than expected barriers to rotation. Contrastingly tetrasubstituted enamides with rigid β- and β'- substituents e.g. **239** and **240** have high enough barriers to rotation to allow separation at room temperature by chiral HPLC with half lives ranging from 5.5 days to 128 years at 298 K. This suggests that enamides of general structure **239** and **240** are suitable for further investigations into the possibility of chirality transfer in copper mediated ATRC reactions.



195 239 240

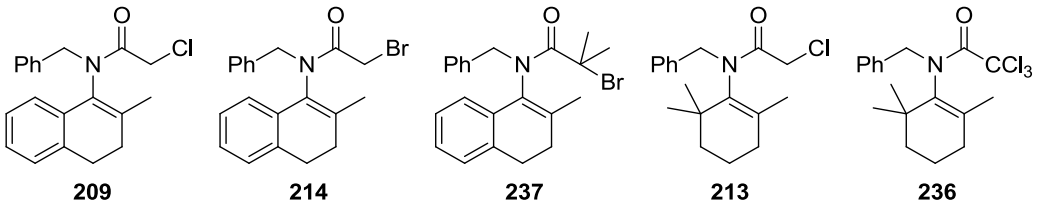
Figure 2.41: Tetrasubstituted enamides.

However, for hindered tetrasubstituted enamides with large acyl groups (**232** - **237**) both *E*- and *Z*- amide rotamers were observed in solution at room temperature. This may affect the efficiency of any cyclisation reaction as in the *Z*-amide rotamer the halogen is not positioned in proximity of the alkene. Heating the enamides to 373 K was found to lead to fast interconversion of the *E*- and *Z*- amide rotamers on the NMR timescale so cyclisations at elevated temperatures may be more efficient, although at higher temperatures the half lives of the atropisomers will be significantly lower.

3.0: 5-*Endo* Cyclisations of Atropisomeric Enamides

3.1 Introduction

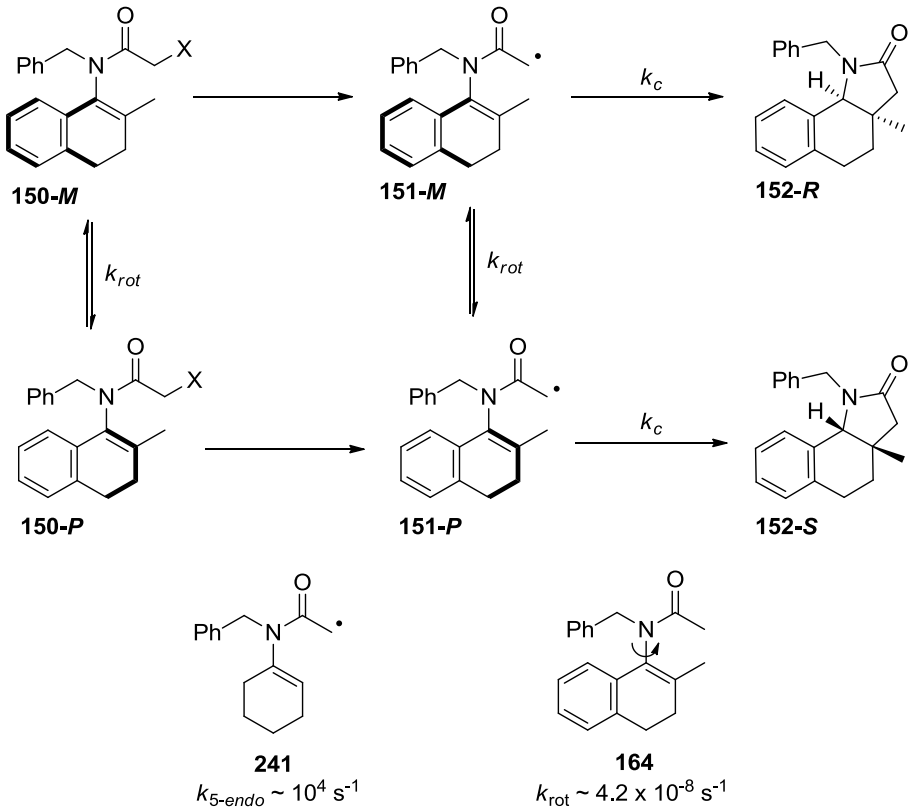
Having successfully synthesised a variety of tetrasubstituted enamides, including a number of which it was possible to separate their atropisomers at room temperature, we next investigated the radical cyclisation of these enamides, and the results are described in this chapter.



209 **214** **237** **213** **236**

Figure 3.1: Atropisomeric enamides with high barriers to rotation.

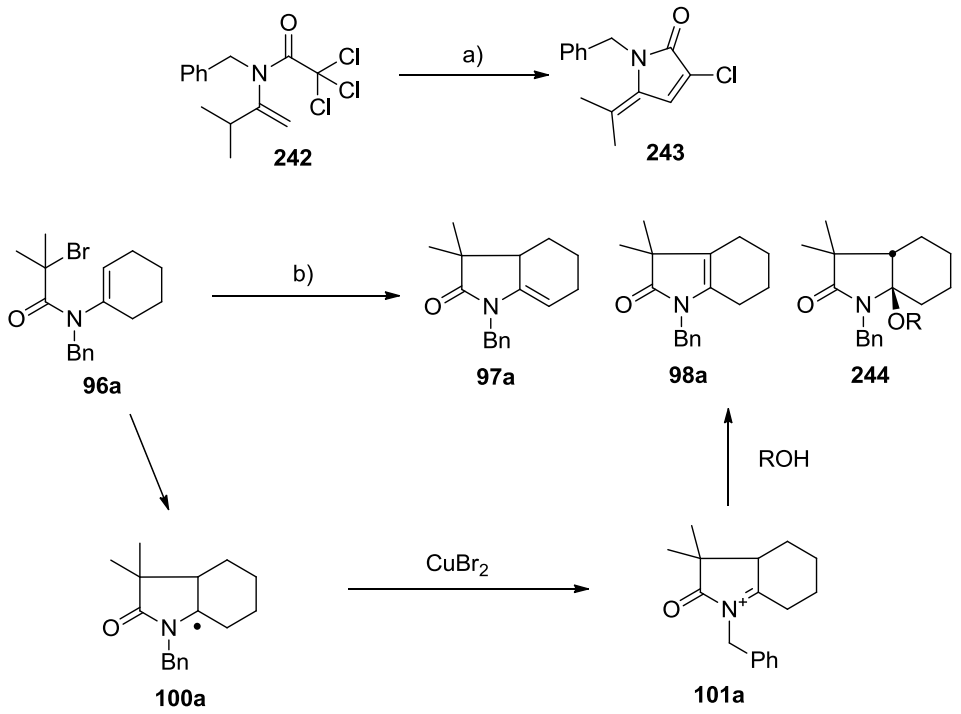
We envisaged that cyclisation of enantiomerically pure samples of these enamides could lead to chirality transfer to the product if k_{rot} of the radical intermediate is slower than k_c (Scheme 3.1). Radical **241** has been shown to undergo 5-*endo trig* radical cyclisation reactions at rates in the order of 10^4 s^{-1}.[153] If we assume **164** is a model for radical **151** we can estimate that the k_{rot} for this radical is in the order of 4.2×10^{-8} s^{-1} at room temperature,[157] indicating that there is some merit in exploring this hypothesis.



Scheme 3.1: Possible chirality transfer in the cyclisation of enamides.

3.1.1. Existing Conditions for Cyclisation

Over the past couple of decades there have been many developments in conditions for the cyclisation of enamides (see Chapter 1, section 1.2 in particular section 1.2.4 for 5-*endo* cyclisations) with ligand accelerated copper mediated conditions proving very popular. Common ligands are based upon polydentate nitrogen compounds such as bipy,[104] TMEDA,[105] hexamethyl triethylenediamine (Me_6-tren),[71] or tris(2-pyridylmethyl)amine (TPA)[174] with the latter being the ligand of choice for slow cyclisations. The vast majority of published cyclizations involve disubstituted structures such as **242**[71] or trisubstituted structures where the alkene is part of a ring (e.g **96a**),[71] with only limited examples of the cyclisation of tetrasubstituted enamides in the literature.[173]

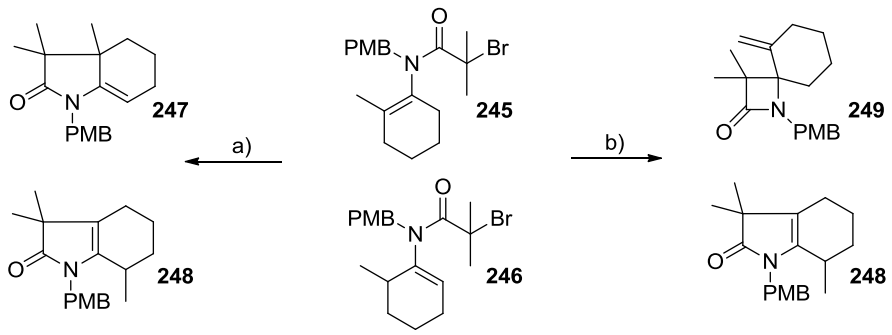


Scheme 3.2: Copper mediated 5-*endo* cyclisations. *Reagents and conditions:* a) CuCl, ligand **42a**, DCM, 40 ^{o}C. b) CuBr, ligand.

These processes generally proceed to give an α-amido radical **100a** which is then oxidised to an acyl iminium ion **101a** by the $CuBr_2$ liberated in the first step. This acyl iminium ion **101a** can eliminate a proton to give alkene regioisomers **97a** and **98a**, or it can be trapped by external nucleophiles (e.g. alcohols) to give **244** depending upon the reaction conditions.[5] Although lactam **98a** is not chiral, lactams **97a** and **244** contain stereocentres produced during the cyclisation process and therefore provide opportunity for chirality transfer upon cyclisation.

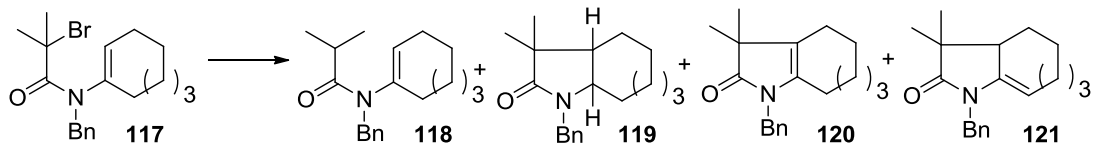
McDonagh has carried out the cyclisation of an inseparable mixture of tetrasubstituted enamide **245** and trisubstituted enamide **246** using both Me_6-Tren and TPA as ligands.[173] When treated with 30 mol% CuBr:TPA in toluene at reflux both enamides cyclised in a 5-*endo* fashion to yield lactams **247** and **248**. However

when treated with 30 mol% CuBr:Me_6-tren in DCM at room temperature lactam **249**, formed from the 4-*exo* cyclisation of **245** followed by elimination, was observed alongside **248**, and the 5-*endo* cyclisation product **247** was not observed (Scheme 3.3).[173] Both the 5-*endo* and the 4-*exo* products from the cyclisation of **245** contain stereocentres formed in the cyclisation process, therefore suggesting compounds of similar structure could be possible candidates for chirality transfer upon cyclisation.



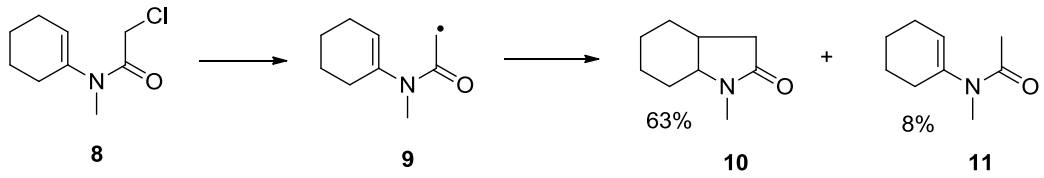
Scheme 3.3: Cyclisation of enamides 245 and 246. *Reagents and Conditions:* a) 0.3 eq. CuBr, 0.3 eq. TPA, toluene, reflux. b) 0.3 eq. CuBr, 0.3 eq. Me_6-tren, DCM, r.t.

The AGET ATRC conditions of Clark have also been shown to mediate the cyclisation of bromo enamides, giving a mixture of reduced (**118** and **119**) and oxidatively terminated products (**120** and **121**).[81]



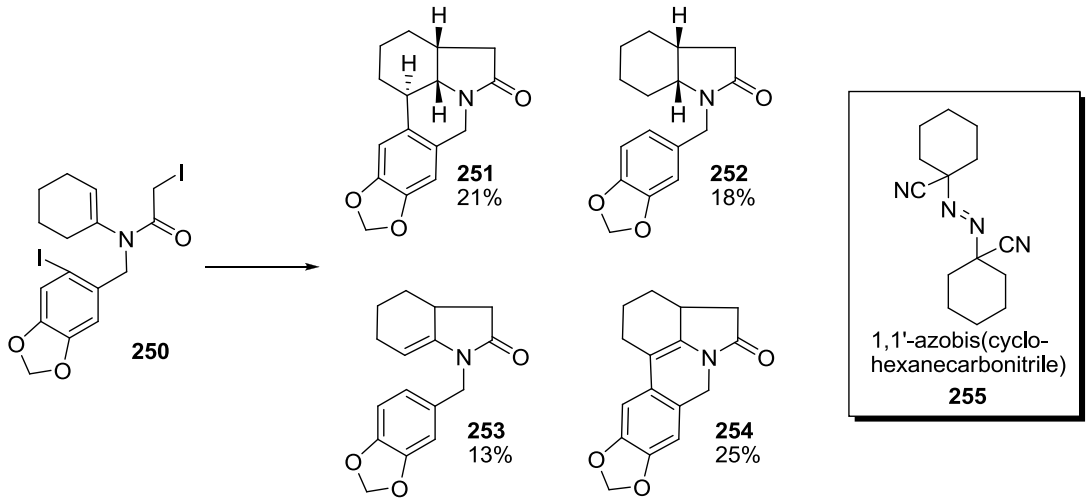
Scheme 3.4: $CuSO_4$/KBH_4 mediated 5-*endo* cyclisation. *Reagents and Condition:* 1 mol% $CuSO_4.5H_2O$, 100 mol% KBH_4, MeOH, r.t., 30 min.

Successful copper mediated conditions have not been reported for the cyclisation of primary α-halo enamides such as **209** and **214**, instead the more traditional tin mediated conditions must be used. Ishibashi has reported that 5-*endo-trig* cyclisation of α-chloroenamides can be mediated by Bu_3SnH to give 5-membered lactams.[23] Treatment of enamide **8** with Bu_3SnH in the presence of AIBN led to the 5-*endo* cyclisation product **10** in 63% yield along with the reduced non-cyclised compound **11** as a minor product (Scheme 3.5).



Scheme 3.5: Tin mediated cyclisation of *N*-vinylic α-chloroacetamides: *Reagents and conditions*: Bu_3SnH (1.1 eq.), AIBN (cat.) toluene, reflux.

1,1'-Azobis(cyclohexanecarbonitrile) (ACN) **255** has also been used as an initiator instead of AIBN and has been shown to lead to better conversions.[175] Ishibashi used the ACN initiator in the sequential radical cyclisation of **250**.[6]



Scheme 3.6: Sequential radical cyclisation of 250 initiated by ACN. *Reagents and Conditions:* 2.4 eq. Bu_3SnH, 5 eq. Bu_3SnF, 0.1 eq. ACN, toluene, reflux.

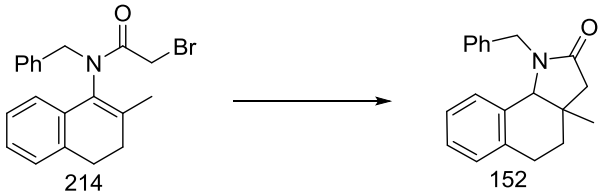
3.2 Results and Discussion

Due to the lack of precedent for the cyclisation of tetrasubstituted enamides we decided to first investigate the cyclisation of racemic mixtures to determine how easily the tetrasubstituted enamides underwent cyclisation, allowing us to determine suitable conditions for the reactions and to identify the products of the cyclisations.

3.2.1 Tin Mediated Cyclisations of α-Halo Enamides.

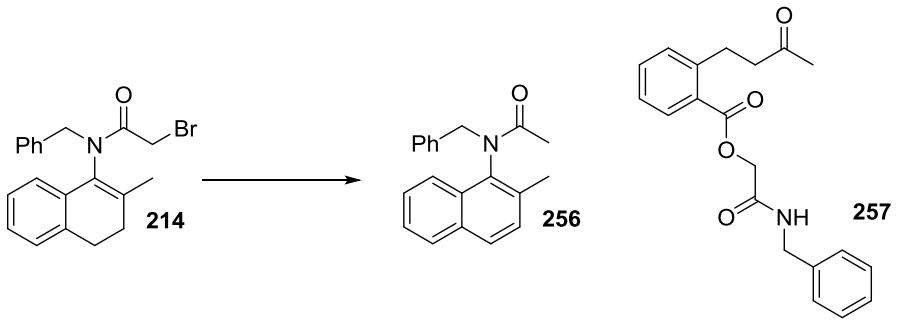
We first turned our attention to the methyl-tetralone analogues **209** and **214**. Calculations showed that enamide **209** had an estimated half life of 312 s at 110 ˚C, whereas bromide **214** had a significantly longer half life of 18.6 h at 80 ˚C or 39 mins at 110 ˚C. As Bu_3SnH mediated cyclisations of enamides are generally carried out at elevated temperatures for example in refluxing toluene, chirality transfer is much more likely in the cyclisation of **214** than **209**. We therefore chose to

investigate the Bu_3SnH mediated cyclisation of **214** first. A 0.12M solution of bromide **214** was treated with 1.5 eq. of Bu_3SnH and 0.2 eq. of ACN at reflux. After 22 hours there was still a large amount of starting material present so a further 1.5 eq. of Bu_3SnH and 0.2 eq. of ACN were added and the reaction refluxed for a further 2 hours.



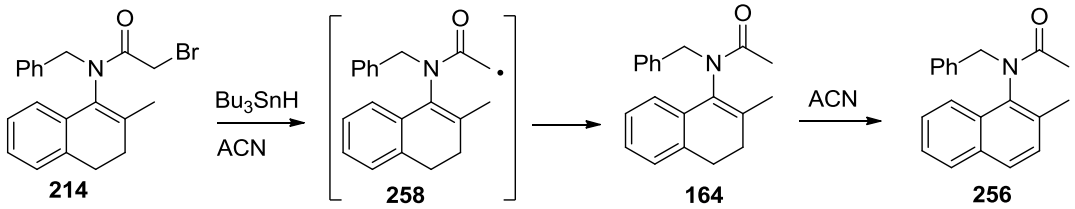
Scheme 3.7: Predicted product from Bu_3SnH mediated radical cyclisation of 214. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux.

It was apparent that the reaction was proceeding slowly under these conditions due to significant amounts of starting material remaining and that these conditions (>39 mins at 110 ˚C) would NOT be suitable for efficient asymmetry transfer in the cyclisation of **214**. It appeared that any radical chain process was inefficient and significant amounts of initiator was required. In fact a further 0.2 eq. of ACN was added, in two further portions after a further 4 and 6 hours before starting material was not detected by tlc. The reaction mixture was then concentrated in *vacuo* and partitioned between acetonitrile and hexane and the acetonitrile phase concentrated to give the crude product.



Scheme 3.8: Attempted cyclisation of tetrasubstituted enamide 214. *Reagents and conditions:* Bu_3SnH, ACN, toluene, 110 ^oC, 18h, syringe pump.

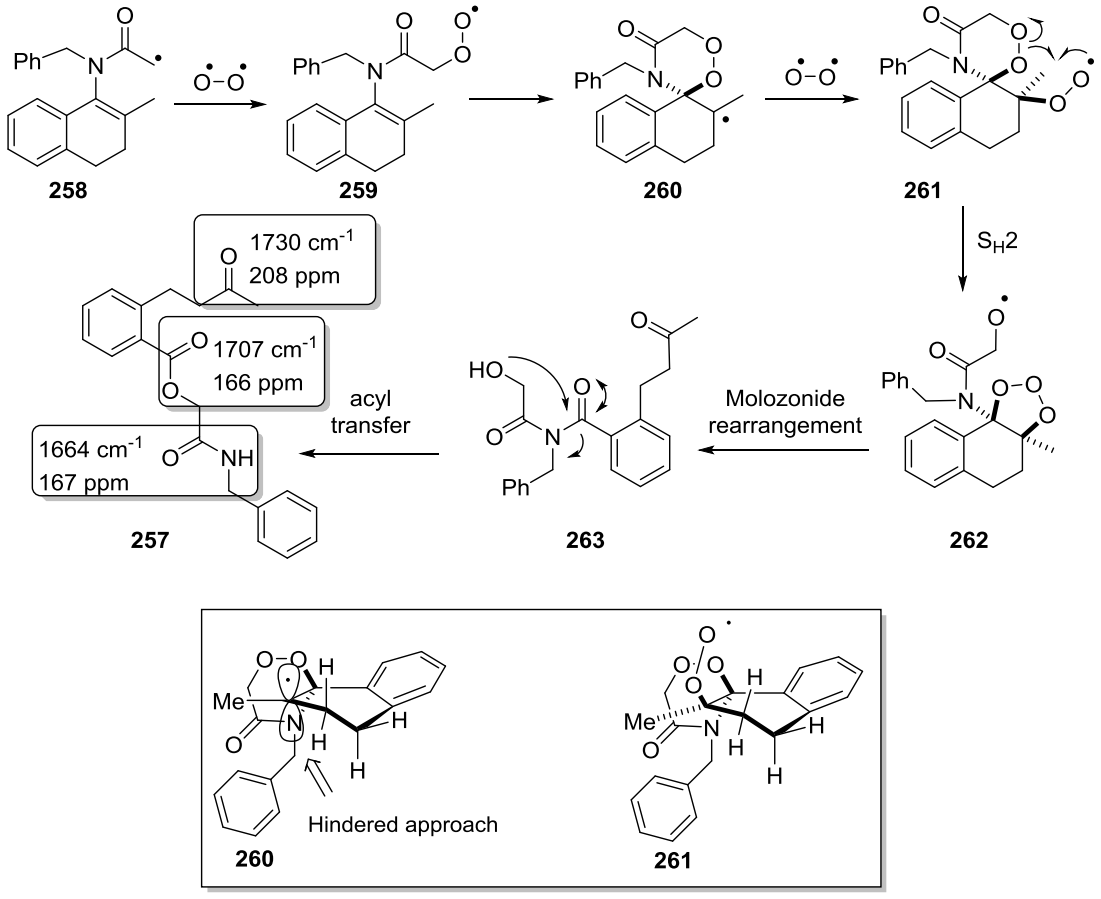
The 400 MHz ^1H NMR of the crude reaction mixture was complicated indicating a number of products, but importantly no cyclised product **152** could be identified. Although no products could be isolated pure, the naphthalene **256** and oxidatively cleaved product **257** were identified in the reaction mixture based upon previous characterization of these compounds and comparison of their reported ^1H spectra, Scheme 3.8.[157] The naphthalene **256** was thought to be formed by initial radical formation **258** via homolysis of the C-Br bond and reduction by Bu_3SnH without cyclisation, followed by ACN mediated oxidation / aromatisation of the tetralene ring to the naphthalene. This would explain why such a large amount of initiator was needed in the reaction.



Scheme 3.9: Formation of naphthalene 256. *Reagents and conditions:* Bu_3SnH, ACN, toluene, 110 ^oC, 18h.

Mechanistically is postulated that **257** was formed *via* the mechanism shown in Scheme 3.10. 5-*Endo* cyclisation of radical **258** may be hindered due to the

significant steric crowding from the alkenyl substituents on moving to planarity, which could lead to alternative reaction manifolds for radical **258** in the reaction mixture. Reaction of **258** with advantageous O_2 would likely furnish the peroxy radical **259** which after 6-*exo* cyclization to give **260** could be trapped by a second molecule of O_2 to give **261**. Cyclisation of **259** is likely to be more facile than **258**. A model of the intermediate tertiary radical **260** indicates attack of the second molecule of oxygen is likely to take place at the least hindered face giving **261**.



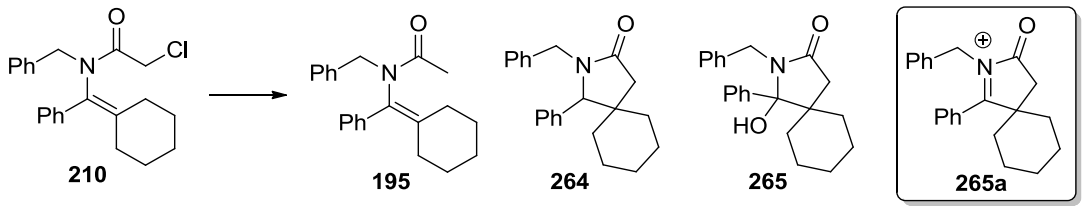
Scheme 3.10: Speculated mechanism for the formation of 257.

At this point we speculate that the oxygen radical in **261** is close enough to the second peroxide bond for an intramolecular homolytic substitution to occur which would lead to molozonide **262**. Collapse and reduction of the molozonide by Bu_3SnH would initially lead to the keto-imide **263** which after acyl transfer would

furnish the observed ketone **257**. The same rearrangement was also observed for cyclisation of the iodo analogue **165**.[157]

As the cyclisation of the both the bromo- and the iodo analogues **214** and **165** had been unsuccessful we chose not to attempt the cyclisation of the chloro- analogue **209**, presuming it would give similar results. Instead we turned our attention to the cyclisation of α-chloroenamides not based upon methyltetralone. While structure **210** was known to have too low a barrier to rotation around the N-C alkenyl bond for the separation of atropisomers at room temperature to be accomplished, we investigated its reaction with Bu_3SnH in order to gain an understanding of the scope and limitation of cyclisations onto hindered enamides.

A 0.02M solution of **210** in toluene was treated with 1.5 eq. of Bu_3SnH and 0.2 eq. ACN and refluxed for 26 hours. The reaction mixture was then concentrated in *vacuo*, partitioned between acetonitrile and hexane and the acetonitrile phase concentrated to give the crude product.

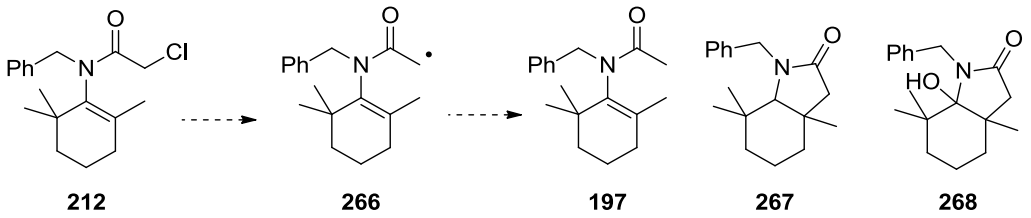


Scheme 3.11: Bu_3SnH mediated cyclisation of 210. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux 26 h.

The reaction did not go to completion, with some starting material still observed in the crude reaction mixture (21%). Three other products were also identified; the reduced pre-cyclised product **195**, the reduced 5-*endo* cyclisation product **264** and the oxidatively terminated 5-*endo* cyclisation product **265**. The ratio of the products

was determined from the 300 MHz ^{1}H NMR as 1 : 1.44 : 1.28 : 0.79 (**210** : **195** : **264** : **265**) with the non-cyclised reduced product **195** as the major product. The ratio of **195/[264** + **265]** indicates that the rate constant of cyclisation is in the order of 1 x 10^6 $M^{-1}s^{-1}$ (assuming the rate constant for reduction of an α-amide radical with Bu_3SnH at 383K is 9.3 x 10^6 $M^{-1}s^{-1}$).[176,177] Mechanistically, the cyclisation has been terminated both reductively **264** (presumably by conventional reduction of the radical by Bu_3SnH) and oxidatively **265**. Oxidative termination of 5-*endo* cyclisation reactions mediated by Bu_3SnH is well known and is thought to proceed via the acyl iminium ion,[153] normally by loss of a proton to give an alkene. In this case elimination is not possible and the reaction is terminated by trapping with water (either by advantageous moisture or upon work-up). Unfortunately the cyclisation of **210** does not result in a stereocentre formed in the cyclisation step and is therefore not a suitable candidate for chirality transfer. It does however show that Bu_3SnH mediated cyclisation of tetrasubstituted α-halosubstrates is possible at synthetically useful rates.

We next investigated the cyclisation of enamide **212**, which, should it cyclise in the same manner as **210** to give 5-*endo* products **267** and **268** would form a chiral centre in the cyclisation step. Enamide **197**, a model for the radical **266**, was found to have a half-life of 128 years at room temperature or 10.6 days at 100 ^oC suggesting that even prolonged heating over 24 hours in toluene at reflux should not lead to significant racemisation.



Scheme 3.12: Possible outcome of Bu_3SnH mediated cyclisation of 212. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux 22 h.

Disappointingly the treatment of **212** with Bu_3SnH and ACN resulted in 100% conversion to the reduced precyclised compound **197**. Presumably the hindered nature of **212** and the corresponding radical **266** slows the rate of the cyclisation significantly so that reduction of radical **266** dominates.

3.2.2 Copper mediated cyclisations of enamides with tertiary halides.

Enamides of general structure **204** and **205** are known to undergo copper mediated cyclisations.[5] These cyclisations can generally be achieved at room temperature and this would provide a significant advantage when attempting asymmetry transfer in reactions of atropisomers. We initially chose to investigate the Cu(I)X mediated radical-polar crossover reactions of structures **229** and **231**.

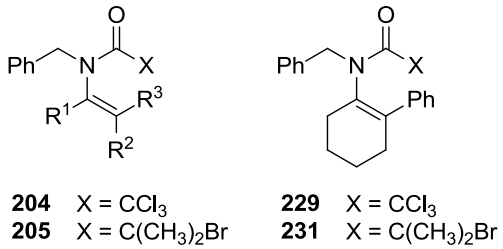
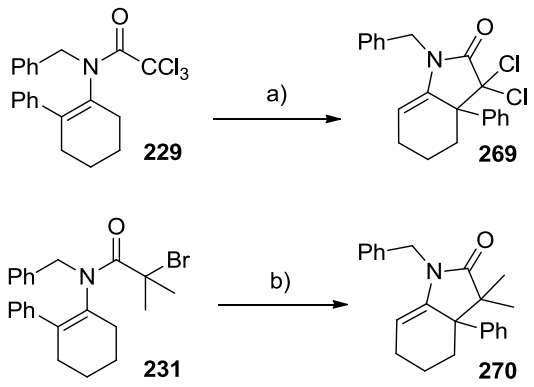


Figure 3.2: Enamides for copper mediated cyclisation.

Based upon the conditions used by McDonagh for the cyclisation of **245** and **246** (30 mol% Cu(TPA)Br or 100 mol% Cu(TPA)Cl in toluene at reflux, and 30 mol% Cu(Me_6-Tren)Br or 100 mol% Cu(Me_6-Tren)Cl in DCM at room temperature)[173] we chose four sets of conditions (two temperatures and two solvents) for our initial investigations altering one variable at a time (Table 3.1) and applied these to the cyclisation of enamides **229** and **231**.



Scheme 3.13: Copper Mediated Cyclisation of enamides 229 and 231. *Reagents and Conditions:* a) 100 mol% CuCl, 100 mol% ligand, solvent, 24 h. b) 30 mol% CuBr, 30 mol% ligand, solvent, 24 h.

Entry	Substrate	Copper Ligand	Solvent	Temp	Products	Product ratio[a]
1	**229**	Me_6-tren	DCM	r.t.	**269 + 229**	1:2.9
2	**229**	TPA	DCM	r.t.	**269 + 229**	1:3.4
3	**229**	TPA	Toluene	r.t	**269 + 229**	1:2
4	**229**	TPA	Toluene	110 ^oC	**269**[b]	1:0
5	**231**	Me_6-tren	DCM	r.t.	No reaction	N/A
6	**231**	TPA	DCM	r.t.	No reaction	N/A
7	**231**	TPA	Toluene	r.t.	No reaction	N/A
8	**231**	TPA	Toluene	110 ^oC	**270 + 231**	2.6:1

Table 3.1: Cyclisation conditions and products for compounds 229 and 231. [a] Taken from crude NMR. [b] 100% conversion by crude NMR

In contrast to the results of McDonagh, the 4-*exo* product was not observed in any of the cyclisations. Disappointingly low yields of **269** from **229** were obtained at room temperature and because copper mediated cyclisations of trichloroacetamides are generally faster than those of monobromoacetamides it came as no surprise to find that there was no reaction for derivative **231** under these conditions. With the trichloro substrate **229** the 5-*endo* product **269** was observed under all conditions, although TPA in toluene at reflux (Table 3.1, entry 4) were the only conditions that gave full conversion to product. For compound **231** only TPA, in toluene at reflux yielded any of the 5-*endo* product **270** (Table 3.1, entry 8). The X-ray structure of **229** (Chapter 2, Figure 2.40) showed a (*Z*)-amide configuration in the solid state (as opposed to the normal (*E*)-configuration). This may have a bearing on the need for high temperatures for successful reaction of these substrates, as the (*E*)-configuration is the only one that can lead to successful cyclisation.

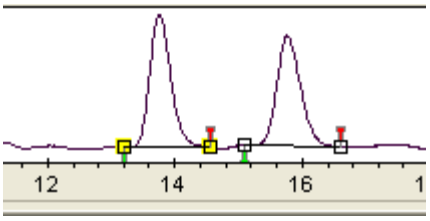


Figure 3.3. Chiral HPLC trace of compound 269.

While the cyclisation of enamides **229** and **231** proceeded successfully, and the enantiomers of one product **269** could be separated by chiral HPLC on a Chiracel AD column (Figure 3.3), these substrates **229** and **231** were not suitable candidates for investigating chirality transfer during their cyclisations. As discussed in Chapter 2 (section 2.2.4), it was not possible to separate the atropisomeric starting materials **229** and **231** at room temperature by chiral HPLC due to relatively low barriers to rotation. Cyclisation of these substrates did however identify suitable conditions for the further study on copper mediated cyclisations of tetrasubstituted enamides; CuX, TPA, toluene, at reflux.

These conditions were subsequently applied to the cyclisation of enamides **232** – **235**. These substrates would not lead to any chirality transfer during cyclisation, as no chiral centre would be formed in the cyclisation step, however they would provide us further insight into the cyclisations of tetrasubstituted enamides. All four of these substrates exhibited a doubling up of peaks in the ^{1}H NMR, indicating the presence of both the *E*- and *Z*- amide rotamers in solution (see chapter 2, section 2.2.4.2). As for **229** this could potentially hinder the cyclisation of these substrates as in the *Z*-rotamer the halogen is positioned to far away from the alkene to allow cyclisation. Pleasingly heating the samples to 100 ^{o}C led to coalescence of the two sets of signals to a single sharp set, indicating rapid interconversion of the rotamers

at high temperatures, suggesting that this should not be a problem when carrying out the cyclisation in refluxing toluene.

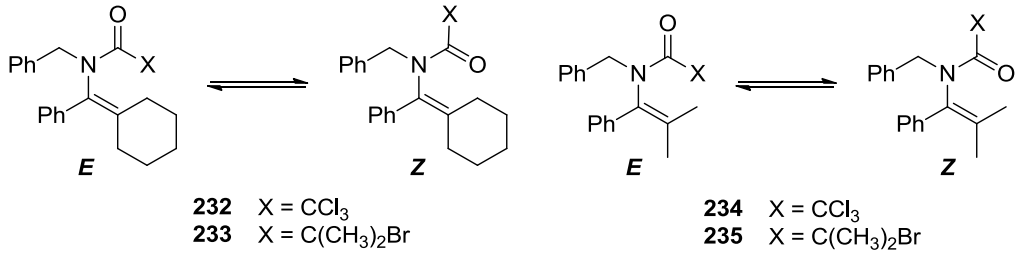
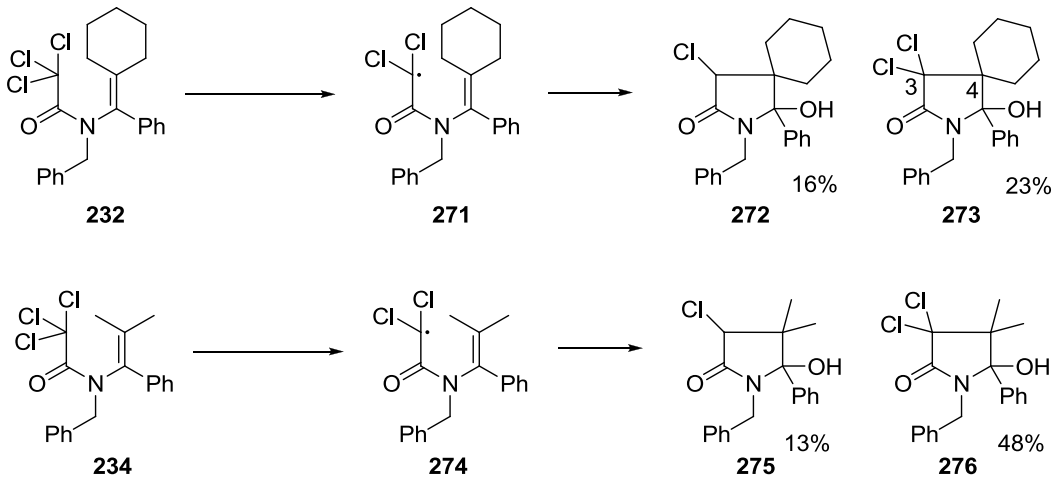


Figure 3.4: Atropisomeric enamides.

Trichloroenamides **232** and **234** were treated with 1 eq. CuCl and 1 eq. TPA in refluxing toluene for 2 hours followed by a simple work-up procedure of filtration through a silica plug. In both cases two hydroxyl terminated products were isolated (**272, 273** and **275**, **276** respectively, Scheme 3.14). Unlike the cyclisation of enamides **245** and **246** the intermediate acyl iminium ion cannot eliminate to give the unsaturated product, instead the products are derived from trapping of the intermediate acyl iminium ion with water (as observed for the Bu_3SnH mediated cyclisation of **210**, Scheme 3.11). In addition to the expected products **273** and **276** containing an α-gem dichloro group two monochloro structures **272** and **275** were obtained. Stick models of **273** and **276** indicate that the gem-dichloro substituents at C-3 are eclipsed by the carbons attached at C-4. It is postulated that facile reduction of one of the chlorine atoms occurs to relieve this steric strain between the gem-dichloride and gem-dimethyl groups. This is likely to occur by a second atom transfer from Cu(TPA)Cl giving an α-amide radical which is then reduced by the solvent. It was pleasing to see that no starting material was left in the reaction mixture, showing that the existence of the *Z*-amide rotamer in the starting material did not hinder the cyclisation at 110 ˚C.



Scheme 3.14: Copper mediated cyclisation of tetrasubstituted trichloroenamides. *Reagents and Conditions:* 100 mol% CuCl, 100 mol% TPA, toluene, reflux, 2 h

Lactams **272** and **275** were obtained as single diastereomers and nOe experiments were carried out to determine the stereochemistry. **272** was tentatively assigned with the chloro- and hydroxyl- groups *cis* to one another (Figure 3.5), however the data for **275** proved inconclusive and it was not possible to assign the stereochemistry.

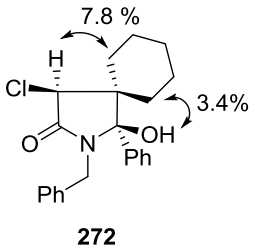
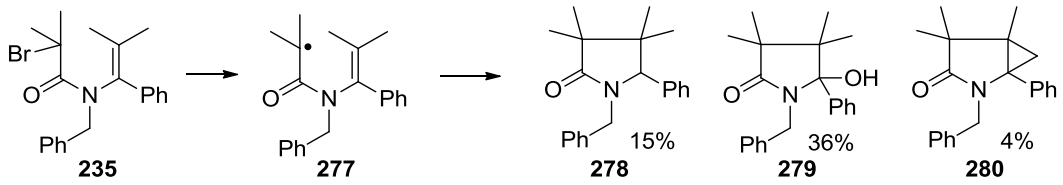


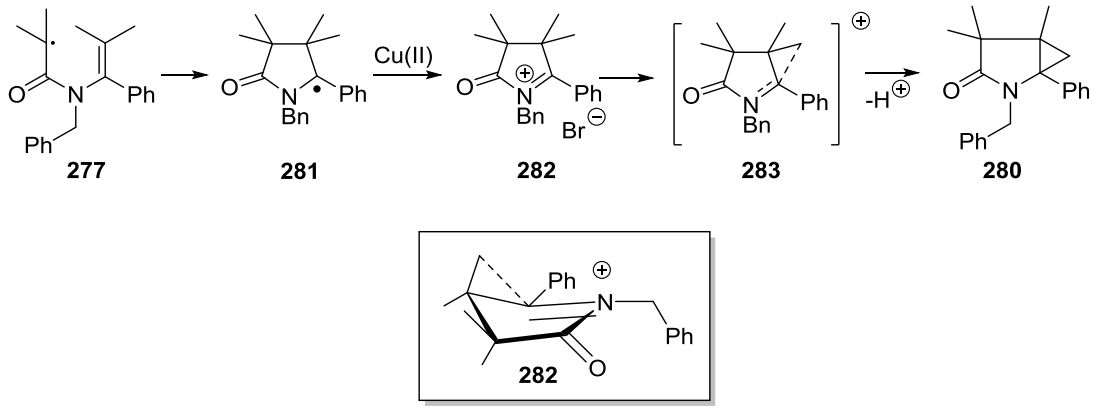
Figure 3.5: nOe data and assigned stereochemistry of 273

We next looked at the cyclisation of bromo analogues **233** and **235**. Treatment of enamide **235** with 0.6 eq. CuBr and 0.6 eq. TPA in refluxing toluene yielded three products **278**, **279** and **280** in 15%, 36% and 4% yields respectively. The major product **279** is thought to arise from trapping of the acyl iminium ion **282** with H_2O as before, while the reduced product **278** may arise from abstraction of a hydrogen atom from the solvent.



Scheme 3.15: Copper mediated cyclisation of enamide 235. *Reagents and Conditions:* 0.6 eq. CuBr, 0.6 eq. TPA, toluene, reflux, 24 h.

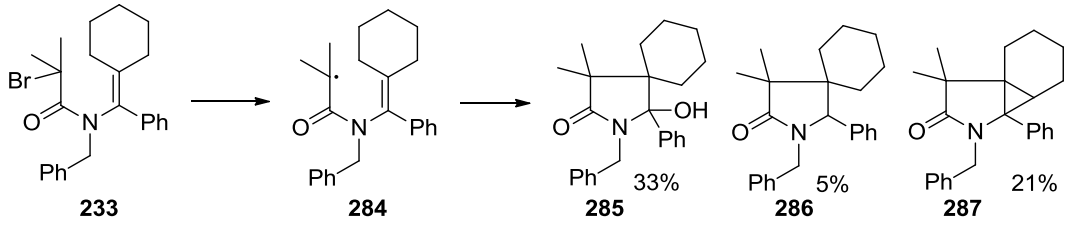
Cyclopropyl compound **280** was unexpected and was isolated in very low yield, however its formation deserves comment. Trapping of an alkyl group to give a cyclopropane by loss of a proton during a 1,2-migration is rare.[178] Nevertheless it is possible that within the acyl imimium ion intermediate **282** there is a significant steric clash between the two different gem-dimethyl groups (as in **273**) and that in order to relieve these steric clashes a twisting of the ring occurs, placing the migrating carbon close in space to the carbon of the acyl iminium ion **283** initiating the process (Scheme 3.16).



Scheme 3.16: Formation of cyclopropyl product 280.

Cyclisation of enamide **233** under the same conditions yielded the same set of products, the hydroxyl product **285** (33%), the reduced product **286** (5%) and the cyclopropyl product **287** (21%). However in this case significantly more of the

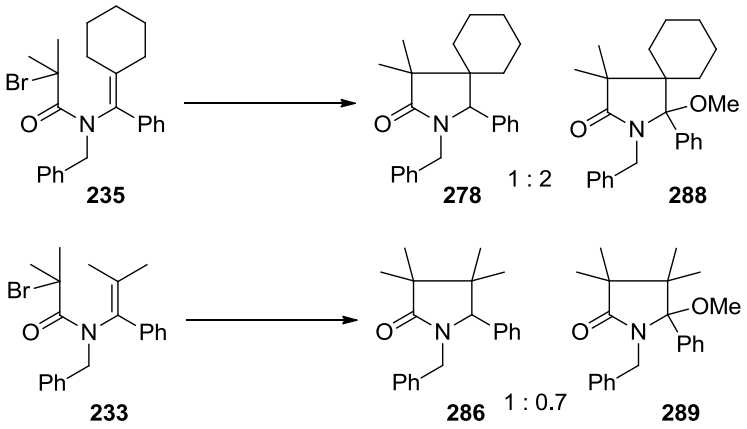
cyclopropyl product **287** was isolated than in the analogous reaction of **235** (21% as opposed to 4%). Presumably, the more electron rich nature of methylene group compared to the methyl group is responsible for the greater yield of migration product **287.**



Scheme 3.17: Copper mediated cyclisation of enamide 233. *Reagents and Conditions:* 0.6 eq. CuBr, 0.6 eq. TPA, toluene, reflux, 24 h.

It was also possible to mediate 5-*endo* cyclizations of **233** and **235** using the AGET ATRC protocol[81] with $CuSO_4.5H_2O$ and KBH_4. In this instance the KBH_4 acts in a dual role as catalyst generator and acyl iminium ion reducing agent. It was hoped that inclusion of a reducing agent (KBH_4) might suppress termination by oxidation and migration and increase the yield of **278** and **286**. Hence, **235** was reacted with with 2.5 mol% $Cu(TPA)SO_4$ and 1 equivalent of KBH_4 in MeOH for 30 min at room temperature. The reductively terminated **278** was identified in the crude NMR in a 1:2 ratio with another product tentatively assigned as the solvent trapped methoxy terminated **288** based upon mass spec and a characteristic methoxy peak at ~3.1 ppm in the ^{1}H NMR. Unfortunately the crude reaction mixture proved more complex than the Cu(TPA)Br mediated cyclisation and it was not possible to isolate the products. The cyclisation of **233** under identical conditions gave similar results. Again the crude reaction mixture was complex, but the corresponding products **286** and **289** were identified in a 1:0.7 ratio in the crude ^{1}H NMR. As with **288**, the methoxy terminated product **289** was assigned based upon mass spec and the characteristic

methoxy peak at ~3.1 ppm in the ^{1}H NMR. Despite the presence of a number of unidentified products, the cyclopropyl products **280** and **287** were not observed in either reaction. It is likely that in comparison to the standard Cu(TPA)Br process the nucleophilic solvent (MeOH) and stoichiometric reductant employed provide a rapid trap of the intermediate acyl iminium ion shutting down the methyl migration pathway.



Scheme 3.18: Cyclisation of enamides 233 and 235 under AGET ATRC conditions. *Reagents and Conditions:* 2.5 mol% $CuSO_4.5H_2O$, 2.5 mol% TPA, 100 mol% KBH_4, methanol, r.t.

3.2.2.1 Copper Mediated Cyclisations of Enamides with High Barriers to Rotation.

Both enamides **197** and **164** were separable by chiral HPLC and had high barriers to rotation of 31.0 kcal mol^{-1} and 27.5 kcal mol^{-1} respectively. Based upon the barriers calculated for **197** and **164** we can assume that the halogenated analogues **236** and **237** would also have high barriers to rotation. Cyclisation of both enamides **236** and **237** would also lead to the generation of a chiral centre in the cyclisation step making them ideal candidates for investigating chirality transfer upon cyclisation. The tertiary nature of the halides would make them ideal substrates for Cu(TPA)X mediated cyclisations.

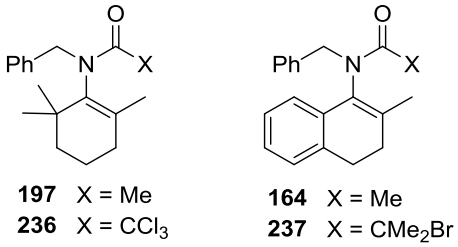
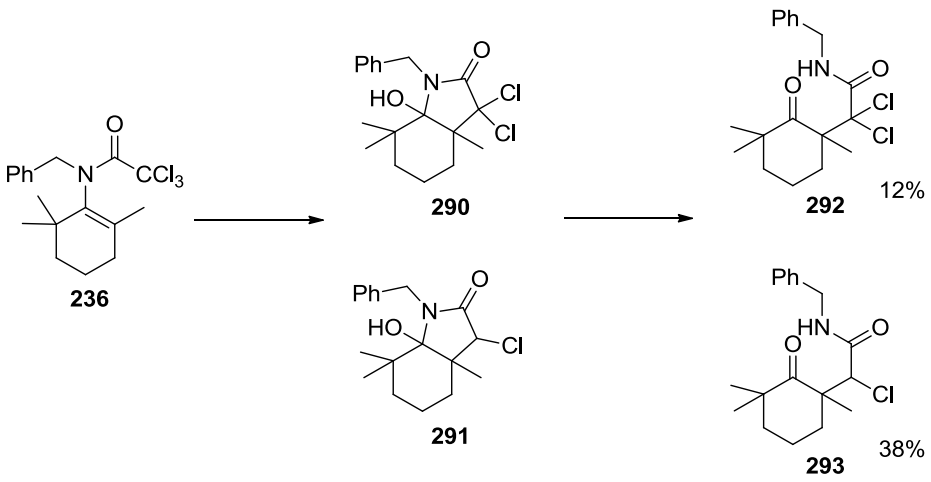


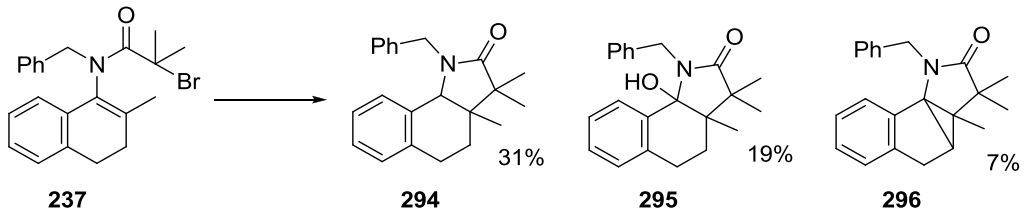
Figure 3.4: Tetrasubstituted enamides separable by chiral HPLC.

Enamide **236** was treated with CuCl and TPA in reluxing toluene. Based upon the products obtained in the cyclisation of the related enamides **232** and **234** (Scheme 3.14, page 114), the expected products were **290** and **291**, however these were not observed. Instead the ring opened products **292** and **293** were isolated in 12% and 38% respectively, along with 25% recovered starting material. The more hindered nature of the starting material **236** is likely to slow down the rate of cyclisation therefore it is not surprising that the reaction did not go to completion. Presumably the products **292** and **293** are formed by ring opening of the cyclised products **290** and **291** to relieve strain caused by steric hinderance. The chiral centre formed in the cyclisation step is still present in the final products, so it is possible that chirality transfer could still occur, however at the time of writing we have not investigated this.



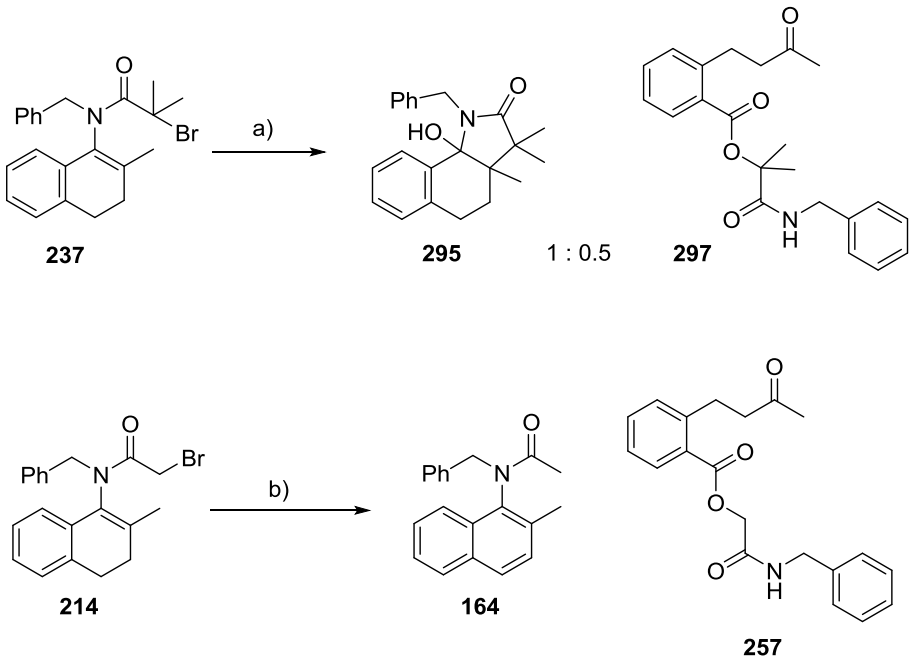
Scheme 3.19: Copper mediated cyclisation of enamide 236. *Reagents and Conditions:* 1 eq. CuCl, 1 eq. TPA, toluene, reflux, 2 h.

Enamide **237** was cyclised twice under slightly different conditions providing different results. Heating **237** with 60 mol% Cu(TPMA)Br in anhydrous degassed toluene (freeze/pump/thaw technique) at reflux for 15 hours hours led to three products **294**-**296** in 31%, 19%, and 7% yields respectively. These are the expected products based upon the results of the related cyclisations of **233** and **235**, (Section 3.2.2, page 109). Hence, cyclisation was terminated reductively **294**, oxidatively by trapping with water **295** and by alkyl migration to give the cyclopropyl derivative **296**. In this case it is interesting to note that 1,2-migration of the more electron rich methylene group is observed rather than the methyl group. The significant amount of hydroxyl terminated product **295** observed (19%) and the fact that anhydrous toluene was used in the reaction suggests that the source of the hydroxyl group is likely to be from water provided upon work-up of the reaction. nOe experiments of **294** and **295** allowed tentative assignment of *cis* stereochemistry at the ring junction in both compounds.



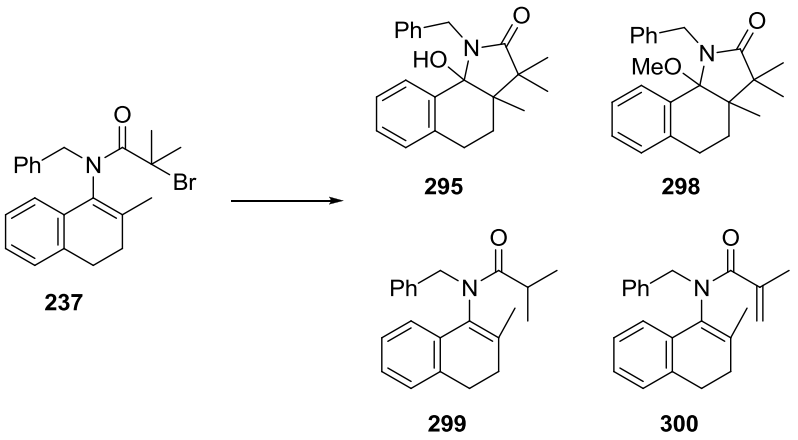
Scheme 3.20: Copper mediated cyclisation of 237. *Reagents and Conditions:* 0.6 eq. CuBr, 0.6 eq. TPA, toluene, reflux, 15 h.

If the reaction was repeated without the solvent being thoroughly degassed then significant amounts of the ring-cleaved structure **297** were obtained alongside the hydroxyl terminated product **295**. There was a significant amount of starting material left after 24 h, and therefore a further 0.6 eq. of CuBr and 0.6 eq. of TPA were added and the reaction refluxed for a further 20 h to try and push the reaction to completion. After 20 h there was no starting material left and the two products **295** and **297** were still present in the same ratio as they were after 24 h. (**295**:**297** = 1:0.5). The by-product **297** is structurally similar to that observed **257** in the attempted cyclisation of **214** and we propose that it is formed *via* the same mechanism (see Scheme 3.8).



Scheme 3.21: Generation of by-products in cyclisations of methyltetralone based enamides. *Reagents and Conditions:* a) 1.2 eq. CuBr, 1.2 eq. TPA, toluene, reflux, 15 h. b) Bu_3SnH, AIBN, toluene, 110 ^oC, 18h, syringe pump.

We also attempted the cyclisation of **237** using the AGET ATRC conditions. As before we expected that the reactions would lead to a methoxy terminated heterocycle **298** and that the cyclopropyl terminated **296** would be absent (See Scheme 3.18). Disappointingly upon treatment of **237** with 2.5 mol% $Cu(TPA)SO_4.5H_2O$ and 100 mol% of KBH_4 in MeOH at room temperature for 8 hours a complex mixture of products was obtained. Due to the complexity of the mixture it was not possible to isolate any of the products pure, however we tentatively assigned the presence of structures **295**, **298-300** based on key peaks in the ^1H NMR and mass spec data.



Scheme 3.22: Attempted cyclisation of enamide 237 under AGET ATRC conditions. *Reagents and Conditions:* 2.5 mol% Cu(TPA)SO_4.5H_2O, 100 mol% of KBH_4, MeOH, r.t., 8 h.

3.2.3 Chirality Transfer in Radical Cyclisations

The Cu(TPA)Br mediated cyclisation of **237** has the potential to proceed with chirality transfer; the two atropisomers can be partially resolved by chiral HPLC (although the barrier to rotation has not been calculated), and the three cyclisation products **294** – **296** have a chiral centre formed in the cyclisation step of the reaction. We therefore sent a sample of the enamide **237** to our collaborators in the Dennis Curran research group in Pittsburg in order to separate the atropisomers on a preparative scale by HPLC and use the enantiomerically enriched samples **237** in a cyclisation reaction to investigate the possibility of asymmetry transfer. In addition we sent authentic racemic samples of each of the cyclisation products **294 – 296** as well as the achiral ring-opened tricarbonyl derivative **297** so these could be resolved to facilitate enantiomeric excess determination after cyclisation. The three enantiomeric cyclisation products **294 – 296** could all be resolved on a Whelk-O chiral HPLC column. Pleasingly a co-injection of all three racemic cyclisation products along with structure **297** indicated that each component of the mixture

could be resolved (Figure 3.5), meaning that it should be a relatively simple task to assess any chirality transfer following cyclisation of an enatiomerically enriched sample of **237**.

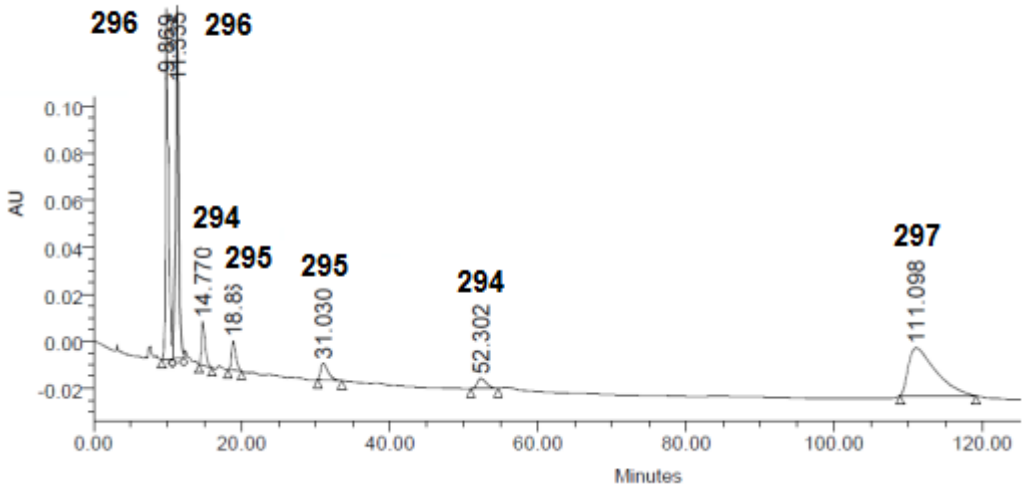


Figure 3.6: Chiral HPLC trace of co-injection of the products from the cyclisation of 237.

Unfortunately the cyclisation of the enantiomerically enriched enamide resulted in a racemic mixture of products, with no chirality transfer observed. The barrier to rotation of enamide **237** had not previously been measured, however based on previous results we predicted the barrier to be >29.3 kcalmol^{-1}. Other methyl tetralone enamides with smaller acyl substituents gave high barriers to rotation >27.5 kcalmol^{-1} (see compounds **164**, **209** and **214** numbers, page 92), and increasing the size of the acyl group had been shown to result in an increase in the barrier to rotation (see section 2.1.1.1, page 58).

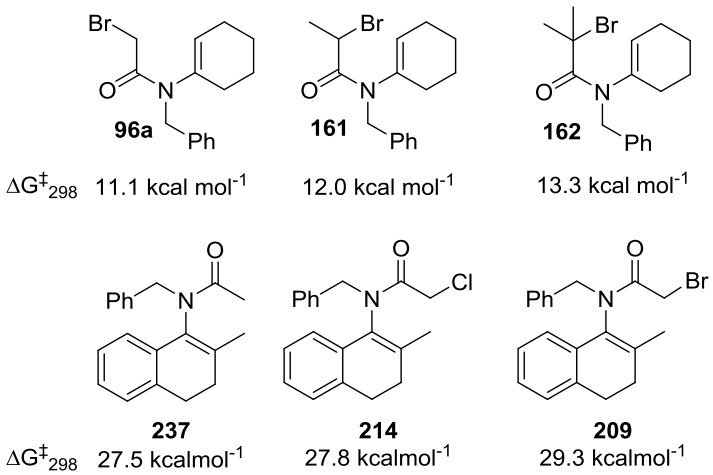


Figure 3.7: Previous calculated barriers to rotation.

However, the barrier to rotation was subsequently measured to be significantly lower than expected at 25.6 kcalmol^{-1}, giving a half life of only 0.1 hours at 80 ^{o}C, and therefore unlikely to result in any chirality transfer under our cyclisation conditions of 15 hours at 110 ^{o}C. It appears that the high level of steric hinderance about the N-alkenyl bond resulting from the large acyl group and the highly substituted enamide causes the enamide to adopt predominantly the *Z* rotamer, moving the large bromoisobutyryl group away from the n-alkenyl bond, and hence reducing the steric clashing and lowering the barrier to rotation. Previous tetrasubstituted enamides with large acyl groups were shown to adopt both the *E* and *Z* rotamers rather than the expected *E* rotamer (see section 2.2.4.2.3, page 89-91). The methyl tetralone enamides have been shown to be more hindered so it is not surprising that in this case the enamide predominantly adopts the Z rotamer, resulting in the lower barrier to rotation.

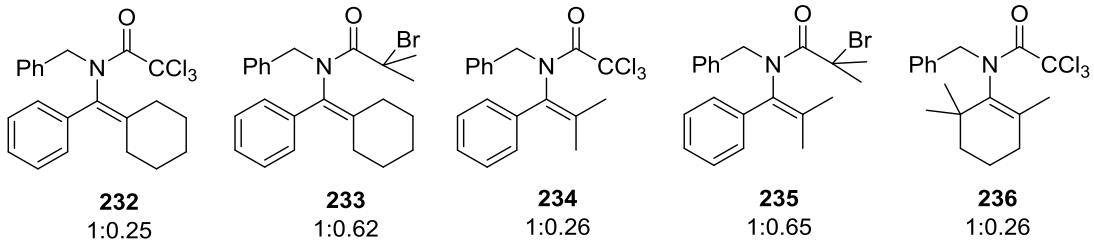
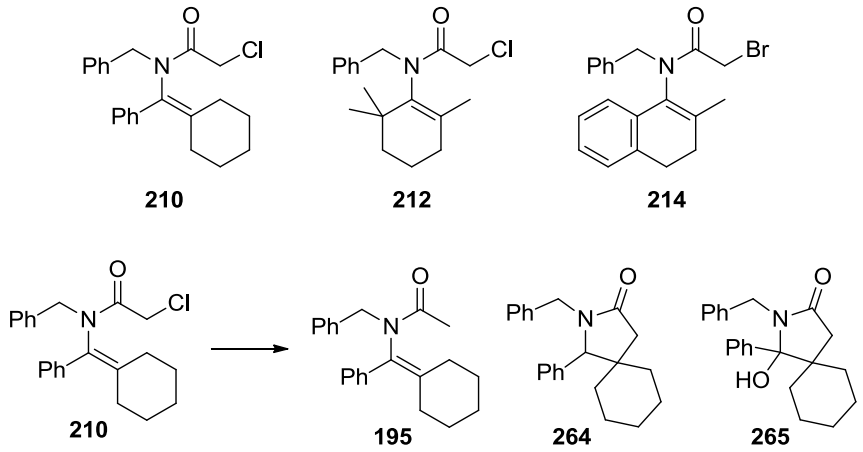


Figure 3.8: Enamides occupying both *E* and *Z* rotamers. *E* and *Z* rotatmers not assigned.

3.3 Conclusions

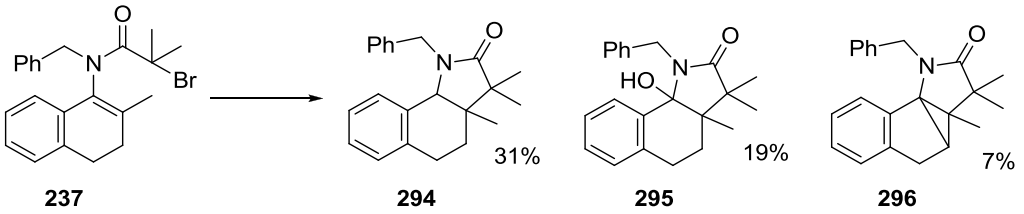
A number of tetrasubstituted enamides have been subjected to both Bu_3SnH and copper mediated cyclisation conditions with varying results. Primary α-halo enamides **210**, **212** and **214**, were treated with Bu_3SnH and ACN, and unfortunately only **210** yielded any cyclised products. The major product was the precyclised reduced product **195,** however the reductively terminated **264** and the oxidatively terminated **265** were also observed alongside recovered starting material. In the attempted cyclisations of the more hindered enamides **212** and **214** there was no evidence of any cyclised products, instead **212** yielded solely the reduced compound **197** and **214** gave the reduced naphthalene **256** and oxidatively cleaved product **257**.



Scheme 3.23: Bu_3SnH mediated cyclisations of α-halo enamides. *Reagents and conditions:* Bu_3SnH, ACN, toluene, 110 ^oC, 18h.

The copper mediated cyclisations of tetrasubstituted enamides with tertiary halides (**229** and **231** - **237**) were then investigated. Cyclisations of **229** and **231** showed Cu(TPA)X in toluene at reflux to be the most effective conditions, yielding the unsaturated products **269** and **270.** These conditions were used for the cyclisations of **232 – 235** yielding a range of both reductively and oxidatively terminated cyclised products (Scheme 3.14 - 3.16). When **236** was subjected to the same conditions the ring opened products **292** and **293** were obtained, presumably these were formed by ring opening of the cyclised products to release strain caused by steric hinderance. Cyclisation of **237** with Cu(TPA)Br led to the three cyclised products **294 – 296**, all of which have a chiral centre formed in the cyclisation step. The barrier to rotation of **237** is high enough to allow reasonable separation of the two atropisomers by chiral HPLC at room temperature, and therefore this reaction is suitable for investigating chirality transfer upon cyclisation. We have shown that the products can all be resolved by chiral HPLC. However although the barrier to rotation was high enough to allow reasonable separation of the atropisomers at room temperature, it was

significantly lower than expected, and not high enough to result in chirality transfer upon cyclisation.

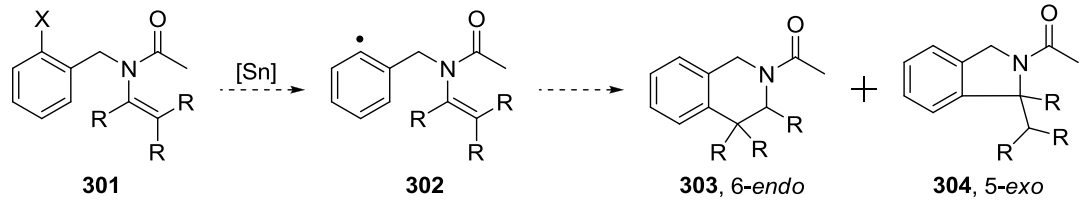


Scheme 3.24: Copper mediated cyclisation of 237. *Reagents and Conditions:* 0.6 eq. CuBr, 0.6 eq. TPA, toluene, reflux, 15 h.

4.0 Synthesis and Cyclisation of 2-Bromobenzyl Enamides

4.1 Introduction

In Chapter 3 we investigated the cyclisation of α-acyl radicals derived from enamides by copper and tin mediated methods to give a variety of lactam products. In theory, lactams can also be prepared by cyclisation of aryl radicals **302**, generated from the corresponding aryl halide **301**, onto enamide functionality. In this chapter we investigate the tin mediated 5-*exo* and 6-*endo* cyclisations of **302** to give nitrogen heterocycles **303** and **304**.

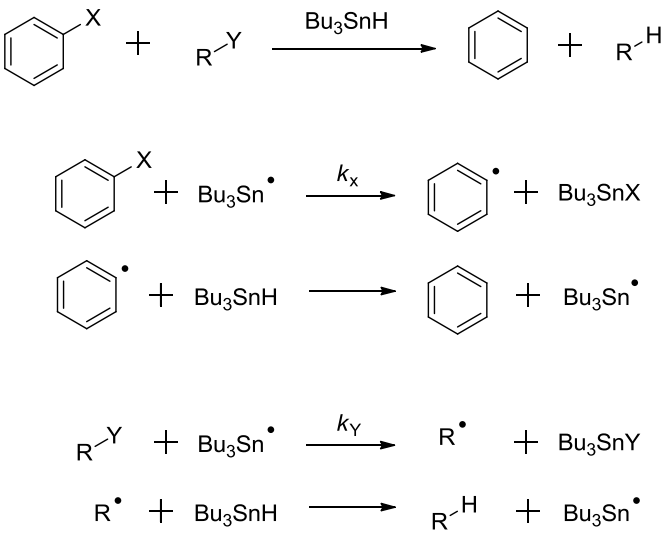


301 **302** **303**, 6-*endo* **304**, 5-*exo*

Scheme 4.1: Tin mediated cyclisation of enamides with aryl radicals.

4.1.1 Generation of Aryl Radicals

There are a number of methods for the generation of aryl radicals from aryl halides, of which the most common by far is the use of Bu_3SnH and AIBN.[179–181] In 1991 Curran reported the determination of rate constants for halide abstraction by a tributyltin radical from a series of aryl halides, comparing them to the more widely studied abstraction from sp^3-hybridised carbon atoms.[179] Relative reactivities were measured by competition reactions against a known standard of either 1-bromooctane or benzyl chloroacetate (Scheme 4.2).



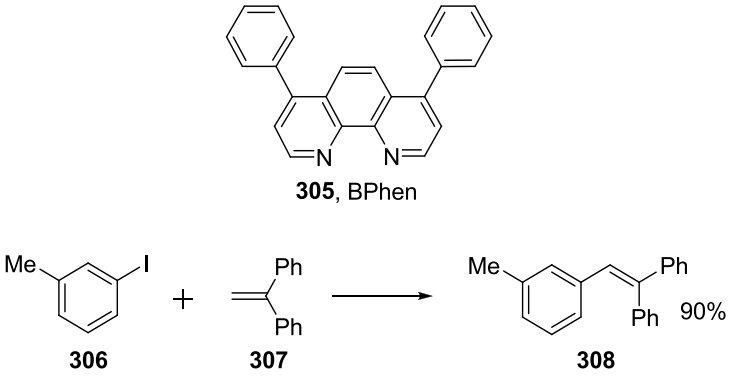
Scheme 4.2: Studies into halide abstraction from aryl halides by a tributyltin radical. R-Y = 1-bromooctane or benzyl chloroacetate.

The compounds were shown to have relatively high reactivity towards the tributyltin radical in view of the increased energies of sp^2 C-X bonds compared to sp^3 C-X bonds. Aryl iodides were shown to be as effective radical precursors as alkyl bromides, whilst aryl bromides were also shown to have a good level of activity towards the tributyltin radical and were shown to be more reactive than many classes of sp^3 C-X chloride and phenyl selenide precursors (Table 4.1, entry 1).[179] Within the series, differences in reactivity were small, with many of the trends consistent with a small polar effect on the halogen abstraction. This can be seen with the increasing reactivity from bromoanisole < bromoacetophenone < bromobenzonitrile (Table 4.1, entries 2/5/8, 3/6/9 and 4/7/10). The substituent position was also shown to have a small effect on the reactivity with increasing reactivity from para < meta < ortho substitution (Table 4.1, entries 2-4, 5-7, and 8-10). This trend was not thought to be steric in origin, but again reflecting the polar effect with bromine atoms closer to the inductive electron-withdrawing groups more reactive.[179]

Entry	Precursor	k (M^{-1} s^{-1}) (80 °C)
1	4-iodoanisole	8.8×10^8
2	4-bromoanisole	2.4×10^6
3	3-bromoanisole	4.0×10^6
4	2-bromoanisole	4.5×10^6
5	4-bromoacetophenone	3.9×10^6
6	2-bromoacetophenone	4.6×10^6
7	3-bromoacetophenone	1.6×10^7
8	4-bromobenzonitrile	6.8×10^6
9	3-bromobenzonitrile	9.0×10^6
10	2-bromobenzonitrile	1.6×10^7

Table 4.1: Studies into halide abstraction from aryl halides by a tributyltin radical.

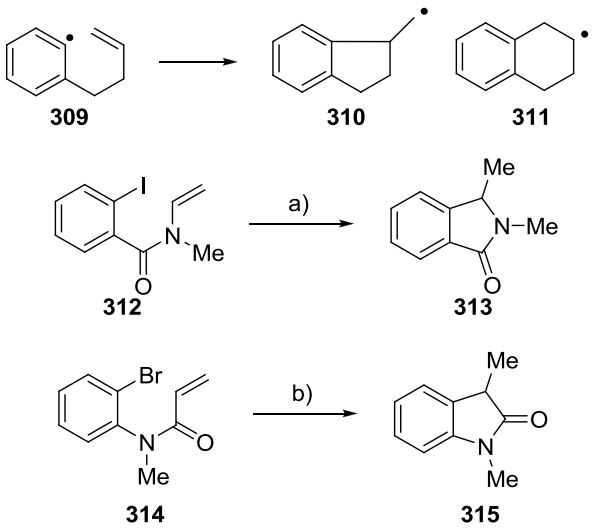
Effective replacements of tin hydrides for the generation of aryl radicals have included silanes such as tris(trimethylsilyl)silane[182,183] and metals such as samarium diiodide[184,185] as well as cathodic reduction[186] and irradiation under reducing conditions.[187] Potassium *t*-butoxide (KO*t*Bu) has also been shown to be able to generate aryl radicals; Wang reported a KO*t*Bu and bathophenanthroline (BPhen) **305** mediated radical arylation of polysubstituted alkenes with aryl halides (Scheme 4.3).[188] Arenediazonium salts can also be dissociated to aryl radicals and nitrogen by the reductive formation of an aryl diazenyl radical. Numerous methods have been used to generate such radicals and this area has been reviewed by Galli.[189]



Scheme 4.3 KO*t*Bu mediated radical arylation of poly substituted alkenes. *Reagents and Conditions:* KOtBu, BPhen, benzene, 110 °C.

4.1.2 Cyclisation of Aryl Radicals

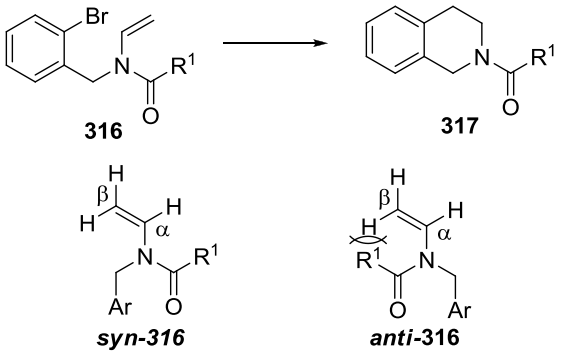
Cyclisations of aryl radicals are useful for formation of a range of different carbocyclic and heterocylic compounds.[148,181,190–193] Radicals of type **309** can cyclise in either an *exo* or an *endo* fashion with different selectivities observed dependent upon the substrates. In those systems with an alkene at the 5-position relative to the aryl radical centre, a 5-*exo trig* cyclisation is generally preferred over a 6-*endo trig* cyclisation. For example Bu_3SnH mediated cyclisation of enamide **312** and acryloylanilide **314** yielded only the five membered lactams **313**[194] and **315**[190] respectively (Scheme 4.4).



Scheme 4.4: 5-*exo trig* cyclisations of aryl radicals. *Reagents and Conditions:* a) Bu_3SnH, ACN, toluene, b) Bu_3SnH, AIBN, toluene.

In contrast, when the carbonyl group is exocyclic to the forming ring, as in the cyclisation of **316**, the reaction favours the 6-*endo-trig* pathway (Scheme 4.5).[181] This *endo* selectivity was postulated to occur due to the conformation of the precursor. Enamides of type **316** were shown to occupy the *syn* conformer in solution at room temperature irrespective of the nature of R^1.[181] In this conformer the

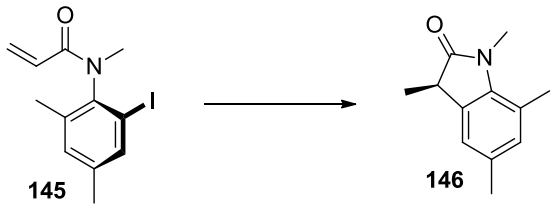
reacting radical is more proximate to the β-carbon leading to the observed *endo* selectivity.



Scheme 4.5: Favoured 6-*endo* cyclisation of aryl radicals. *Reagents and Conditions:* Bu_3SnH, ACN, toluene.

4.1.1 Chirality Transfer in Cyclisation of Aryl Radicals

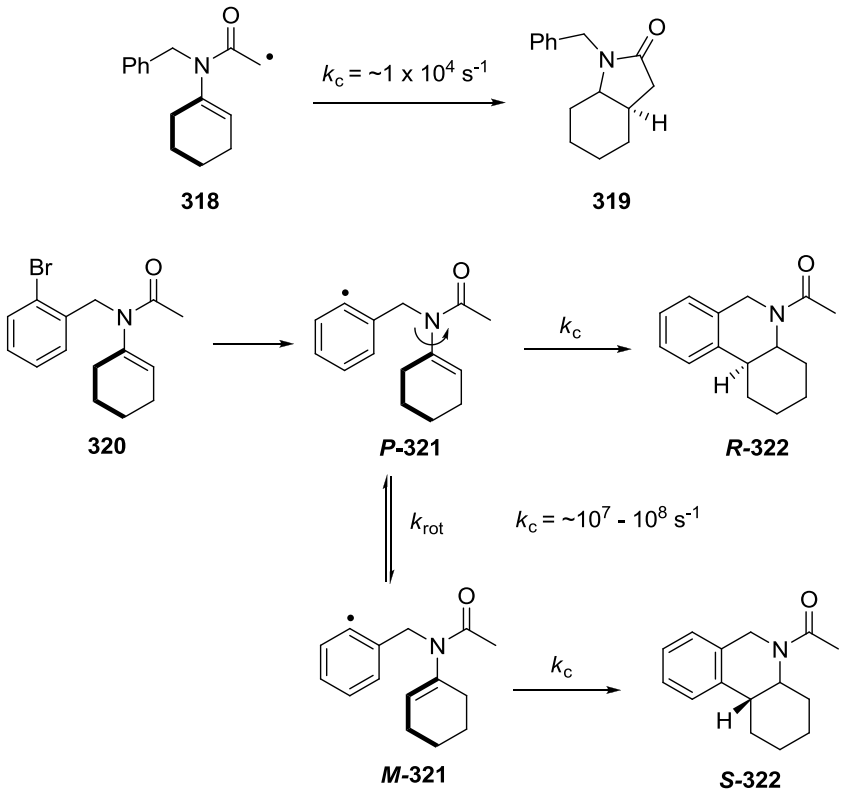
Curran showed that the aryl radical derived from atropisomeric acrylanilide **145** underwent 5-*exo* cyclisation with ~90% chirality transfer.[150]



Scheme 4.6: Chirality transfer in the 5-*exo* cyclisation of acrylanilides. *Reagents and conditions:* Bu_3SnH, Et_3B, O_2, 20 ^oC, benzene.

As shown in Chapter 2 enamides also exhibit atropisomerism and therefore also have the potential to result in chirality transfer upon cyclisation. The cyclisations of aryl radicals are normally relatively fast processes (~10^7 – 10^8 s^{-1}) in comparison to the 5-*endo* cyclisations of acyl radicals (1 x 10^4 s^{-1}) and are more likely to be faster than

rotation about the *N*-alkenyl bond (k_{rot}), suggesting chirality transfer is possible in the cyclisations of enamides **320**.



Scheme 4.7: Chirality transfer in radical cyclisations.

In Chapter 2 we showed that level of substitution at the alkene played a large role in influencing the barrier to rotation about the *N*-alkenyl bond with the more substituted enamides having significantly higher barriers to rotation (Scheme 4.1).

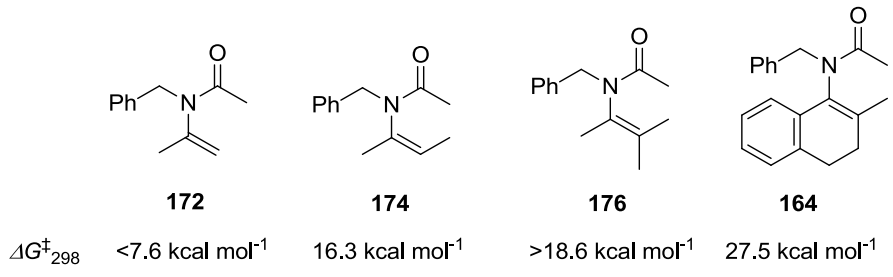
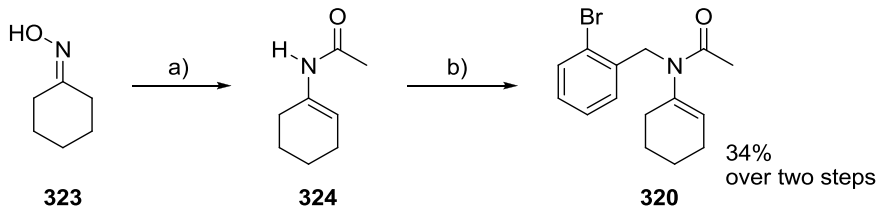


Figure 4.1: Effect of alkene substitution on barrier to rotation.

There has been little information reported in the literature on the outcome of aryl radical cyclisations onto tri- and tetrasubstituted enamides and this chapter reports our results in this area.

4.2 Results and Discussion

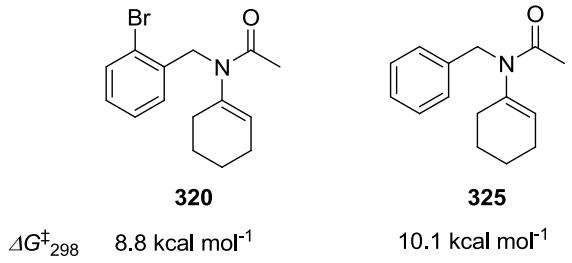
We began our investigations with the trisubstituted cyclic enamide **320** which was synthesised *via* copper mediated acylation of cyclohexanone, followed by deprotonation and benzylation with 2-bromobenzyl bromide.



Scheme 4.8: Synthesis of 2-bromobenzyl enamide 320. *Reagents and Conditions:* a) Ac_2O, $NaHSO_3$,CuI, DCE, 120 ^oC, 16 h. b) NaH, 2-bromobenzyl bromide, THF, 0 ^oC 10 mins, reflux 16 h.

Analysis of **320** by 400 MHz ^1H NMR showed the benzyl protons to resonate as a broad singlet at room temperature, indicative of restricted rotation about the *N*-alkenyl bond. The 500 MHz ^1H VT NMR showed two mutually coupled doublets at low temperature (183 K) which coalesced at 268 K and appeared as a sharp singlet at high temperature (373 K). Line shape analysis using the WINDNMR[145] software allowed $\Delta G^{\ddagger}_{298}$ to be calculated following the method described in chapter 2, section 2.1.1.1 as 8.8 kcal mol^{-1}. Interestingly, the addition of the relatively large bromine atom in the *ortho* position causes a lowering of the barrier to rotation compared to enamide **325** ($\Delta G^{\ddagger}_{298}$ = 10.1 kcal mol^{-1}). Presumably this is due to the extra steric bulk of the *ortho* bromine twisting the sp^3-sp^2 C-C bond of the benzyl group so that

the aryl ring is located further away from the cyclohexene ring, hence having less influence on the barrier to rotation.



320 **325**

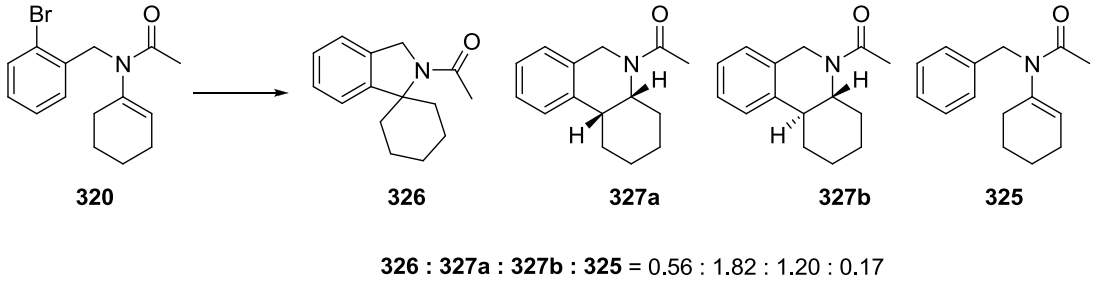
$\Delta G^{\ddagger}_{298}$ 8.8 kcal mol^{-1} 10.1 kcal mol^{-1}

Figure 4.2: Barriers to rotation of enamides 320 and 325.

4.2.1 Cyclisation of bromobenzyl enamide 320.

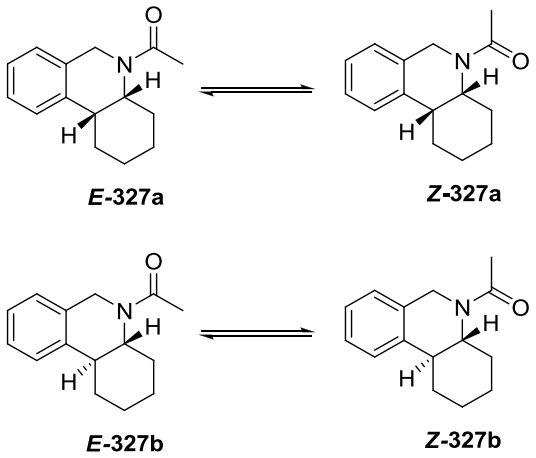
As we were uncertain as to the rate of cyclisation of the radical **318** derived from **320** and in order to limit the amount of competitive reduction to give **325** prior to cyclisation we first carried out the reaction using a low concentration of Bu_3SnH. This was achieved via the gradual addition of Bu_3SnH via a syringe pump. Hence, 1.5 eq. of Bu_3SnH and 0.2 eq. of 1,1-azobis(cyclohexanecarbonitrile) (ACN) was added over 7 hours using a syringe pump to a refluxing solution of **320** in toluene, followed by a further 9 hours at reflux. After cooling the reaction mixture was concentrated *in vacuo* to give the crude product. Following the procedure of Berge and Roberts,[32] the crude reaction mixture was then partitioned between acetonitrile and hexane to aid with the removal of the tin residue. 400 MHz ^{1}H NMR of both extracts were compared to that of the crude reaction mixture showing a significant amount of the tin residue had been extracted into the hexane fraction with minimal amounts remaining in the acetonitrile fraction. In addition it was possible to confirm that no cyclised materials were lost in the hexane layer. This allowed crude ratios of

the cyclised products to be determined more easily by measurement from the acetonitrile fraction.



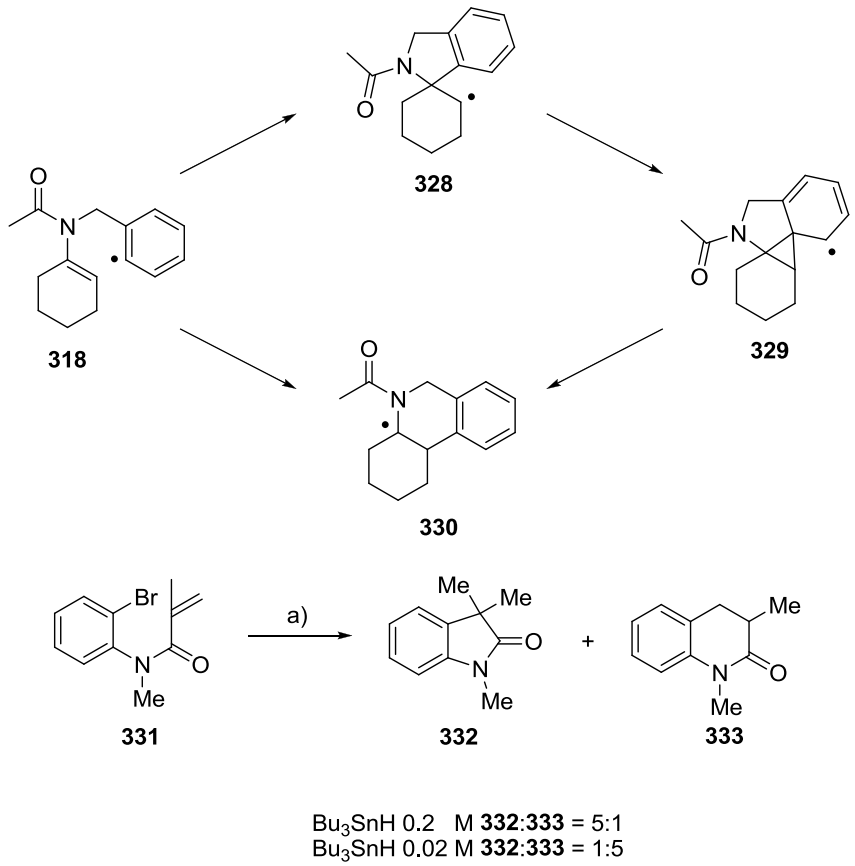
Scheme 4.9: Cyclisation of Enamide 320 with a syringe pump. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux, 16 h.

The cyclisation was found to proceed in both a 5-*exo* and a 6-*endo* fashion to give a range of products; the 5-*exo* product **326** and both the *cis* **327a** and *trans* **327b** isomers of the 6-*endo* product were observed alongside the reduced pre-cyclised product **325** in a ratio of 0.56 : 1.82 : 1.20 : 0.17 (**326** : **327a** : **327b** : **325**). The relative stereochemistry of the 6-*endo cis* and *trans* isomers was assigned based upon previous reported results[195] which were based upon nOe analysis and decoupling experiments. Both isomers **327a** and **327b** were found to exist as two amide rotamers respectively in $CDCl_3$ (*cis* isomer = 1 : 0.82 ratio, *trans* isomer = 1 : 0.62). Unfortunately the acetate peaks were too close in the 500 MHz ^{1}H NMR to allow the *E* and *Z* rotamers to be assigned by nOe.



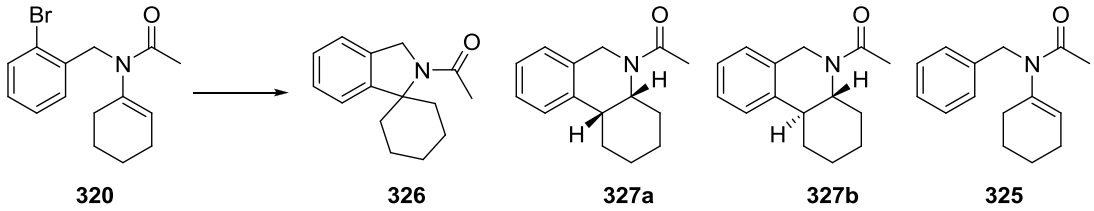
Scheme 4.10: Amide rotamers of 6-*endo* products.

The 6-*endo* cyclisation pathway was found to predominate, as found by Ishibashi in the cyclisation of the related disubstituted enamide **316** (Scheme 4.5).[181] This preference is thought to be partly due to the starting material **320** existing predominantly in the *syn* conformer where the radical is in closer proximity to the β-carbon. Alternatively, the 6-*endo* product could arise *via* a neophyl rearrangement of the intermediate radical **328** arising from 5-*exo* cyclisation. This rearrangement was first observed in an aryl radical cyclisation by Parker[196] and later observed by Jones in the synthesis of oxindoles **332** and **333**,[197] (Scheme 4.11). Formation of radical **329** will be reversible but ring opening to give the more stable tertiary radical **330**, followed by reduction would give the observed 6-*endo* products **327a** and **327b** (Scheme 4.11). Interestingly, the ratio of 5-*exo* to 6-*endo* products in the cyclisation of oxindoles is temperature and concentration dependent with more neophyl rearrangement taking place with lower concentrations of Bu_3SnH. This makes sense as lower concentrations would provide radical **328** with a longer lifetime giving it a chance to rearrange.



Scheme 4.11: Formation of the 6-*endo* product *via* a neophyl rearrangement. *Reagents and Conditions:* a) 1.5 eq. Bu_3SnH, 0.2 eq. AIBN, *t*-butyl benzene, 169 ˚C.

We next repeated the reaction without the use of the syringe pump adding all the Bu_3SnH and ACN at the start of the reaction (0.02M). Pleasingly this did not significantly affect the ratio of the cyclised (**326**, **327a** and **327b**) to reduced pre-cyclised material **325** (0.02 M Bu_3SnH **326**+**327a**+**327b**:**325** = 1 : 0.062 compared to syringe pump addition of Bu_3SnH **326**+**327a**+**327b**:**325** = 1 : 0.047). Consequently in future reactions a syringe pump was not used.



Scheme 4.12: Cyclisation of enmide 320 without a syringe pump. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux, 16 h.

4.2.2 Rate Studies in Cyclisation of enamide 320.

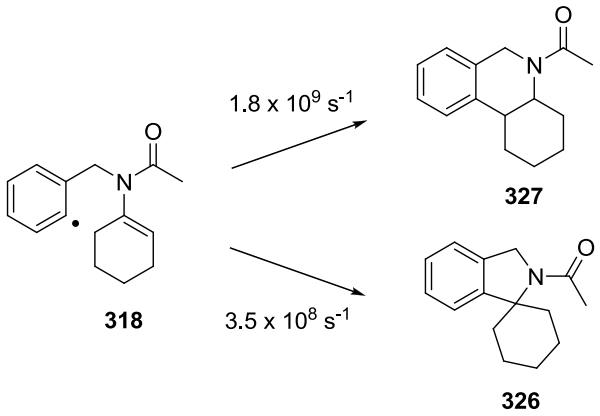
We next carried out studies in order to gain information on the approximate rate constants for the two modes of cyclisation. We reacted a 0.02M solution of **320** with different concentrations of Bu_3SnH and determined the ratio of reduction product **325**, 5-*exo* cyclisation product **326** and 6-*endo* cyclisation products **327a** and **327b** by integration of representative protons in the 400 MHz ^1H NMR of the crude mixture.

Entry[a]	Bu_3SnH (Equiv.)	$[Bu_3SnH]_c$ (M)[b]	Reduction : 5-exo : 6-endo[c]	Red/5-*exo*	Red/6-*endo*
1	1.5	0.02	0.22 : 0.60 : 2.95	0.367	0.075
2	3	0.05	0.23 : 0.60 : 2.87	0.383	0.080
3	5	0.09	0.24 : 0.59 : 2.75	0.401	0.087
4	12.5	0.24	0.44 : 0.63 : 2.74	0.698	0.161
5	25	0.49	0.64 : 0.55 : 2.63	1.164	0.243
6	37.5	0.74	0.79 : 0.52 : 2.64	1.519	0.299

Table 4.2: Data for determination of 5-*exo* and 6-*endo* cyclisation rate constants. [a] 0.649 mmol of substrate **320** in 32.5 mL of solvent was used in each run. [b] The average Bu_3SnH concentration was used as recommended by Newcomb[198] and was obtained from $[Bu_3SnH]_c = \{[Bu_3SnH]_{initial} + ([Bu_3SnH]_{initial} + [Substrate]\}/2$. [c] Determined by integration from the crude 400MHz ^1H NMR.

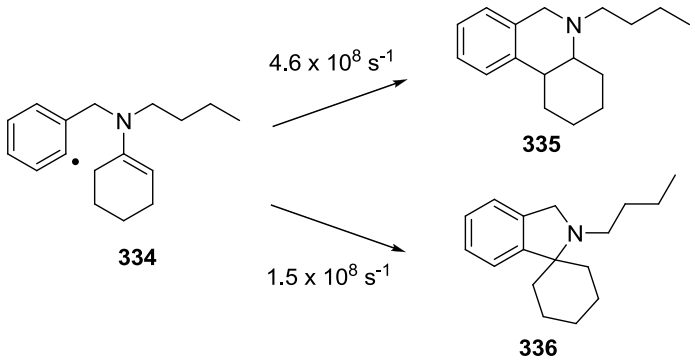
Whereas Jones found the ratio of 5-*exo* **322** and 6-*endo* **333** products to be dependent on the concentration of Bu_3SnH[197] (Scheme 4.11) we found the ratio of 5-*exo* and 6-*endo* products to remain constant indicating that the 6-*endo* product is not arising from a neophyl rearrangement.

We plotted the ratio of reduction **325** / cyclisation product against the mean $[Bu_3SnH]_c$ for each entry as recommend by Newcomb.[198] Using Chatigilialoglu's published 'radical clock' for reduction of an aryl radical by Bu_3SnH (5.9×10^8 M^{-1} s^{-1})[176] it was possible to determine approximate rate constants for the 5-*exo* cyclisation reaction pathway of **318** to be 3.5×10^8 s^{-1} and the 6-*endo* cyclisation pathway to be 1.8×10^9 s^{-1} at 110° C.



Scheme 4.13: 5-*Exo* vs 6-*endo* cyclisation of enamide radical 318.

These are about 4 times and 2 times greater respectively than the reported 5-*exo* (1.5×10^8 s^{-1}) and 6-*endo* (4.6×10^8 s^{-1}) aryl cyclisations onto the related enamine **334** at the same temperature.[199]



Scheme 4.13: 5-Exo vs 6-endo cyclisation of enamide radical 334.

It is notable that both plots do not pass through the origin and in fact at low Bu_3SnH concentrations both show a trend away from the linear nature suggested by the trendlines, this is most notable for the 5-exo cyclisation data, Figure 4.4 (the points in question have been highlighted with a cross × instead of a diamond ♦).

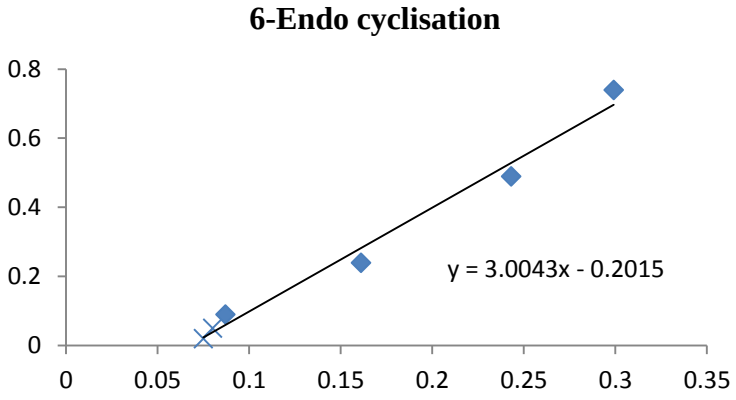


Figure 4.3: Plots of reduced (325) / 6-*endo* cyclised products (327) against [Bu3SnH]c.

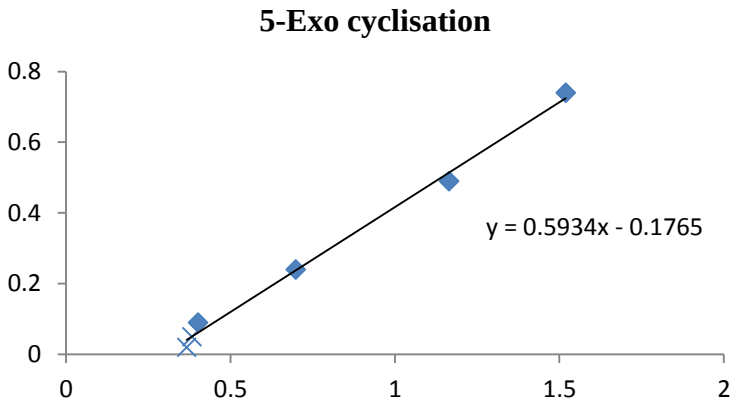


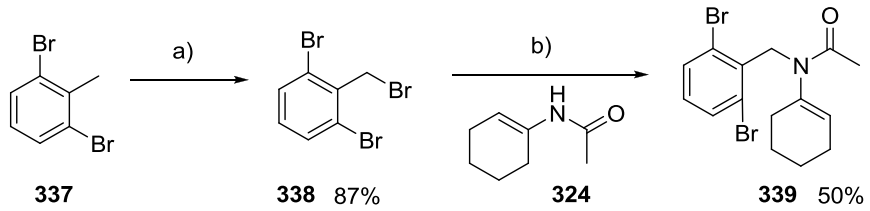
Figure 4.4: Plots of reduced (325) / 5-*exo* cyclised products (326) against [Bu3SnH]c

This is indicative of a background reduction mechanism of the aryl radical independent of Bu_3SnH concentration. Theoretically this background reduction could arise either from competitive reduction of the aryl radical **318** by toluene, the solvent, or by a competing 1,6-radical translocation pathway *via* intramolecular abstraction of either an allylic H-atom from the cyclohexenyl group or by a H-atom from the acetyl group.[200] It should be possible to determine which mechanism is responsible for this 'background' reduction by either carrying out the reaction with d^8-toluene or with Bu_3SnD. In any case, a very rough estimate of the rate of this process can be determined by extrapolating either the reduction / 5-*exo* ratio or the reduction / 6-*endo* ratio to zero Bu_3SnH concentration. Both extrapolations should in theory give the same answer. This suggests that the rate of the background reduction for a 0.02M toluene solution of **320** is 14.95 times slower than $k_{c\ 6\text{-}endo}$ (estimate $k_{\text{background red at 0.02M}} = 1.2 \times 10^8\ s^{-1}$) or 3.37 times slower than $k_{c\ 5\text{-exo}}$ (estimate $k_{\text{background red at 0.02M}} = 1.0 \times 10^8\ s^{-1}$). Both extrapolations give similar magnitudes for $k_{background\ red\ at\ 0.02M}$ ±20% with the errors largely due to uncertainty in the extrapolation as both plots move away from linearity at low Bu_3SnH concentration.

The value is similar in magnitude, albeit slightly lower, than that reported for a related 1,5-hydrogen translocation from an aryl radical (5 x 10^8 s^{-1}).[201]

4.2.3 Synthesis and Cyclisation of Dibromo Enamide 339

We next synthesised the dibromo analogue **339**. Enamide **324** was deprotonated with sodium hydride and then reacted with **338**, formed from the bromination of 2,6-dibromotoluene with *N*-bromosuccinimide in the presence of benzoyl peroxide.[202]



Scheme 4.14: Synthesis of dibromo enamide 339. *Reagents and Conditions:* a) 1.1 eq. NBS, 0.05 eq. benzoyl peroxide, CCl_4, reflux. b) 5 eq. NaH, THF, reflux, 12 h.

The barrier to rotation about the *N*-alkenyl bond was calculated by line shape analysis of the 500 MHz ^{1}H VT NMR following the method described in chapter 2, section 2.1.1.1 and was found to be 12.6 kcal mol^{-1}. Whereas the addition of one *ortho* bromo group was found to lower the barrier to rotation, thought to be due to aromatic ring twisting out of position, the addition of the second *ortho* bromo group increases the barrier to rotation, presumably due to the aromatic group twisting back to the original position along with increased steric bulk. These results indicate that gearing of the benzyl substituent during *N*-alkenyl bond rotation is likely.

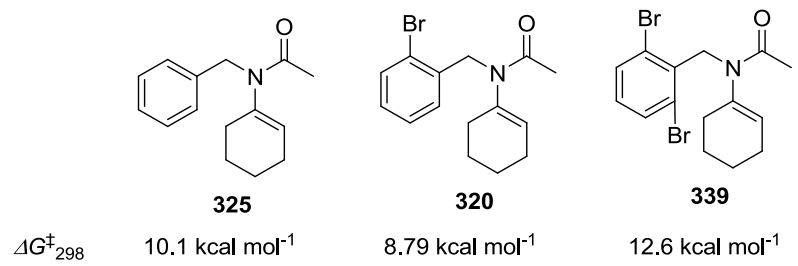
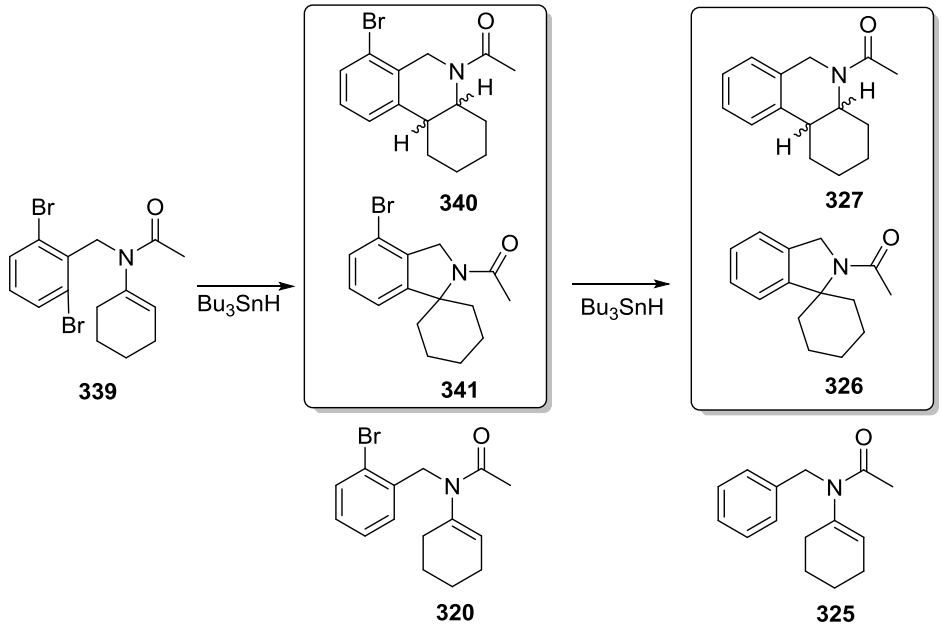


Figure 4.5: The effect of *ortho* bromo groups on the barrier to rotation.

Enamide **339** was then cyclised with 1.5 eq. Bu_3SnH and 0.2 eq. ACN added to a solution of **339** in toluene and the resulting solution refluxed for 16 hours.



Scheme 4.15: Cyclisation of enamide 339. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux, 16 h.

The same 5-*exo* **326** and 6-*endo* **327** products were obtained in low yield (17% and 22% respectively) as in the cyclisation of the monobromo compound **320**, however none of the reduced pre-cyclised product **325** was observed. This is to be expected as assuming the rate of cyclisation of dibromide **339** to give **340** and **341** is similar in magnitude to **320** giving **326** and **327**, then at 0.02M concentration of Bu_3SnH we

would expect to obtain about a 16:1 ratio of (**340** + **341**) : **320**. A second equivalent of Bu_3SnH would then reduce the monobrominated cyclised products **340** and **341** to **327** and **326** respectively as well as mediating the reaction of **320** to give cyclisation and reduction products (**327** + **326**) : **325** again in a 16:1 ratio. Ultimately this should lead to a theoretical yield of 99.6% of cyclised products **327** and **326** and a 0.3% yield of **325.** The crude mass spec also indicated the presence of a monobrominated compound such as **340** or **341** however neither product was isolated from the reaction mixture.

4.2.4 Synthesis of Tetrasubstituted 2-Bromobenzyl Enamides

In order to investigate the possibility of chirality transfer in the Bu_3SnH mediated cyclisation of hindered 2-bromobenzyl enamides we next synthesised tetrasubstituted enamides **342** – **345**.

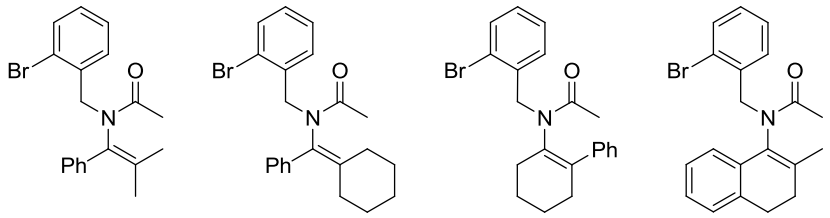
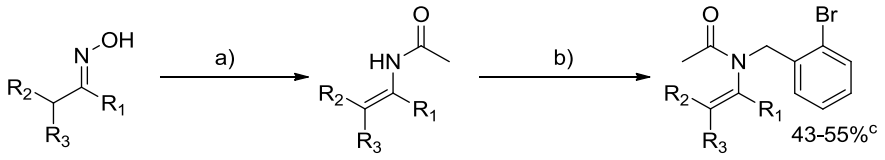


Figure 4.6: Tetrasubstituted 2-bromobenzyl enamides.

The enamides were synthesised *via* iron mediated acylation of the corresponding oxime followed by deprotonation with sodium hydride and benzylation with 2-bromobenzyl bromide, Scheme 4.16.



Scheme 4.16: Synthesis of tetrasubstituted enamides with 2-bromobenzyl bromide. *Reagents and conditions:* a) 2eq. Fe(0), 3eq. AcOH, 3eq. Ac_2O, toluene, 85 ^oC, b) 5eq. NaH, 1.1 eq 2-bromobenzyl bromide, THF, 0 ^oC – reflux. ^{c} Yield over two steps.

4.2.5 Analysis of barriers to rotation in tetrasubstituted enamides

As expected the tetrasubstituted 2-bromobenzyl enamides **342** – **345** all had high barriers to rotation with the benzyl protons appearing as two well resolved mutually coupled doublets in the 400 MHz ^1H NMR at room temperature. Enamides **343** and **345** were sent to our collaborators, Curran and co-workers, in Pittsburg, America for attempted separation on a Whelk-O column (Figure 4.7).

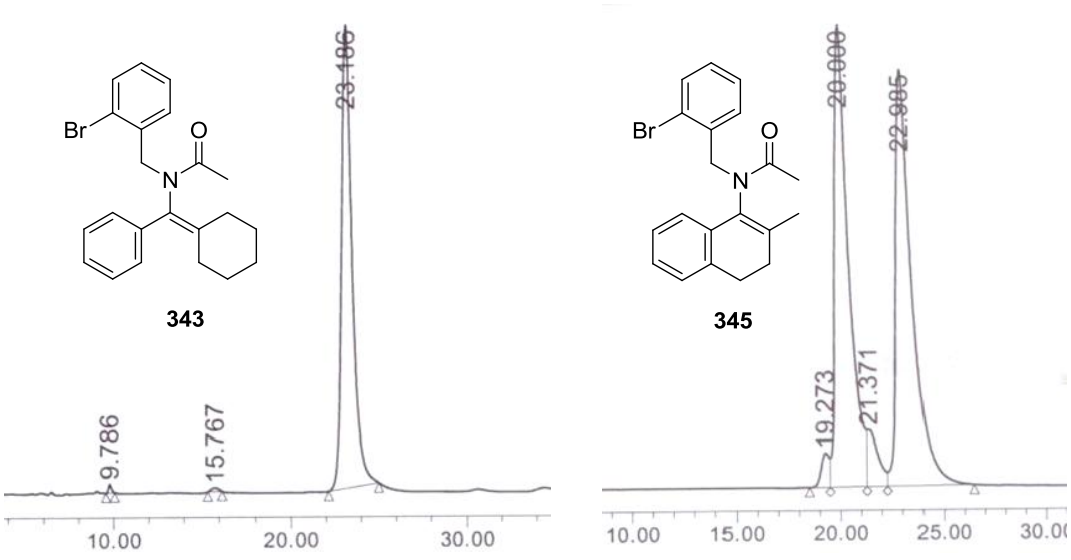


Figure 4.7: Chiral HPLC traces of enamides 343 and 345.

It was not possible to separate the atropisomers of enamide **343**, however good separation was achieved with enamide **345** (20.0 min and 22.9 min). Isolation of a

single atropisomer was possible with >99:1 er. This isomer then underwent slow racemisation in *i*PrOH at 82 ^{o}C allowing the barrier to rotation to be calculated as 28.5 kcal mol^{-1}. Whereas the addition of an *ortho* bromo substituent to trisubstituted enamide **325** caused the barrier to rotation to decrease by ~1.3 kcal mol^{-1}, addition of an *ortho* bromo substituent to tetrasubstituted enamide **164** caused the barrier to rotation to increase by ~1.0 kcal mol^{-1}. We had postulated that the decrease in barrier to rotation between **325** and **320** resulted from a gearing mechanism of the benzyl group during rotation about the *N*-alkenyl bond. In the case of enamides **345** and **164** it is possible that due to the extra steric bulk of the bromine atom and that around the *N*-alkenyl bond the benzyl group is no longer able to rotate to a position that aids rotation.

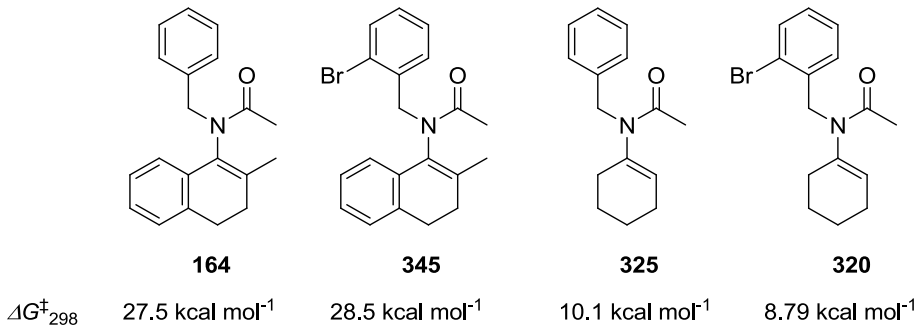


Figure 4.8: Barriers to rotation in 2-bromobenzyl enamides.

A crystal structure of compound **345** (figure 4.9) showed a torsion angle between the *N*-alkenyl bond and the plane of the N-CO bond of 79^{o}, showing that they prefer to lie in orthogonal planes, as observed with other tetrasubstituted enamides. It is also interesting to see from this crystal structure that the bromine is situated over the alkene making cyclisation possible, and that this is the only detected conformer.

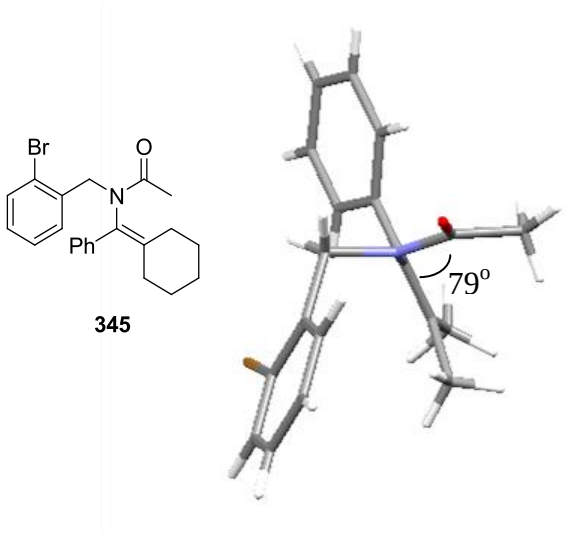
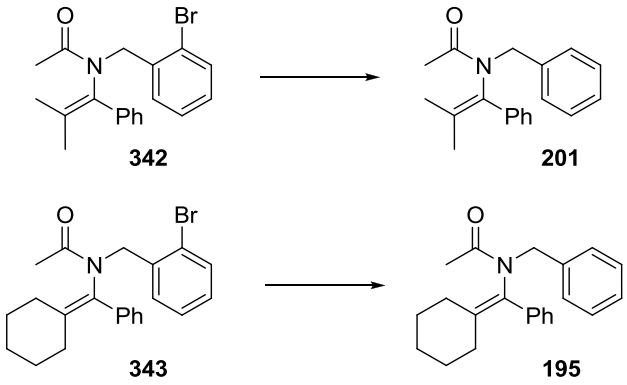


Figure 4.9. Crystal Structure of enamide 345.

4.2.6 Cyclisation of Tetrasubstituted 2-Bromobenzyl Enamides

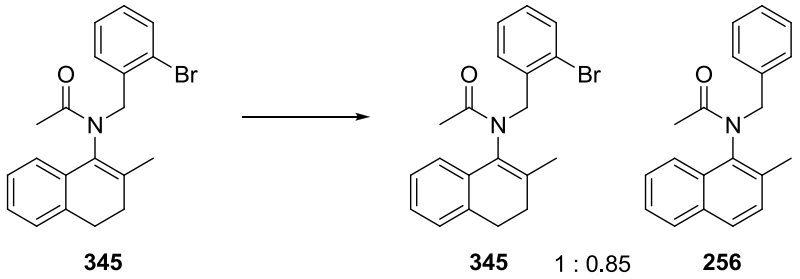
Cyclisation of the four tetrasubstituted enamides **342** – **345** was attempted by treatment with 1.5 eq. Bu_3SnH and 0.2 eq. of ACN.



Scheme 4.17: Attempted cyclisations of enamides 342 and 343. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux, 16 h.

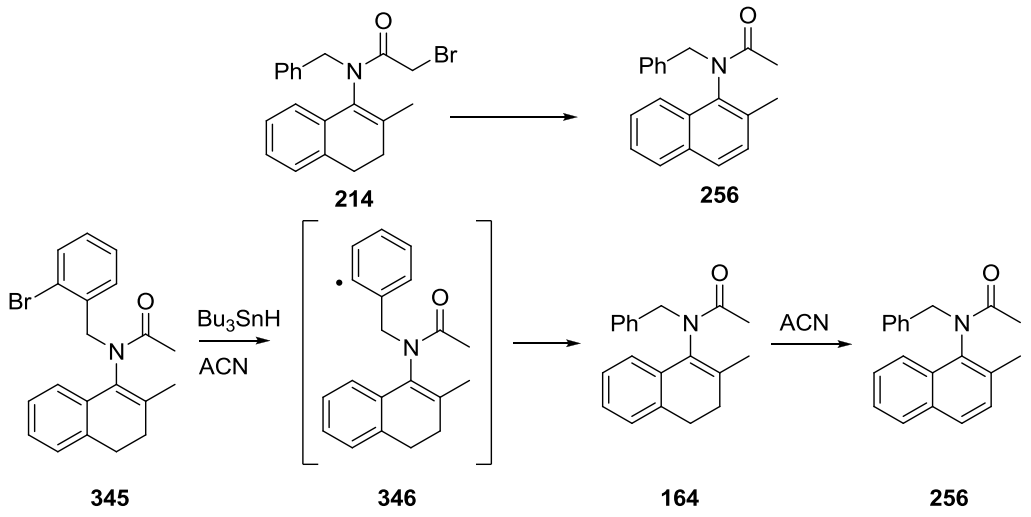
Unfortunately the cyclisations of enamides **342** and **343** yielded a complicated mixture from which the major products identified were the reduced compounds **201** and **195**. It is not that surprising that the reduced product is formed as the major

product, comparing the rates calculated earlier (section 4.2.2) for the 5-*exo* (3.5×10^8 s^{-1}) and 6-*endo* (1.8×10^9 s^{-1}) cyclisations of **320** to Chatgilialoglu's published rate for reduction of an aryl radical (5.9×10^8 M^{-1} s^{-1})[176] the rate of cyclisation only needs to be slowed by one order of magnitude in order for reduction to dominate. The alkene bonds in **342** and **343** are significantly more hindered than that in the trisubstituted enamide **320** and therefore the rate of cyclisation may be significantly lowered leading to the reduced compounds **201** and **195** as the major products.



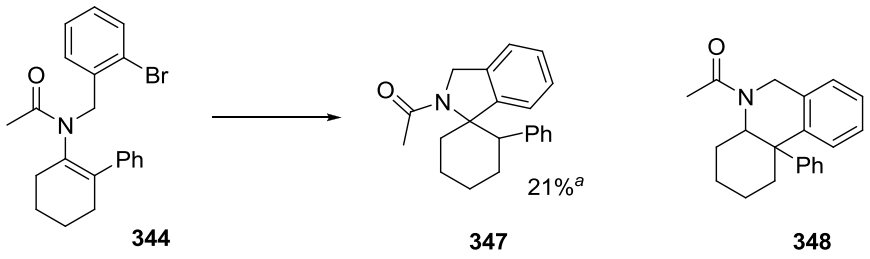
Scheme 4.18: Attempted cyclisations of enamide 345. *Reagents and Conditions:* 1.5 eq. Bu_3SnH, 0.2 eq. ACN, toluene, reflux, 16 h.

The attempted cyclisation of enamide **345** also proved unsuccessful. In this case the major product obtained was identified as the naphthalene compound **256** along with unreacted starting material **345** in a 0.85 : 1 ratio (**256** : **345**). The formation of the naphthalene product had been observed previously in the attempted Bu_3SnH mediated cyclisation of related methyltetralene enamide **214** (see Chapter 3, Section 3.2.1). It is thought to arise from initial formation of radical **346** *via* homolysis of the C-Br bond followed by reduction by Bu_3SnH without cyclisation, and then ACN mediated oxidation / aromatisation of the tetralene ring to the naphthalene (Scheme 4.19).



Scheme 4.19: Formation of naphthalenes 256. *Reagents and conditions:* Bu_3SnH, ACN, toluene, 110 ^{o}C, 18h.

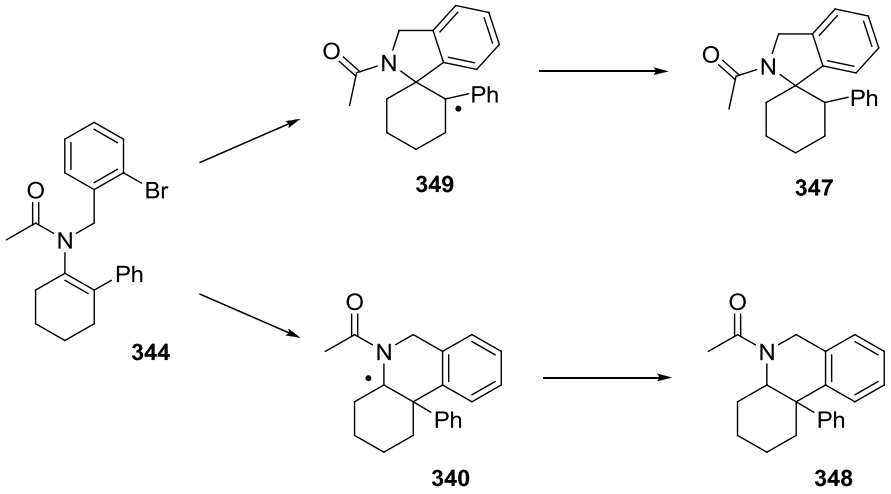
Pleasingly, the treatment of enamide **344** with Bu_3SnH and ACN did yield some cyclised products. The similarity of the products meant separation proved difficult however the 5-*exo* compound **347** was identified as the major product and was isolated in a 21% yield. Interestingly, only one diastereomer was observed however at the time of writing it has not been possible to determine its stereochemistry. The 6-*endo* product was also tentatively assigned, however it could not be obtained pure.



Scheme 4.20: Cyclisation of enamide 344. *Reagents and conditions:* Bu_3SnH, ACN, toluene, 110 ^{o}C, 18h. ^{a}Isolated yield.

The preference for the 5-*exo* cyclisation was not expected based upon the cyclisation of trisubstituted enamide **320** and the results of Ishibashi's cyclisations of related

enamides.[181] However, 5-*exo* cyclisation of enamide **344** gives rise to a resonance stabilised benzyl radical which is trapped by Bu_3SnH.



Scheme 4.21: Competitive 5-*exo* vs 6-*endo* cyclisation of enamide 344.

Comparing enamide **344** to the other tetrasubstituted enamides **342**, **343** and **345** which did not undergo successful cyclisation, enamide **344** is less hindered with substitution at only the β-position, whereas enamides **342**, **343** and **345** are substituted at both the β- and β'-positions, and this may explain why cyclisation occurred only in this instance.

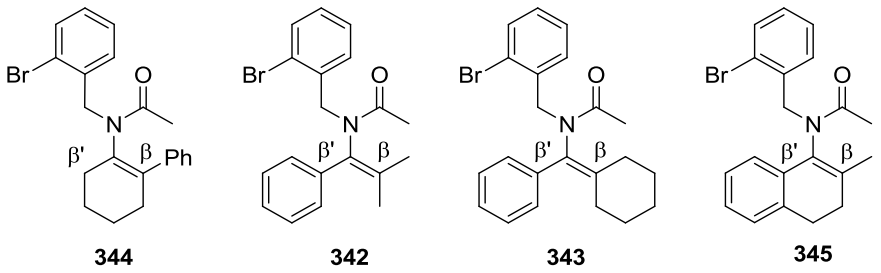


Figure 4.10: Tetrasubstituted 2-bromobenzyl enamides.

4.3 Conclusion

A selection of 2-bromobenzyl enamides have been synthesised and their barriers to rotation about the *N*-alkenyl bond investigated. It was found that the addition of an *ortho* bromo group to the non halogenated enamide **325** resulted in a decrease in the barrier to rotation, however the addition of a second *ortho* bromo group increased the barrier again. This is indicative of gearing of the benzyl group taking place during rotation about the *N*-alkenyl bond. In contrast in the more hindered tetrasubstituted enamides the addition of an *ortho* bromo group was found to increase the barrier to rotation by ~1 kcal mol^{-1}.

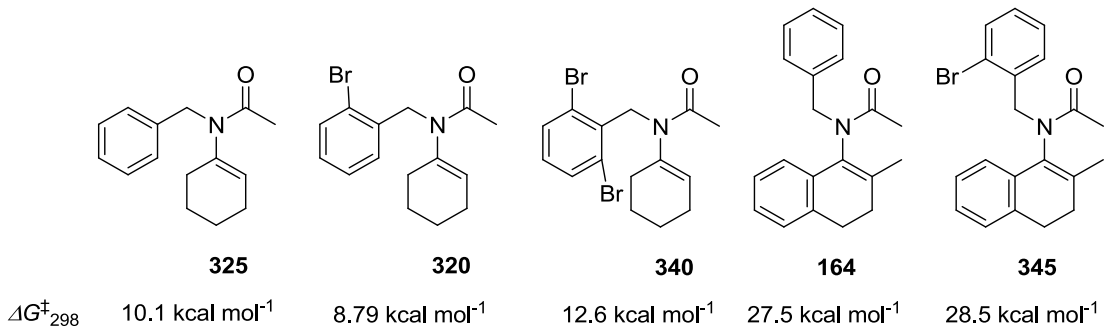
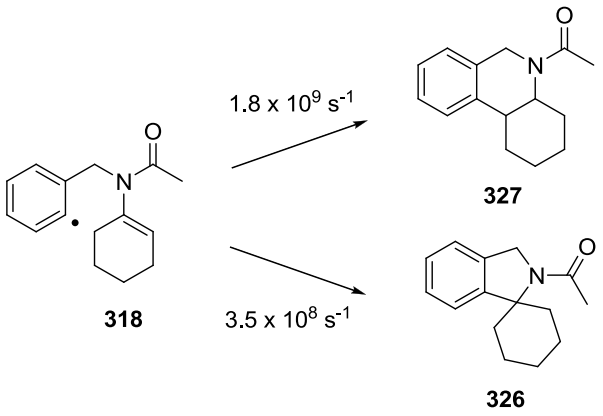


Figure 4.11: Barriers to rotation in 2-bromobenzyl enamides.

The Bu_3SnH mediated cyclisation of these enamides has also been investigated. Initial cyclisation of enamide **320** showed the 6-*endo* pathway to be favoured over the 5-*exo* pathway. Based upon the results of Ishibashi,[181] this is postulated to be due to the starting material existing in the *syn* conformer where the radical is in closer proximity to the β-carbon. Carrying out cyclisations of **320** at varying concentrations of Bu_3SnH allowed us to calculate the rates of 5-*exo* and 6-*endo* cyclisations as 3.5 x 10^8 s^{-1} and 1.8 x 10^9 s^{-1} at 110 °C respectively.



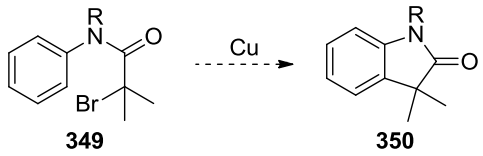
Scheme 4.22: 5-*Exo* vs 6-*endo* cyclisation of enamide 320.

The cyclisations of tetrasubstituted 2-bromobenzyl enamides **342 – 345** were less successful with only the cyclisation of **344** yielding cyclised product. In this case the 5-*exo* cyclisation was the favoured route, most likely due to the formation of the stabilised intermediate benzyl radical **349**. It appears that the extra steric bulk of the tetrasubstituted enamides significantly hinders the rate of cyclisation leading to the formation of other products such as the reduced compounds **195** and **201** and the naphthalene **256** instead. Further work would have to be carried out in this area to find more successful cyclisation conditions before investigating chirality transfer in the cyclisation of 2-bromobenzyl enamides.

5.0 Oxindole Synthesis by Copper-Mediated Cyclisation

5.1 Introduction

In previous chapters we have shown that we can produce a number of lactam products *via* cyclisation of an α-acyl radical onto an alkene, and nitrogen heterocycles *via* cyclisation of an aryl radical onto an alkene. In this chapter we investigate the use of copper mediated radical cyclisations as a route to oxindoles *via* cyclisation of an α-acyl radical onto an aromatic nucleus in an oxidative fashion.



Scheme 5.1: Synthesis of oxindoles *via* copper mediated cyclisation.

Oxindoles are a class of heterocycles present in a number of natural products, *e.g.* speciophylline **351**[203] and horsfiline **352**,[204] and are of great interest in medicinal chemistry due to their biological properties. They have proven activity as protein kinase inhibitors[205] and phosphodiesterase inhibitors[206] as well as exhibiting anti-rheumatic,[207] anti-tumoral,[203] and anti-viral[208] properties.

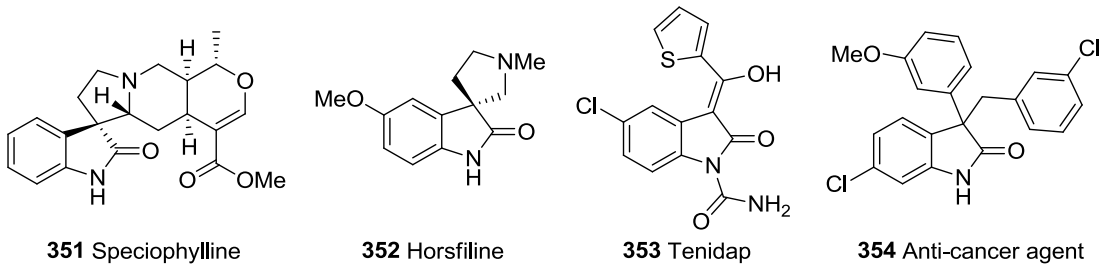


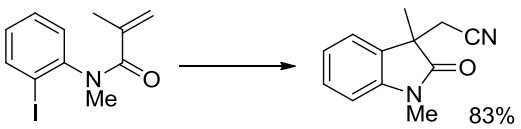
Figure 5.1:Oxindole containing natural products and pharmaceutical compounds.

5.1.1 Synthesis of Oxindoles

There are many approaches in the literature for the synthesis of oxindoles. A classical approach is Friedel-Crafts cyclisation onto α-halo[209] and α-hydroxy[210] acetanilides, however the strongly acidic conditions and high temperatures required limit the range of functional groups that can be tolerated. Palladium catalysed reactions have been particularly popular such as intramolecular Heck couplings[211–213] and Buchwald-Hartwig type reactions. Direct coupling between C-H and Ar-H bonds has also been successful, both with a palladium catalyst and without. A number of different radical approaches have also been employed.

5.1.1.1 Palladium Catalysed Heck Reactions

Zhu has reported a domino intramolecular Heck-cyanation sequence; when *ortho*-iodoanilide **355** was dissolved in DMF and treated with potassium ferro(II)cyanide in the presence of palladium acetate and sodium carbonate the oxindole **356** was afforded in 83% yield.[211] The conditions were successful with a wide range of substrates with varying electronic properties, and the use of (*S*)-DIFLUOROPHOS[214] allowed for the reaction to be carried out enantioselectively giving 79% ee.[211]

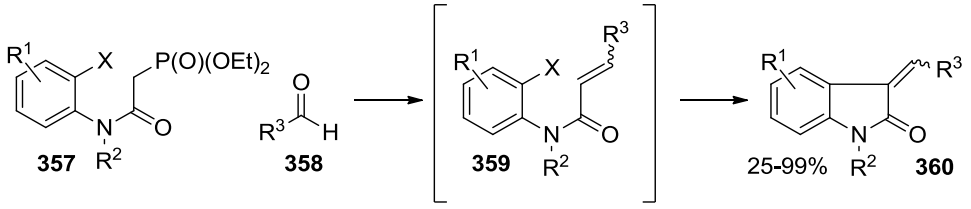


355 **356**

Scheme 5.2: Palladium catalysed domino Heck-cyanation reaction. *Reagents and Conditions:* 1.5 mol% $Pd(OAc)_2$, 0.22 eq. $K_4[FeCN]_6$, 1.0 equiv. Na_2CO_3, DMF, Argon, 120 ^oC, 3h.

Taylor has also used a intramolecular Heck reaction as part of a tandem sequence to give 3-alkenyloxindoles **360** from haloanilides **357**.[212] The one-pot, microwave

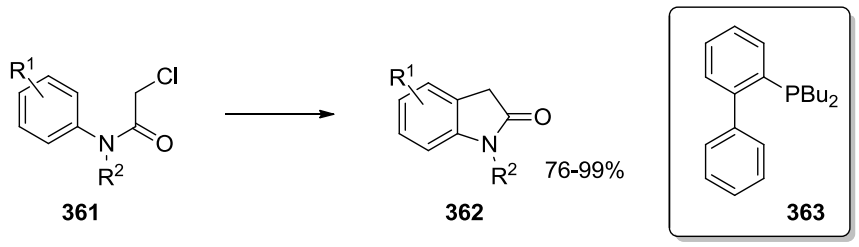
accelerated process involves a Horner-Wadsworth-Emmons olefination followed by a palladium catalysed Heck reaction. A range of aldehyde trapping reagents **358** can be employed to give a range of both *N*-alkylated and NH oxindole products (R^2 = H) in 30 – 60 mins.



Scheme 5.3: Tandem Horner-Wadsworth-Emmons/Heck reaction. *Reagents and Conditions:* 5 eq. R^3COH, 6 eq. Cs_2CO_3, 5 mol% $Pd(OAc)_2$, 11 mol% PPh_3, THF, 100 ^oC, MW, 30-60 mins.

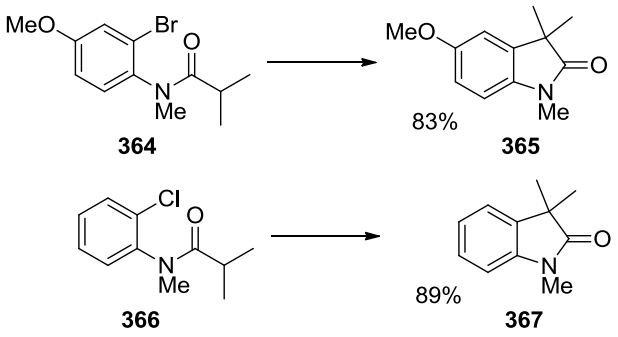
5.1.1.2 Buchwald and Hartwig Palladium Catalysed Oxindole Synthesis

Buchwald has reported a development of the Friedel-Crafts procedure using palladium catalysed functionalisation, obviating the need for harsh reaction conditions. The combination of palladium acetate, 2-(di-*tert*-butylphosphino)biphenyl **363** as a ligand and triethylamine as a base allowed smooth conversion of α-chloroacetanilides **361** into oxindoles **362** with high yields and high levels of regioselectivity.



Scheme 5.4: Buchwald palladium catalysed synthesis of oxindoles. *Reagents and Conditions:* 1-3 mol% $Pd(OAc)_2$, 2-6 mol% **363**, 1.5 eq. Et_3N, toluene, 80 ^oC, 2.5-6 h.

Hartwig has applied similar conditions, with a palladium source, a phosphino ligand and a base, to the synthesis of oxindoles from *ortho*-haloanilides. Both bromo- and chloro-anilides were shown to react to give a range of substituted oxindoles with good yields.[215–217]

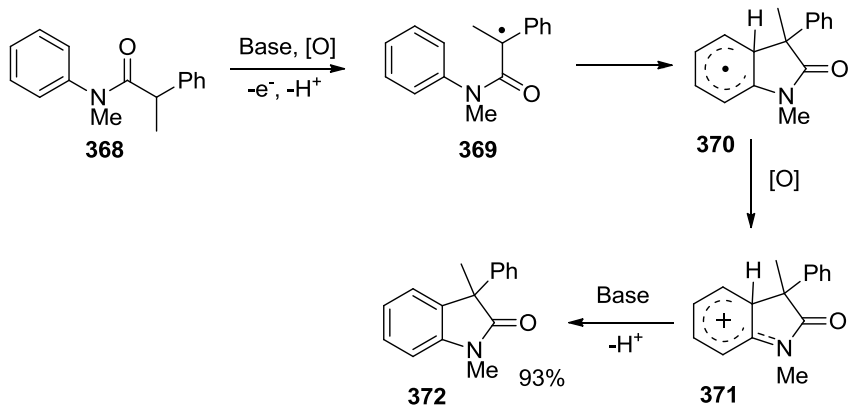


Scheme 5.5: Hartwig palladium catalysed synthesis of oxindoles. *Reagents and Conditions:* 5 mol% $Pd(OAc)_2$, 5 mol% PCy_3, 1.5 eq. NaOtBu, 1,4-dioxane.

Although these palladium catalysed reactions give good yields with relatively low catalyst loadings, the palladium and ligands can prove expensive on an industrial scale.

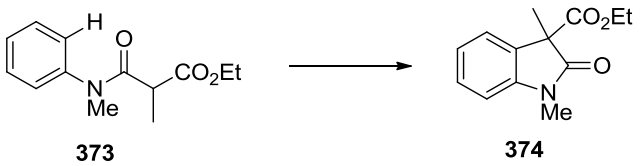
5.1.1.3 Direct Coupling of C-H and Ar-H

The methods of Buchwald and Hartwig require a functionalised precursor with either an *ortho* halogen, an α-halogen or an α-hydroxy group. Kündig and co-workers reported the synthesis of oxindoles without this functionalisation *via* the direct coupling of two C-H centres.[218] The proposed pathway for this reaction is an intramolecular oxidative coupling process. The initial radical **369** is formed *via* amide enolate oxidation and then cyclises onto the aromatic ring to give the cyclohexadienyl radical **370** which readily aromatises to the oxindole product **372**.



Scheme 5.6: Kündig's synthesis of oxindoles by direct coupling of two C-H centres. *Reagents and Conditions:* 2.2 eq. $CuCl_2$, 5.0 eq. NaO*t*Bu, DMF, 110 ^oC, 5 h.

Taylor has also reported a C-H, Ar-H coupling method for the synthesis of oxindoles (Scheme 5.7).[219] The reaction required significantly less metal than Kündig's method, however stoichiometric amounts were still required along with DMF as the solvent and high reaction temperatures.

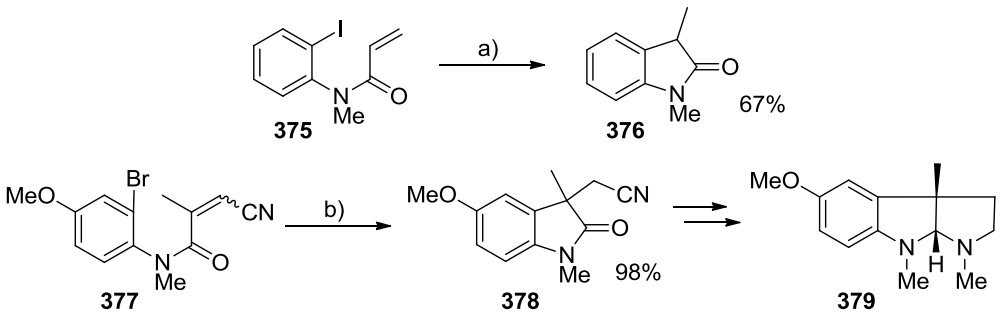


Scheme 5.7: Taylor's synthesis of oxindoles by direct coupling of two C-H centres. *Reagents and Conditions:* 2.2 eq. $CuCl_2$, 5.0 eq. NaO*t*Bu, DMF, 110 ^oC, 5 h.

5.1.1.4 Radical Cyclisations in Oxindole Synthesis

Intramolecular aryl radical cyclisation reactions have also been widely used in the synthesis of oxindoles. Bowman showed that the radical derived from **375** can undergo intramolecular addition to the α-position of the α,β-unsaturated *N*-alkylamide using Bu_3SnH and AIBN to give exclusively the *exo*-cyclisation product

376.[20] This approach was used by Ishibashi towards the synthesis of (±)-Physostigmine **379**, with the cyclisation of **377** giving the oxindole intermediate **378** in 98% yield.[220]



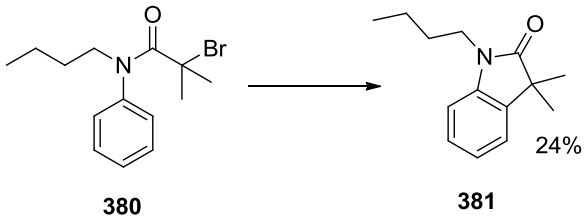
Scheme 5.7: Intramolecular aryl radical cyclisations to afford oxindoles. *Reagents and Conditions:* a) 1.1 equiv. Bu_3SnH, 0.2 equiv. AIBN, toluene, 110 ^oC. b) 1.25 equiv. Bu_3SnH, 0.12 equiv. AIBN, benzene, reflux.

The major disadvantage of these reactions is the use of stoichiometric amounts of the toxic tin hydride at high temperatures, therefore alternative redox conditions using transitions metals such as samarium[221] and cobalt[222] have been developed, however these reactions still require large amounts of metal and excess additives.

5.1.1.5 Previous work in the Clark group on oxindole synthesis

Previously the Clark group have investigated the cyclisation of anilides such as **380** using copper mediated cyclisation conditions to give oxindoles.[223] In particular the AGET-ATRC conditions using KBH_4 were investigated, however the reactions were not that efficient with average to low yields (23-50%) and stoichiometric amounts of KBH_4 required. In this chapter we investigate further the use of copper mediated cyclisations of anilides towards oxindoles to try and improve upon the poor

performance of the reductive CuBr / KBH_4 procedure and to probe the mechanism of the process.

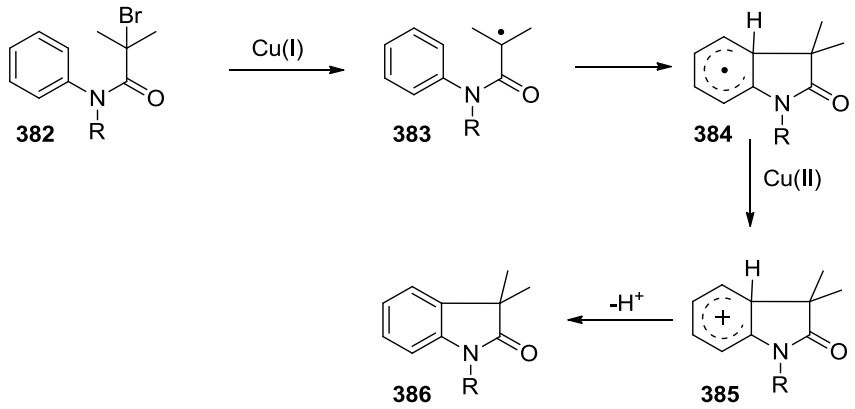


380 **381**

Scheme 5.8: Copper mediated cyclisation to give oxindoles. *Reagents and Conditions:* 10 mol% CuBr/TPA, 100 mol% KBH_4, 0.1M, 50 ^{o}C, 16 h.

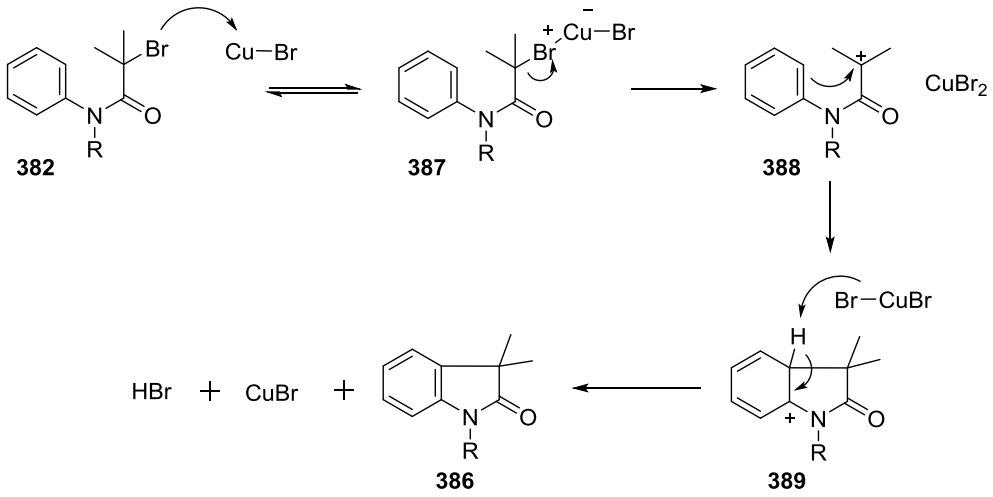
5.2 Results and Discussion

We first decided to probe the mechanism of the copper mediated cyclisation process. Two mechanisms could be envisaged. Firstly, a conventional oxidative radical cyclisation (*via* copper(I) mediated homolysis of the C-Br bond followed by a Cu(II) mediated oxidation aromatisation reaction, Scheme 5.9) or a conventional Friedel-Crafts (non-radical) process with CuBr acting as the Lewis acid, Scheme 5.10.



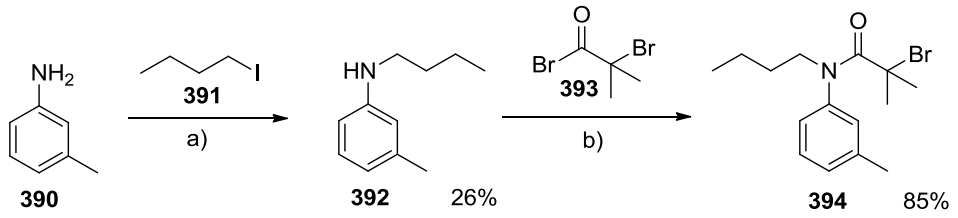
382 **383** **384** **385** **386**

Scheme 5.9: Possible mechanism *via* conventional oxidative radical cyclisation.



Scheme 5.10: Possible mechanism *via* Friedel-Crafts type reaction.

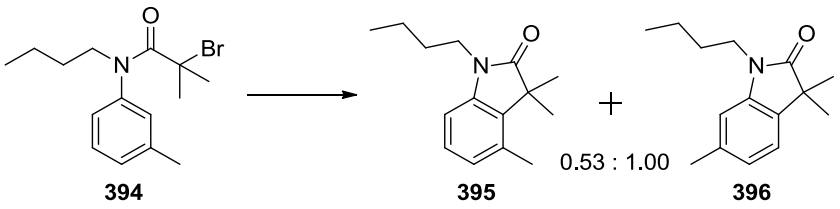
We synthesised the *meta*-substituted anilide **394** so that the regiochemistry of the cyclisation could be investigated. Aniline **390** was deprotonated with sodium hydride and subsequent addition of iodobutane yielded **392** in 26% yield after workup and purification by column chromatography. Treatment of **392** with 2-bromoisobutyryl bromide **393** in the presence of triethylamine yielded pure anilide **394** after a standard organic workup.



Scheme 5.11: Synthesis of anilide 394. *Reagents and Conditions:* a) 1 eq. NaH, 1 eq. BuI, DMF, b) 1.2 eq. **393**, 1.2 eq. Et_3N, Et_2O, r.t. 24 h.

The two possible oxindole regioisomers **395** and **396** that could be formed from the cyclisation of **394** had been characterised previously[223] allowing us to analyse the reactions and determine the ratio of the regioisomers from the crude ^{1}H NMR's. We first carried out an intramolecular Friedel-Crafts acylation, treating **394** with

aluminium trichloride at elevated temperature under nitrogen. The reaction proceeded cleanly in 94% yield to give a 0.53:1.0 ratio (**395**:**396**) of the two regioisomers with the less hindered regioisomer **396** as the major product.



Scheme 5.12: Friedel-Crafts cyclisation of anilide 394. *Reagents and Conditions:* 2.5 eq. $AlCl_3$, 50°C 10 min, 160°C 1 h.

The aromatic region of the 300 MHz ^{1}H NMR clearly showed the two regioisomers; the aromatic protons of **395** resonate as a triplet at 7.14 ppm, and two doublets at 6.81 ppm and 6.71 ppm (highlighted in blue), whereas the aromatic protons in **396** appear as two doublets at 7.08 ppm and 6.86 ppm and a singlet at 6.68 ppm (highlighted in red).

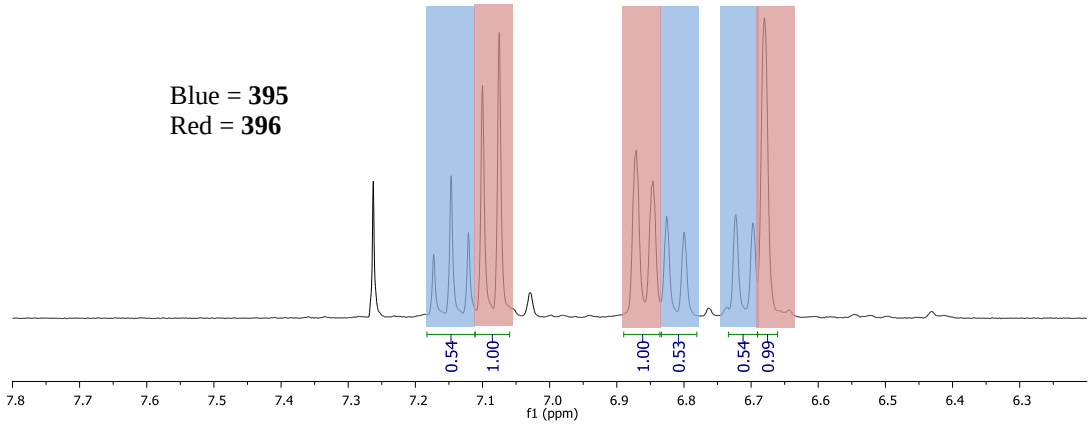
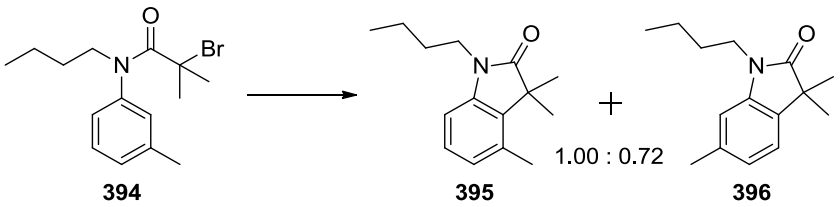


Figure 5.2: Aromatic region of 300 MHz ^{1}H NMR of the intramolecular Friedel-Crafts reaction of 394.

We next carried out a conventional radical cyclisation using Bu_3SnH and AIBN. 1.1 eq. of Bu_3SnH and 0.125 eq. of AIBN were added by syringe pump to a boiling solution of **394** in toluene over two hours and the reaction left to reflux for a further 6 hours at this temperature. A further 1.1 eq. of Bu_3SnH and 0.125 eq. of AIBN were then added over an hour and the reaction mixture refluxed for a further 8 hours. It is known that greater amounts of AIBN are necessary to accomplish radical cyclisations onto aromatic groups as the generated radicals are thought to initiate the oxidation of the intermediate radicals.[224]



Scheme 5.13: Bu_3SnH mediated cyclisation of anilide 394. *Reagents and Conditions:* 2.2 eq. Bu_3SnH, 0.25 eq. AIBN, reflux, 16 h.

The 300 MHz ^1H NMR of the crude reaction mixture was significantly messier than the Friedel-Crafts method, with a number of other unidentified products present, although there was no starting material left in the crude reaction mixture. Both oxindole regioisomers were observed in a 1.00:0.72 ratio (**395**:**396**), however in contrast to the Friedel-Crafts method the more hindered regioisomer **395** was the major product. This suggested that the two approaches led to different regiochemistries.

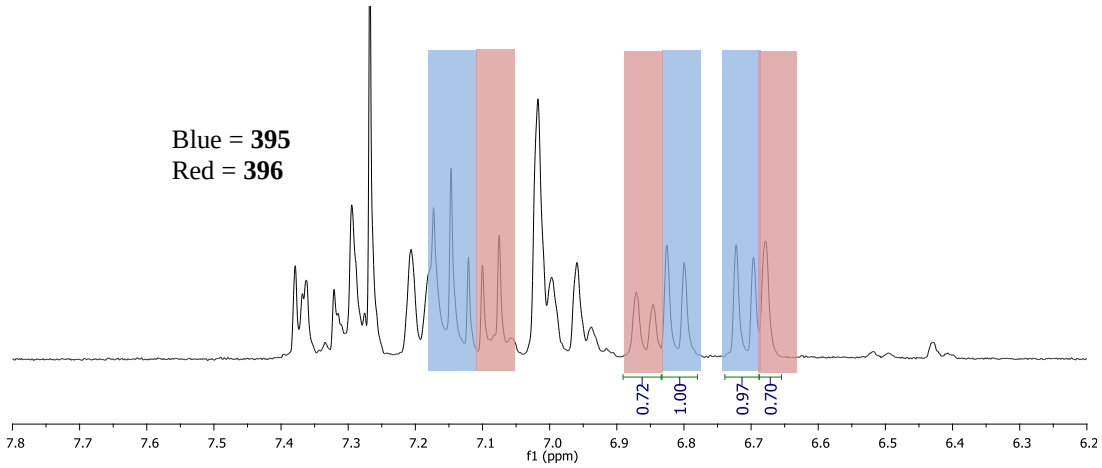
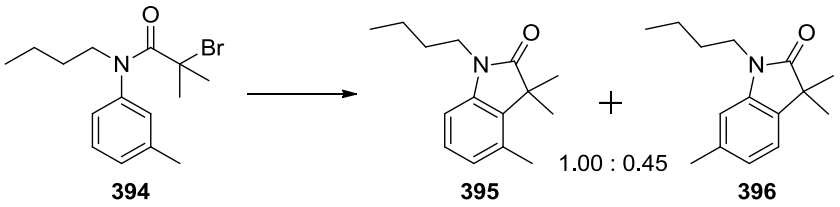


Figure 5.3: Aromatic region of 300 MHz ^{1}H NMR of the Bu_3SnH mediated cyclisation of 394.

We next carried out the cyclisation of **394** using the AGET ATRC conditions, hence 30 mol% CuBr/TPA was added to a solution of **394** in methanol, followed by the portion-wise addition of 3 eq. KBH_4. The reaction mixture was then refluxed for 24 h before filtering through a silica plug and an aqueous workup to give the crude product with a 93% mass conversion.



Scheme 5.14: Copper mediated cyclisation of anilide 394. *Reagents and Conditions:* 0.3 eq. CuBr, 0.3 eq. TPA, 3 eq. KBH_4, MeOH, 50^{o}C.

Disappointingly the crude 300 MHz ^{1}H NMR was very complicated showing many products, with the desired compounds **395** and **396** present only as minor components. However the ratio of the two regioisomers could still be calculated and the more hindered **395** was found to be the favoured regioisomer (**395**:**396** = 1.00:0.45), the same favoured regioisomer as the Bu_3SnH mediated radical

cyclisation giving tentative evidence that the process was a radical reaction rather than a Friedel-Craft process. However, the results need to be treated with caution as the products were only detected in minor amounts.

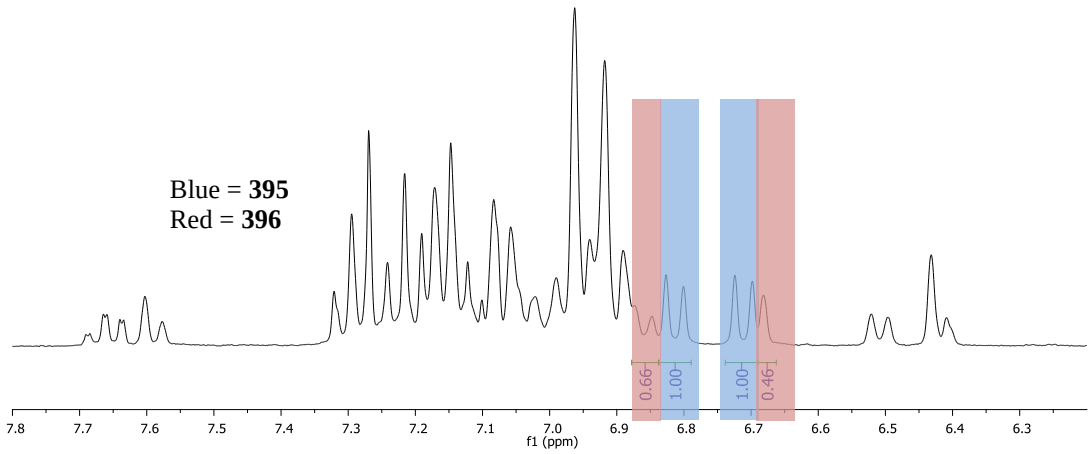
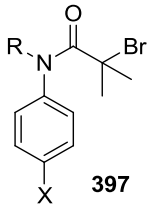


Figure 5.4: Aromatic region of 300 MHz ^{1}H NMR of the copper mediated cyclisation of 394.

5.2.1 Development of Copper Mediated Cyclisation Conditions

While the cyclisation of **394** with CuBr and KBH_4 was disappointing due to its low yield and the many by-products produced we decided to initially explore the scope of the process further. It has been reported that the replacement of CuBr with $CuSO_4$ in KBH_4 mediated ATRC reactions can improve the yields and rates of the processes.[81] We chose a series of anilide precursors **397a-f** for our investigations, varying the electronics of the aromatic group and the size of *N*-alkyl group.



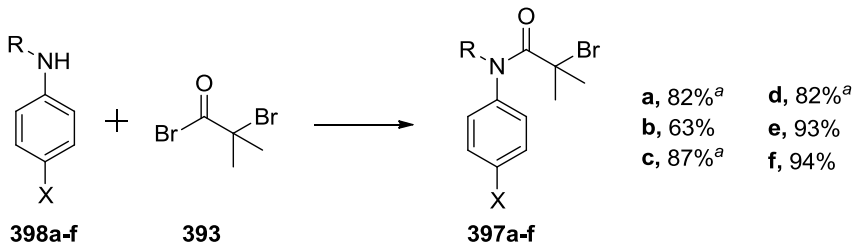
397

a, R = Me, X = H
b, R = iPr, X = H
c, R = Bn, X = H
d, R = Me, X = Cl
e, R = Me, X = OMe
f, R = Me, X = NO_2

Figure 5.5: Anilides synthesised with varying aromatic subsituents and *N*-alkyl group.

5.2.1.1 Synthesis of Substrates 397a-f

The anilide precursors were synthesised by acylation of the appropriate *N*-alkylated aniline with 2-bromoisobutyryl bromide in the presence of Et_3N. Standard organic work up after 24 h yielded the pure products in good yields.



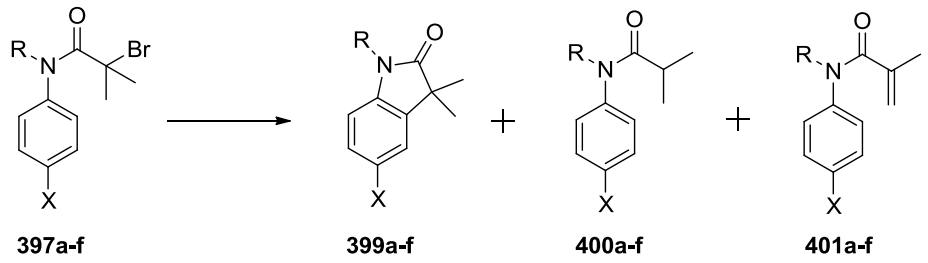
398a-f **393** **397a-f**

a, 82%[a]
b, 63%
c, 87%[a]
d, 82%[a]
e, 93%
f, 94%

Scheme 5.15: Synthesis of oxindole precursors. *Reagents and Conditions:* 1.2 eq. Et_3N, 1.1eq. **393**, 24 h., r.t. [a]The compound used was synthesised previously by Hemal Parekh.

5.2.2 Cyclisations of Anilides 397a-f

We initially cyclised the compounds using AGET ATRC conditions, replacing CuBr with $CuSO_4$. Hence, reaction of **397** with 0.2 eq. $CuSO_4.5H_2O$, 0.2 eq. TPA and 2 eq. KBH_4 over 24 hours at 50 ^oC in MeOH led to a complex mixture of products.



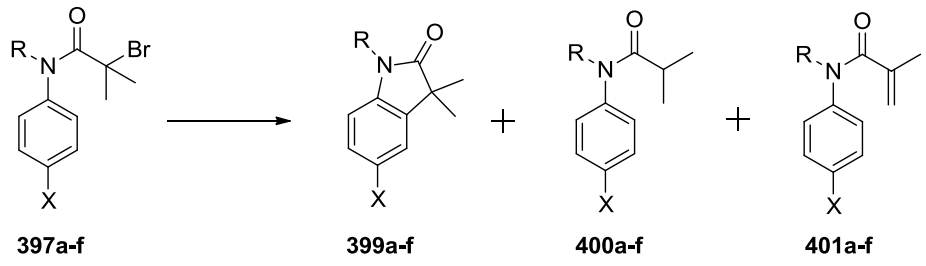
Scheme 5.16: $CuSO_4.5H_2O$ /TPA, KBH_4 mediated cyclisation of anilides. *Reagents and Conditions:* 0.2 eq. $CuSO_4.5H_2O$, 0.2 eq. TPA, 2 eq. KBH_4, MeOH, 50°C.

While the reactions generally did yield the cyclised products **399a-f,** yields were low and there were a number of other by-products. Due to difficulties with separation the by-products were not obtained pure however the main by-products were assigned as the reduced products **400a-f** and the methacrylates **401a-f** based upon characteristic peaks in the ^{1}H NMR along with mass spectrum. The methacrylates **401a-f**, formed by the elimination of HBr from the starting materials **397a-f**, showed two characteristic singlets ~5 ppm for the two alkene protons. In the majority of cases (Table 5.1) the reduced products **400a-f** were observed as the major compounds and were identified by a characteristic septet at ~2.5 ppm and a doublet ~1.1 ppm representing the *iso*-propyl group. The best yield and cleanest crude reaction mixture was obtained from the cyclisation of the chlorinated analogue **397d** (Table 5.1, entry 4).

Entry	Starting Material	R	X	Isolated Yield of Cyclised product	Ratio 399:400:401
1	**397a**	Me	H	10%	1 : 2.81 : 1.80
2	**397b**	*i*Pr	H	[a]	1 : 1.40 : 1.28
3	**397c**	Bn	H	24%[b]	1 : 0.63 : 0.50
4	**397d**	Me	Cl	33%	1 : 0.33 : 0.16
5	**397e**	Me	OMe	20%	1 : 1.58 : 1.38
6	**397f**	Me	NO_2	22% [b]	1 : 2.64 : 0.36

Table 5.1: $CuSO_4.5H_2O$/TPA, KBH_4 mediated cyclisation of anilides. [a]Product was only isolated as a mixture with an unidentified product. [b]Product only isolated as a mixture of two compounds, the yield is calculated based on the ratio of the compounds.

The role of KBH_4 in 'normal' ATRC is supposed to be as a reductant to reduce any 'deactive' copper(II) species to active copper(I) species. However, in these reactions it is likely that we need the copper(II) species to oxidise any cyclised radicals to cations which can then undergo rearomatisation by loss of a proton. Reasoning that the poor yields could be due to the use of 2 eq of KBH_4 within the reaction mixture causing a range of side-reactions we re-investigated the use of CuBr as the copper source, but instead of using a 'catalytic' amount (0.2 eq) we utilised 1 eq with 1 eq of TPA and no KBH_4.



Scheme 5.17: CuBr/TPA mediated cyclisation of anilides. *Reagents and Conditions:* 1eq. CuBr, 1 eq. TPA, MeOH, 0.12M, 50 ^oC.

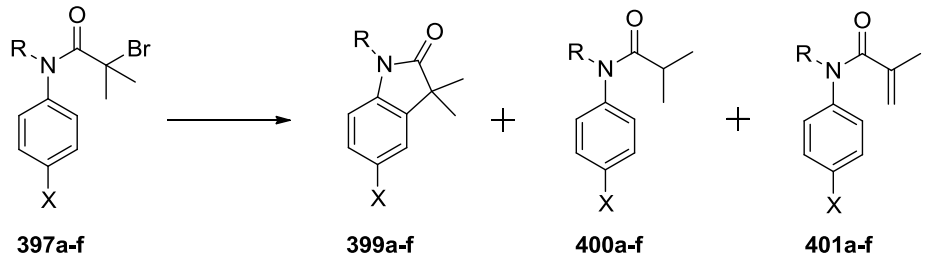
Again the reactions were messy with the three main products being the cyclised product **399**, the reduced product **400**, and the eliminated product **401** along with a number of other unidentified materials. In comparison with the borohydride cyclisations there was significantly less reduced products **400a-f** in the reaction mixtures (presumably due to the absence of the reducing agent), and the cyclised products **399a-f** were the major components in the majority of cases, (Table 5.2). The starting material was fully consumed in most reactions, however for the cyclisation of **397b** and **397e**, significant amounts remained (0.69:1 and 0.46:1 ratio of starting material:cyclised product respectively (Table 5.1, entry 2)). It was found that the smaller *N*-methyl group **397a** led to a higher yield of cyclised product **399a** compared to the bulkier *iso*-propyl **397b** and benzyl groups **397c** (Table 5.1, entries 1-3). Cyclisation of the chlorinated analogue **397d** again gave the best yield and cleanest crude reaction mixture (Table 5.1, entry 4).

Entry	Starting Material	R	X	Isolated Yield of Cyclised product	Ratio 399:400:401:397
1	**397a**	Me	H	35%	1 : 0.22 : 0.48 : 0.00
2	**397b**	*i*Pr	H	8%[a]	1 : 0.59 : 0.78 : 0.69
3	**397c**	Bn	H	13%[a]	1 : 0.87 : 0.56 : 0.00
4	**397d**	Me	Cl	52%	1 : 0.27 : 0.11 : 0.00
5	**397e**	Me	OMe	13%	1 : 0.50 : 0.35 : 0.46
6	**397f**	Me	NO_2	13%	1 : 0.45 : 0.25 : 0.00

Table 5.2: CuBr/TPA mediated cyclisation of anilides. [a]Product only isolated as a mixture of two compounds, the yield is calculated based on the ratio of the compounds.

Conventional ATRC reactions use chlorinated or aromatic solvents rather than alcohols (the latter solvent is necessary for KBH_4 mediated processes). Thus, the next attempt to optimise the process was changing the solvent. We next decided to

try stoichiometric CuBr/TPA in refluxing toluene as opposed to methanol (this also increased the temperature of the reaction from 50 to 110 ^{o}C. Pleasingly this yielded much better results, with significantly cleaner reactions in the majority of cases to give the cyclised products **399**, with mass conversions of 89-99%. The one exception was the cyclisation of **397b** which yielded the cyclised product **399b** as minor product.



Scheme 5.18: CuBr/TPA mediated cyclisation of anilides. *Reagents and Conditions:* 1eq. CuBr, 1 eq. TPA, Tol, 0.12M, 110 ^{o}C.

Entry	Starting Material	R	X	Mass Conversion	Ratio 399:400:401
1	**397a**	Me	H	97%	1 : 0.07 : 0.00
2	**397b**	*i*Pr	H	89%	[a]
3	**397c**	Bn	H	98%	1 : 0.02 : 0.00
4	**397d**	Me	Cl	95%	1 : 0.03 : 0.00
5	**397e**	Me	OMe	99%	1 : 0.02 : 0.00
6	**397f**	Me	NO_2	95%	1 : 0.11 : 0.00

Table 5.3: CuBr/TPA mediated cyclisation of anilides in toluene. [a]Too many products in reaction mixture to allow calculation of ratios.

Figures 5.6 and 5.7 compare the crude 400 MHz ^{1}H NMRs for the CuBr/TPA mediated cyclisation of **397c** and **397e** in both methanol and toluene showing how much cleaner the reactions are in toluene.

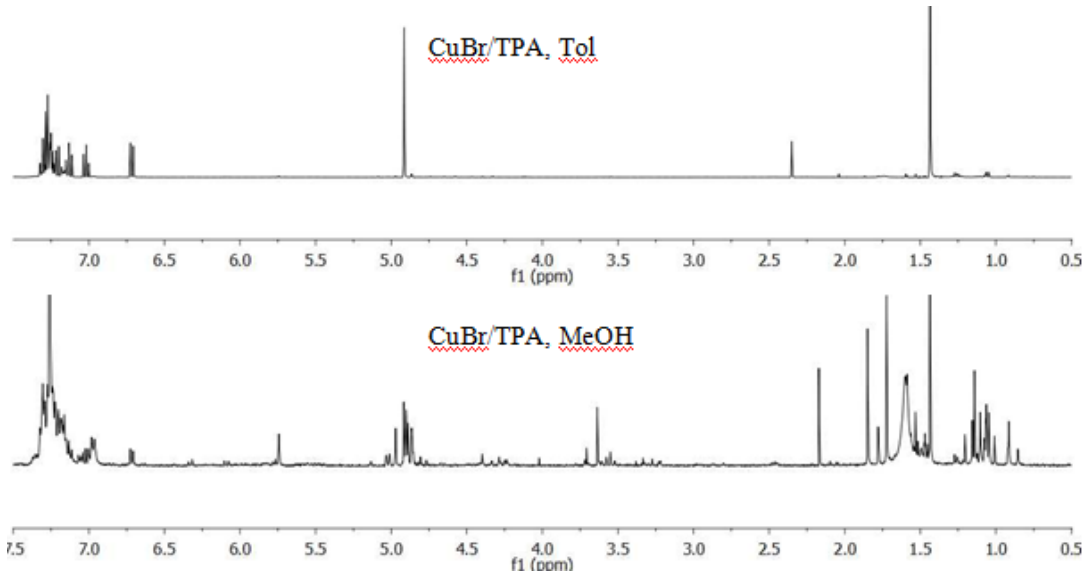


Figure 5.6: Crude 400 MHz ^{1}H NMR for cyclisation of 397c in toluene and methanol.

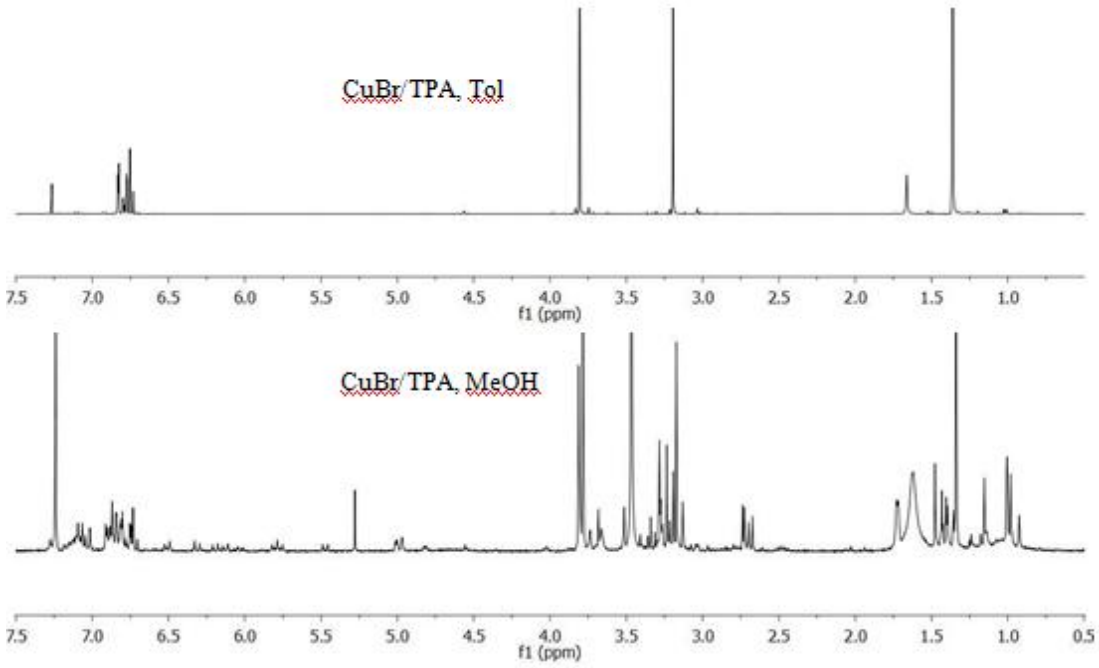


Figure 5.7: Crude 400 MHz ^{1}H NMR for cyclisation of 397e in toluene and methanol.

5.3 Conclusion

Anilides **397a-f** have been shown to undergo copper mediated cyclisations to give oxindole products **399a-f**. Attempts at cyclising the anilides using the AGET ATRC

conditions with catalytic $CuSO_4.5H_2O$ and KBH_4 did yield the cyclised oxindole product, however only in low yields (10-33%). The reactions were messy with several other products, in particular the reduced compounds **400a-f** and the eliminated compounds **401a-f**. Cyclisation mediated by CuBr and TPA in methanol again gave messy reaction mixtures yielding the same products, although with significantly lower amounts of the reduced compounds **400a-f**. Pleasingly however, when the cyclisations were carried out in toluene, in most cases the reactions proceeded cleanly to give the desired oxindole products **399a-f** in pleasing yields.

6.0 Experimental

6.1 General Information and Procedures

Unless stated, the chemicals and solvents, including anhydrous solvents, used in these syntheses were obtained from commercial suppliers and were used without further purification and without exhaustive deoxygenation of solvents. All reactions were performed using oven dried glassware and heat transfer was achieved using drysyn© apparatus. Sodium hydride dispersion in mineral oil (60% w/w) was washed three times with hexane under a constant flow of nitrogen to remove the oil prior to use. Where petroleum ether was used it was the 40-60 ^{o}C fraction and all water used was deionised.

Reactions were followed by TLC, performed on Merck silica gel 60 F-254 TLC sheets; the TLC plate was then visualized with UV fluorescence (254 nm) and then stained with potassium permanganate or vanillin. Flash chromatography was carried out using Merck silica gel 60, 35-75μm as the stationary phase according to the procedure of Still *et. al.*[225]

NMR spectra were obtained at 298 K unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on Bruker DPX-300, DPX-400 and DRX-500 instruments and are referenced to tetramethylsilane (TMS) at 0.00 ppm. Chemical shifts (δ_H) are quoted in parts per million (ppm), coupling constants *J* are quoted in hertz (Hz), and data is quoted as (δ_H, integration, multiplicity). Proton and carbon NMR assignments were routinely confirmed by ^{1}H-^{1}H (COSY), ^{1}H-^{13}C (HMQC) and ^{1}H-^{13}C (HMBC) experiments. For variable temperature NMR samples were submitted to the NMR service and analysis on a Bruker DPX500 spectrometer. Spectra obtained were

analysed using Mestrec© and NUTS© software prior to lineshape analysis using WINDNMR.[145]

Low resolution mass spectra were recorded on Bruker Esquire 2000 for electro spray conditions. Accurate mass spectroscopy was available through the in house mass spec service using either Bruker HCT or Bruker HCT Ultra machines to perform accurate mass ESI analysis. Only molecular ions fractions from molecular ions and other major peaks are reported as mass/charge (*m/z*) ratios.

IR was achieved using a Perkin-Elmer Avatar 320 FTIR spectrometer. Solids were compressed into a thin tablet and oils/non-volatile liquids were analysed as films over a diamond sensor. Absorption maxima (υ_{max}) are recorded in wavenumbers (cm^{-1}).

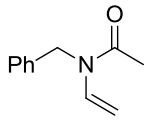
Analytical chiral HPLC was performed by the Curran group in Pittsburgh and was conducted using either an (*S,S*)-Whelk-O 1 column (Pirkle, 250 mm x 4.6 mm ID) or a Chiralcel OD column (Daicel, 250 mm x 4.6 mm ID).

6.2 Compounds Synthesised in Chapter Two

6.2.1 General Procedure for the Synthesis of Enamides *via* an Imine.

Ketone (1 eq.) and benzylamine (1.0 eq.) were dissolved in dry toluene and heated to reflux under Dean-Stark conditions for 4-16 hours. The reaction mixture was then cooled and concentrated *in vacuo* and a crude NMR of the imine intermediate taken, before redisolving in toluene and cooling to 0 ^{o}C. Triethylamine (1.2 eq.) was then added slowly followed by the dropwise addition of the appropriate acid chloride (1.1 eq.). The reaction mixture was then allowed to warm to room temperature and stirred for 12 hours. $NaHCO_3$ (~50 mL) was then added and the layers separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Products were purified by column chromatography.

***N* -benzyl-*N*-vinylacetamide[226] (171)**



171

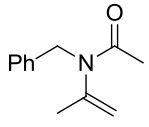
The general procedure for the formation of enamides *via* imines (6.2.1) was applied using acetaldehyde (2 g, 45.4 mmol), benzylamine (4.96 mL, 45.4 mmol), toluene (45 mL, 90 mL), triethylamine (7.56 mL, 54.5 mmol) and acetyl chloride (3.55 mL, 49.9 mmol). The crude product was purified by column chromatography (pet

ether/EtOAc, 4:1) to yield the pure product as an orange oil (1.3 g, 15%). The isolated product was a 1:2 mixture of amide rotamers.

Discernable data for major rotamer: R_f 0.45 (pet ether/EtOAc, 4:1); υ_{max} 2039 (CH), 1670 (C=O), 1619 (C=O); δ_H (300MHz, $CDCl_3$) 7.03 – 7.40 (5H, m, 5 x Ar<u>H</u>), 6.84 (1H, dd, *J* = 15.5, 9.0 Hz, NC<u>H</u>), 4.87 (2H, s, ArC<u>H</u>$_2$), 4.42 (1H, d, *J* = 15.5 Hz, CHC<u>H</u>$_a$H$_b$), 4.30 (1H, dd, *J* = 9.0 Hz, CHCH$_a$<u>H</u>$_b$), 2.31 (3H, s, C<u>H</u>$_3$); δ_C (151 MHz, $CDCl_3$) 169.61 (<u>C</u>=O), 136.93 (Ar<u>C</u>), 133.29 (N<u>C</u>H), 128.52 (Ar<u>C</u>H), 126.99 (Ar<u>C</u>H), 126.79 (Ar<u>C</u>H), 95.32 (CH<u>C</u>H$_2$), 45.39 (N<u>C</u>H$_2$), 22.11 (<u>C</u>H$_3$); *m/z* (ES^+) 198.1 $[M+Na]^+$.

Discernable data for minor rotamer: R_f 0.45 (pet ether/EtOAc, 4:1); υ_{max} 2039 (CH), 1670 (C=O), 1619 (C=O); δ_H (300MHz, $CDCl_3$) 7.60 (1H, dd, *J* = 16.0, 9.5 Hz, NC<u>H</u>), 7.03 – 7.40 (5H, m, 5 x Ar<u>H</u>), 4.76 (2H, s, ArC<u>H</u>$_2$), 4.36 – 4.39 (1H, br m, CHC<u>H</u>$_a$H$_b$), 4.32 (1H, br m, CHC<u>H</u>$_a$H$_b$), 2.15 (3H, s, C<u>H</u>$_3$); δ_C (151 MHz, $CDCl_3$) 169.88 (<u>C</u>=O), 136.04 (Ar<u>C</u>), 131.76 (N<u>C</u>H), 128.95 (Ar<u>C</u>H), 127.42 (Ar<u>C</u>H), 125.58(Ar<u>C</u>H), 94.67(CH<u>C</u>H$_2$), 48.73(N<u>C</u>H$_2$), 22.42(<u>C</u>H$_3$); *m/z* (ES^+) 198.1 $[M+Na]^+$.

_N_ -benzyl- _N_ -(prop-1-en-2-yl)acetamide[227] (172)



172

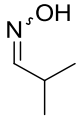
The general procedure for the formation of enamides *via* imines (6.2.1) was applied using acetone (3 g, 51.7 mmol), benzylamine (5.64 mL, 51.7 mmol), toluene (50 mL,

100 mL), triethylamine (8.60 mL, 61.9 mmol) and acetyl chloride (4.04 mL, 56.8 mmol). The crude product was purified by column chromatography (pet ether/EtOAc, 4:1) to yield the pure product as a brown oil (3.11 g, 29%). R_f 0.3 (pet ether/EtOAc, 4:1); υ_{max} 2922 (CH), 1642 (C=O); δ_H (300MHz, $CDCl_3$) 7.11 – 7.38 (5H, m, 5 x Ar<u>H</u>), 4.95 (1H, s, C=C<u>H</u>$_a$H$_b$), 4.64 (1H, s, C=CH$_a$<u>H</u>$_b$), 4.61 (2H, s, NC<u>H</u>$_2$), 2.09 (3H, s, C=OC<u>H</u>$_3$), 1.80 (3H, s, C=CC<u>H</u>$_3$); δ_C (75MHz, $CDCl_3$) 168.97 (<u>C</u>=O), 143.81 (N<u>C</u>=C), 137.21 (Ar<u>C</u>), 127.92 (Ar<u>C</u>H), 127.72 (Ar<u>C</u>H), 126.64 (Ar<u>C</u>H), 115.25 (NC=<u>C</u>H$_2$), 48.33 (N<u>C</u>H$_2$), 21.18 (C=C<u>C</u>H$_3$), 20.36 (C=O<u>C</u>H$_3$); *m/z* (ES^+) 190.2 $[M+H]^+$, 212.2 $[M+Na]^+$.

6.2.2 General procedure for formation of oximes

Ketone (1 eq.), sodium acetate (1.2 eq.) and hydroxylamine hydrochloride (1.2 eq.) in methanol were heated to reflux under an inert atmosphere for 12-16 h. The mixture was then concentrated *in vacuo* and the residue taken up in ethyl acetate (~50 mL) and washed with water (3 × 50 mL). The organic phase was then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the product which was taken on without further purification.

Isobutyraldehyde oxime[228] (173a)



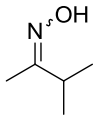
173a

The general procedure for the formation of oximes (6.2.2) was applied using isobutryaldehyde (3 g, 41.6 mmol), sodium acetate (4.10 g, 49.9 mmol), hydroxylamine hydrochloride (3.47 g, 49.9 mmol) and methanol (80 mL). The isolated product was a yellow oil (3.39 g, 94%) and a mixture of isomers in a 1:3.2 ratio.

Major isomer; 0.18 (pet ether/EtOAc, 8:1); υ_{max} 3271 (OH), 2964 (CH);; δ_H (400 MHz, $CDCl_3$) 8.22 (1H, br s, O<u>H</u>), 7.39 (1H, d, *J* = 6.0 Hz, N=C<u>H</u>), 2.53 (1H, dhept, *J* = 7.0, 6.0 Hz, C<u>H</u>$(CH_3)_2$), 1.11 (6H, d, *J* = 7.0 Hz, CH$(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 156.78 (<u>C</u>=N), 29.37 (<u>C</u>H$(CH_3)_2$), 19.81 (CH(<u>C</u>$H_3)_2$); *m/z* (ES^+) 110.1 $[M+Na]^+$.

Minor isomer; R_f 0.18 (pet ether/EtOAc, 8:1); υ_{max} 3271 (OH), 2964 (CH); δ_H (400 MHz, $CDCl_3$) 8.22 (1H, br s, <u>O</u>H), 6.66 (1H, br s, N=C<u>H</u>), 3.23 (1H, apparent octet, *J* = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 1.09 (6H, d, *J* = 7.0 Hz, CH$(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 157.82 (<u>C</u>=N), 24.66 (<u>C</u>H$(CH_3)_2$), 19.51 (CH(<u>C</u>$H_3)_2$); *m/z* (ES^+) 110.1 $[M+Na]^+$.

3-Methylbutan-2-one oxime[158] (176a)



176a

The general procedure for the formation of oximes (6.2.2) was applied using 3-methyl-2-butanone (5 g, 58.1 mmol), sodium acetate (5.71 g, 69.7 mmol), hydroxylamine hydrochloride (4.84 g, 69.7 mmol) and methanol (100 mL). The product was isolated as a colourless liquid (3.59 g, 61%) and a mixture of isomers in a 1:7.9 ratio.

Discernable data for major isomer: R_f 0.36 (pet ether/EtOAc, 6:1); υ_{max} 3240 (OH), 2965 (CH) ; δ_H (400MHz, $CDCl_3$) 8.22 (1H, br s, O<u>H</u>), 2.50 (1H, hept, *J* = 7.0 Hz, C<u>H</u>), 1.86 (3H, s, N=CC<u>H</u>$_3$), 1.10 (6H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 161.89 (N=<u>C</u>), 33.86 (<u>C</u>H(CH$_3$)$_2$), 19.04 (CH(<u>C</u>H$_3$)$_2$), 10.55 (N=C<u>C</u>H$_3$); *m/z* (ES^+) 102.4 $[M+H]^+$.

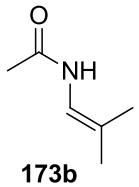
Discernable data for minor isomer: R_f 0.36 (pet ether/EtOAc, 6:1); υ_{max} 3240 (OH), 2965 (CH); δ_H (400MHz, $CDCl_3$) 8.22 (1H, br s, O<u>H</u>), 3.47 (1H, hept, *J* = 7.0 Hz, C<u>H</u>), 1.79 (3H, s, N=CC<u>H</u>$_3$), 1.05 (6H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 162.5 (N=<u>C</u>), 25.1 (<u>C</u>H(CH$_3$)$_2$), 18.2 (CH(<u>C</u>H$_3$)$_2$), 14,8 (N=C<u>C</u>H$_3$); *m/z* (ES^+) 102.4 $[M+H]^+$.

6.2.3 General Procedure for Iron Mediated Synthesis of Enamides

Oxime (1 eq.), acetic acid or chloroacetic acid (3 eq.), acetic anhydride or chloroacetic anhydride (3 eq.) and iron powder (2 eq.) in anhydrous toluene were

heated to reflux under an inert atmosphere for 6-16 hours. The mixture was then filtered through celite, diluted with DCM and washed with 2M NaOH and $NaCl_{(aq)}$. The organic phase was then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. Products were purified by column chromatography or recrystallisation as stated below.

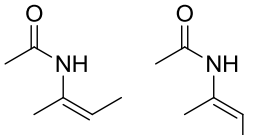
_N_-(2-Methylprop-1-enyl)acetamide[229] (173b)



173b

The general procedure for the iron mediated synthesis of enamides (6.1.3) was applied using isobutryaldehyde oxime (2 g, 22.9 mmol), acetic acid (3.94 mL, 68.9 mmol), acetic anhydride (6.50 mL, 68.9 mmol), iron powder (2.56 g, 45.3 mmol) and anhydrous toluene (30 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 1:1) to give the product as a yellow oil (113 mg, 4%). R_f 0.2 (pet ether/EtOAc, 1:1); δ_H (400MHz, $CDCl_3$) 6.88 (1H, br s, N<u>H</u>), 6.51 (1H, d, *J* = 10.5 Hz, NC<u>H</u>), 2.06 (3H, s, C=OC<u>H</u>$_3$), 1.70 (3H, s, C=C(C<u>H</u>$_3$)(CH$_3$)), 1.63 (3H, s, C=C(CH$_3$)(C<u>H</u>$_3$)); δ_C (100MHz, $CDCl_3$) 167.1 (<u>C</u>=O), 117.0 (N<u>C</u>H), 115.2(HC=<u>C</u>(CH$_3$)$_2$), 23.3 (C=O<u>C</u>H$_3$), 22.4 (C=C(<u>C</u>H$_3$)(CH$_3$)), 16.5 (C=C(CH$_3$)(<u>C</u>H$_3$)); *m/z* (ES^+) 136.2 $[M+Na]^+$.

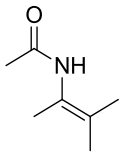
(*Z*)-*N*-(But-2-en-2-yl)acetamide[171] (174a) and (*E*)-*N*-(But-2-en-2-yl)acetamide[171] (175a)



174a **175a**

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using butanone oxime (3 g, 34.4 mmol), acetic acid (5.91 mL, 103 mmol), acetic anhydride (9.74 mL, 103 mmol), iron powder (3.84 g, 68.9 mmol) and anhydrous toluene (60 mL). The product was taken on to the next step without further purification. δ_H (400MHz, $CDCl_3$) 6.53 (1H, br s, N<u>H</u>), 5.72 (1H min, q, *J* = 7.0 Hz, C=C<u>H</u>), 5.04 (1H maj, q, *J* = 6.5 Hz, C=C<u>H</u>), 2.06 (3H maj, s, C=OC<u>H</u>$_3$), 2.01 (3H min, s, C=COC<u>H</u>$_3$), 1.98 (3H maj, s, NHCC<u>H</u>$_3$), 1.86 (3H min, s, NHCC<u>H</u>$_3$), 1.63 (3H min, d, *J* = 7.0 Hz, C=CHC<u>H</u>$_3$), 1.54 (3H maj, d, *J* = 6.5 Hz, C=CHC<u>H</u>$_3$); *m/z* (ES^+) 136.2 $[M+Na]^+$.

_N_-(3-Methylbut-2-en-2-yl)acetamide[230] (176b)



176b

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 3-methylbutan-2-one oxime (3.2 g, 31.6 mmol), acetic acid (5.43 mL, 94.9 mmol), acetic anhydride (8.95 mL, 94.9 mmol), iron powder (3.53 g, 63.3 mmol) and anhydrous toluene (120 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 1:1) followed by recrystallisation from 10:1 pet

ether/EtOAc to give the product as an orange solid (617 mg, 15%). The product was a 4:1 ratio of amide rotamers.

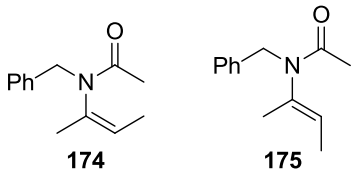
Discernable data for major rotamer: R_f 0.12 (pet ether/EtOAc, 1:1); m.p. 70 - 72 ^oC; υ_{max} 3240 (CH) 2912 (CH), 1643 (C=O); δ_H (400MHz, $CDCl_3$) 6.37 (1H, s, N<u>H</u>), 2.03 (3H, s, C=OC<u>H</u>$_3$), 1.88 (3H, s, C=C(C<u>H</u>$_3$)NH), 1.71 (3H, s, C=C(C<u>H</u>$_3$)(CH_3)), 1.63 (3H, s, C=C(CH_3)(C<u>H</u>$_3$)); δ_C (100MHz, $CDCl_3$) δ 168.0 (C=O), 124.8 (<u>C</u>=C(CH_3)$_2$), 123.5 (C=<u>C</u>(CH_3)$_2$), 22.7 (C=O<u>C</u>H_3), 19.0 (C<u>H</u>$_3$), 18.9 (<u>C</u>H_3), 16.8 (<u>C</u>H_3); *m/z* (ES^+) 128.2 $[M+H]^+$, 150.1 $[M+Na]^+$, 277.0 $[2M+Na]^+$.

Discernable data for major rotamer: R_f 0.12 (pet ether/EtOAc, 3:1); m.p. 70 - 72 ^oC; υ_{max} 3240 (CH) 2912 (CH), 1643 (C=O); δ_H (400MHz, $CDCl_3$) 6.21 (1H, s, N<u>H</u>), 1.90 (3H, s, C=OC<u>H</u>$_3$), 1.83 (3H, s, C=C(C<u>H</u>$_3$)NH), 1.74 (3H, s, C=C(C<u>H</u>$_3$)(CH_3)), 1.69 (3H, s, C=C(CH_3)(C<u>H</u>$_3$)); δ_C (100MHz, $CDCl_3$) 168.0 (C=O), 124.8 (<u>C</u>=C(CH_3)$_2$), 123.5 (C=<u>C</u>(CH_3)$_2$), 19.2 (C<u>H</u>$_3$), 19.1 (C<u>H</u>$_3$), 19.0 (C<u>H</u>$_3$), 18.6 (C<u>H</u>$_3$); *m/z* (ES^+) 128.2 $[M+H]^+$, 150.1 $[M+Na]^+$, 277.0 $[2M+Na]^+$.

6.2.4 General procedure for the alkylation of enamides

Enamide (1 eq.) was added to sodium hydride (5 eq.) in anhydrous THF and cooled to 0 ^oC. Benzyl bromide (1.05 eq.) was then added and the reaction heated to reflux under an inert atmosphere for 10-16 hours. The reaction mixture was then added to water and extracted with ethyl acetate. The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. Products were purified by column chromatography or recrystallisation as stated below.

(*Z*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide (174) and (*E*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide (175)



174 **175**

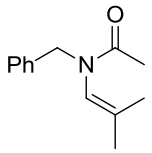
The general procedure for the alkylation of enamides (6.2.4) was applied using *N*-(But-2-en-2-yl)acetamide (200 mg, 1.77 mmol), sodium hydride (354 mg, 8.84 mmol) and benzyl bromide (0.22 mL, 1.86 mmol) and anhydrous THF (25 mL). The crude product showed a 2:1 (*Z:E*) ratio of isomers. This was purified by column chromatography (pet ether/EtOAc, 6:1) to give (*Z*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide as a yellow oil (57 mg, 16%), and a (*E*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide as a 1:1.8 (*Z:E*) mixture with the *Z* isomer (153 mg).

(*Z*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide: R_f 0.1 (pet ether/EtOAc, 6:1); υ_{max} 2934 (CH), 1655 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.08 – 7.34 (5H, m, 5 x Ar<u>H</u>), 5.30 (1H, q, *J* = 7.0 Hz, C=C<u>H</u>), 4.73 (1H, d, *J* = 14.0 Hz, NC<u>H</u>$_a$H$_b$), 4.32 (1H, d, *J* = 14.0 Hz, NCH$_a$<u>H</u>$_b$), 1.93 (3H, s, C=OC<u>H</u>$_3$), 1.67 (3H, s, C=C(N)C<u>H</u>$_3$), 1.11 (3H, d, *J* = 7.0 Hz, C=CHC<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) δ 169.7 (<u>C</u>=O), 137.7 (Ar<u>C</u>), 136.3 (N<u>C</u>=CH), 129.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 124.2 (NC=<u>C</u>H), 48.5 (N<u>C</u>H$_2$Ar), 21.3 (C=C(N)<u>C</u>H$_3$), 21.1 (C=O<u>C</u>H$_3$), 12.6 (NC=CH<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{13}H_{18}NO$ requires 204.1383, found: 204.1383 $[M+H]^+$.

(*E*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide: R_f 0.075 (pet ether/EtOAc, 6:1); υ_{max} 2934 (CH), 1655 (C=O); δ_H (400MHz, $CDCl_3$) δ 76.99 – 7.42 (5H, m, 5 x Ar<u>H</u>), 5.11 (1H, q, *J* = 7.0 Hz, C=C<u>H</u>), 4.53 (1H, s, NC<u>H</u>$_a$<u>H</u>$_b$), 1.97 (3H, s, C=OC<u>H</u>$_3$), 1.64

(3H, s, C=C(N)C$\underline{H}_3$), 1.50 (3H, d, J = 7.0 Hz, C=CHC$\underline{H}_3$); δ_C (100MHz, $CDCl_3$) δ 170.0 ($\underline{C}$=O), 138.1 (Ar$\underline{C}$), 137.3 (N$\underline{C}$=CH), 128.7 (Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 126.4 (Ar$\underline{C}$H), 125.9 (NC=$\underline{C}$H), 49.4 (N$\underline{C}H_2$Ar), 21.7 (C=C(N)$\underline{C}H_3$), 15.7 (C=O$\underline{C}H_3$), 13.2 (NC=CH$\underline{C}H_3$); *m/z* (ES^+) $C_{13}H_{18}NO$ requires 204.1383, found: 204.1383 $[M+H]^+$.

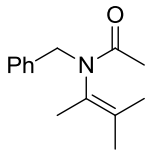
_N_-benzyl-_N_-(2-methylprop-1-enyl)acetamide[231] (173)



173

The general procedure for the alkylation of enamides (6.2.4) was applied using *N*-(But-2-en-2-yl)acetamide (200 mg, 1.77 mmol), sodium hydride (354 mg, 8.84 mmol) and benzyl bromide (0.22 mL, 1.86 mmol) and anhydrous THF (25 mL). The crude product showed a 2:1 (*Z:E*) ratio of isomers. This was purified by column chromatography (pet ether/EtOAc, 4:1) to give the product as a colourless oil (99 mg, 28%). R_f 0.35 (pet ether/EtOAc, 4:1); υ_{max} 2914 (CH), 1647 (C=O); δ_H (400MHz, $CDCl_3$) 7.11 – 7.37 (5H, m, 5 x Ar$\underline{H}$), 5.75 (1H, apparent quintet, J = 1.0 Hz, NC($\underline{H}$)=C), 4.56 (2H, s, N$\underline{C}H_2$Ar), 1.97 (3H, s, C=OC$\underline{H}_3$), 1.65 (3H, d, J = 1.0 Hz, C=C(C$\underline{H}_3$)(CH_3)), 1.39 (3H, d, J = 1.0 Hz, C=C(CH_3)(C$\underline{H}_3$)); δ_C (100MHz, $CDCl_3$) 170.2 ($\underline{C}$=O), 136.8 (Ar$\underline{C}$), 135.7 (C(H)=$\underline{C}$(CH_3)$_2$), 128.1 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 123.2 (N$\underline{C}$(H)=C, 49.9 (N$\underline{C}H_2$Ar), 21.4 (C=O$\underline{C}H_3$), 21.2 (C(H)=C($\underline{C}H_3$)(CH_3), 16.8 (C(H)=C(CH_3)($\underline{C}H_3$); *m/z* (ES^+) 204.1 $[M+H]^+$, 226.1 $[M+Na]^+$, 429.0 $[2M+Na]^+$.

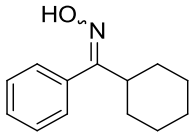
_N_-benzyl-_N_-(3-methylbut-2-en-2-yl)acetamide (176)



176

The general procedure for the alkylation of enamides (6.2.4) was applied using *N*-(3-methylbut-2-en-2-yl)acetamide (500 mg, 3.93 mmol), sodium hydride (786 mg, 19.66 mmol) and benzyl bromide (0.49 mL, 4.13 mmol) and anhydrous THF (60 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 4:1) to give the product as a yellow oil (680 mg, 80%). R_f 0.33 (pet ether/EtOAc, 4:1); υ_{max} 2920 (CH), 1644 (C=O); δ_H (400MHz, $CDCl_3$) 7.18 – 7.44 (5H, m, 5 x Ar<u>H</u>), 4.67 (1H, d, *J* = 14.0 Hz, NC<u>H</u>$_a$H$_b$Ar), 4.53 (1H, d, *J* = 14.0 Hz, NCH$_a$<u>H</u>$_b$), 1.98 (3H, s, C=OC<u>H</u>$_3$), 1.71 (3H, s, NC(C<u>H</u>$_3$)=C(CH$_3$)(CH$_3$)), 1.67 (3H, s, NC(CH$_3$)=C(C<u>H</u>$_3$)(CH$_3$)), 1.30 (3H, s, NC(CH$_3$)=C(CH$_3$)(C<u>H</u>$_3$)); δ_C (375 MHz, $CDCl_3$) 170.2 (<u>C</u>=O), 137.8 (Ar<u>C</u>), 131.1 (NC=<u>C</u>(CH$_3$)$_2$), 129.5 (Ar<u>C</u>H), 129.4 (N<u>C</u>=C), 128.2 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 49.1 (N<u>C</u>H$_2$Ar), 21.3 (C=O<u>C</u>H$_3$), 19.6 (NC(<u>C</u>H$_3$)=C(CH$_3$)$_2$), 19.4 (NC(CH$_3$)=C(<u>C</u>H$_3$)(CH$_3$)), 17.5 (NC(CH$_3$)= C(CH$_3$)(<u>C</u>H$_3$)); *m/z* (ES$^+$) $C_{14}H_{20}NO$ requires 218.1539, found: 218.1540 $[M+H]^+$.

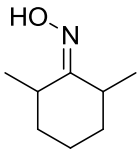
Cyclohexyl phenyl ketoxime[170] (181)



181

The general procedure for the formation of oximes (6.2.2) was applied using cyclohexyl phenyl ketone (2 g, 10.6 mmol), sodium acetate (1.05 g, 12.7 mmol), hydroxylamine hydrochloride (0.886 mg, 12.7 mmol) and methanol (25 mL). The isolated product was an off white solid (2.00 g, 93%) and a mixture of isomers in a 2:1 ratio. R_f 0.34 (pet ether/EtOAc, 6:1); m.p. 162-164 ^oC, lit[232] 158-158.5 ^oC; υ_{max} 3230 (OH), 2925 (CH); δ_H (400MHz, $CDCl_3$) 9.33 (1H, s, O<u>H</u>), 7.23 – 7.56 (5H, m, 5 × Ar<u>H</u>), 3.25 – 3.49 (0.33H, m, N=CC<u>H</u> min), 2.42 – 2.60 (0.67H, m, N=CC<u>H</u> maj), 1.99 – 1.08 (10 H, m, cy); δ_C (100MHz, $CDCl_3$) 162.8 (<u>C</u>=N), 136.1, 134.0 (N=<u>C</u>), 128.4, 128.2, 128.1, 128.0, 127.5 (Ar<u>C</u>), 44.3 (N=C<u>C</u>H), 38.2 (N-C<u>C</u>H), 30.5 (cy) 29.3 (cy), 26.3 (cy), 26.2 (cy), 26.0 (cy); *m/z* (ES^+) 204.2 $[M+H]^+$, 226.2 $[M+Na]^+$.

2,6-dimethylcyclohexanone oxime[233] (182)

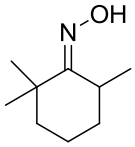


182

The general procedure for the formation of oximes (6.2.2) was applied using 2,6-dimethylcyclohexanone (2 g, 15.8 mmol), sodium acetate (1.56 g, 19.0 mmol), hydroxylamine hydrochloride (1.32 g, 19.0 mmol) and methanol (30 mL). The isolated product was a pale yellow oil (2.18 g, 97%). R_f 0.55 (pet ether/EtOAc, 6:1);

υ_{max} 3249 (OH), 2964 (C-H); The product was identified by GC-MS as the ^{1}H-NMR spectrum was inconclusive, showing a complex mixture of isomers.

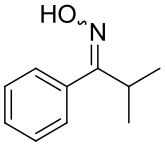
2,2,6-trimethylcyclohexanone oxime[234] 183



188

The general procedure for the formation of oximes (6.2.2) was applied using 2,2,6-trimethylcyclohexanone (3 g, 21.4 mmol), sodium acetate (2.11 g, 25.7 mmol), hydroxylamine hydrochloride (1.78 g, 25.7 mmol) and methanol (40 mL). The isolated product was a white solid (2.74 g, 82%) and a single isomer. R_f 0.24 (pet ether/EtOAc, 6:1); m.p. 102-103 ^{o}C, lit[235] 103 ^{o}C; υ_{max} 3244 (OH), 2936 (CH); δ_H (400MHz, $CDCl_3$) 3.50 – 3.6 (1H, m, C<u>H</u>), 1.73 – 1.88 (1H, m, cy), 1.55 – 1.66 (3H, m, cy), 1.43 – 1.55 (2H, m, cy), 1.24 (6H, s, C(C<u>H</u>$_3$)$_2$), 1.21 (3H, d, *J* = 10.0, CHC<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 168.6 (<u>C</u>=N), 40.5 (<u>C</u>H$_2$), 37.0 (<u>C</u>(CH$_3$)$_2$), 31.3(<u>C</u>H$_2$), 29.1, 28.7 (C(<u>C</u>H$_3$)$_2$), 26.5 (<u>C</u>HCH$_3$), 18.5 (CH<u>C</u>H$_3$), 17.3 (<u>C</u>H$_2$); *m/z* (ES$^+$) 156.1 $[M+H]^+$, 178.1 $[M+Na]^+$.

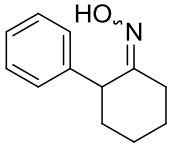
Isobutyrophenoxime[154] (184)



184

The general procedure for the formation of oximes (6.2.2) was applied using isobutyrophenone (5 g, 33.7 mmol), sodium acetate (3.32 g, 40.5 mmol), hydroxylamine hydrochloride (2.81 g, 40.5 mmol) and methanol (60 mL). The isolated product was a colourless crystalline solid (4.93 g, 89%) and a mixture of isomers in a 2:1 ratio. R_f 0.28 (pet ether/EtOAc, 6:1); m.p. 65-67 ^{o}C, lit[236] 58-60 ^{o}C; υ_{max} 3134 (OH), 2959 (CH); δ_H (300MHz, $CDCl_3$) 8.95 (1H, s, O<u>H</u>), 7.23 – 7.46 (5H, m, 5 × Ar<u>H</u>), 3.60 (0.33H, hept, *J* = 7.0, N=CC<u>H</u> min), 2.83 (0.65H, hept, *J* = 7.0, N=CC<u>H</u> maj), 1.22 (2H, d, *J* = 7.0, 2 × C<u>H</u>$_3$ min), 1.12 (4H, d, *J* = 7.0, 2 × C<u>H</u>$_3$ maj); δ_C (100MHz, $CDCl_3$) 165.0 (C=N), 163.4 (C=N), 135.8, 13.7 (quarternary), 128.5, 128.5, 128.2, 128.1, 127.8, 127.6 (Ar<u>C</u>), 34.6 (<u>C</u>H maj), 27.7 (<u>C</u>H min), 20.1 (<u>C</u>H$_3$ maj), 19.4 (<u>C</u>H$_3$ min); *m/z* (ES$^+$) 164.2 $[M+H]^+$, 186.2 $[M+Na]^+$.

2-Phenylcyclohexanone oxime[237] (185)

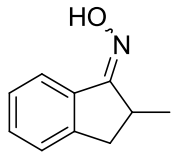


185

The general procedure for the formation of oximes (6.2.2) was applied using 2-phenylcyclohexanone (3 g, 17.2 mmol), sodium acetate (1.69 g, 20.7 mmol), hydroxylamine hydrochloride (1.44 g, 20.7 mmol) and methanol (35 mL). The

isolated product was an off white solid (3.19 g, 98%) and was a mixture of isomers in a 3:1 ratio. R_f 0.64 (pet ether/EtOAc, 6:1); m.p. 169-172 ^oC, lit[238] 174-175 ^oC; υ_{max} 3213 (OH), 2935 (CH); δ_H (400MHz, $CDCl_3$) 7.19 – 7.44 (5H, m, 5 × Ar<u>H</u>), 4.73 – 4.98 (0.25H, m, N=CC<u>H</u> min), 3.45 – 3.61 (0.75H, m, N=CC<u>H</u> maj), 2.88 – 3.04 (0.75H, m, N=CC<u>H</u>H maj), 2.34 – 2.52 (0.50H, m, N=CC<u>H</u>$_2$ min), 2.22 – 2.32 (0.75H, m, N=CCH<u>H</u> maj), 2.01 – 2.18 (2H, m, cy), 1.77 – 1.96 (2H, m, cy), 1.52 – 1.74 (2H, m, cy); δ_C (100MHz, $CDCl_3$) 161.3 (<u>C</u>=N), 139.9 (quarternary), 127.7, 127.6, 125.9 (Ar<u>C</u>), 47.4 (<u>C</u>H), 32.4, 25.1, 24.0, 23.3 (<u>C</u>H_2); *m/z* (ES^+) 190.1 $[M+H]^+$.

2-Methyl-1-indanone oxime[239] (186)

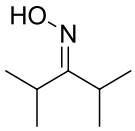


186

The general procedure for the formation of oximes (6.2.2) was applied using 2-methylindanone (3 g, 20.5 mmol), sodium acetate (2.02 g, 24.6 mmol), hydroxylamine hydrochloride (1.71 g, 24.6 mmol) and methanol (40 mL). The isolated product was an orange crystalline solid (3.21 g, 97%) and was a mixture of isomers in an 11:6 ratio. R_f 0.29 (pet ether/EtOAc, 6:1); m.p. 94-96 ^oC, lit[240] 104 ^oC; υ_{max} 3056 (OH), 2866 (CH), 1655 (C=N); δ_H (400MHz, $CDCl_3$) 8.59 – 8.34 (0.35H, m, *J* = 7.5, Ar<u>H</u> min), 7.67 (0.65H, d, *J* = 7.5, Ar<u>H</u> maj), 7.19 – 7.49 (3H, m, 3 × Ar<u>H</u>), 3.54 – 3.65 (0.65H, m, N=CC<u>H</u> maj), 3.34 (1H, dd, *J* = 16.5, 8.0, ArC<u>H</u>H maj + min), 3.12 – 3.23 (0.35H, m, N=CC<u>H</u> min), 2.72 (0.35H, dd, *J* = 16.5, 4.5, ArCH<u>H</u> min), 2.65 (0.65H, d, *J* = 16.5, ArCH<u>H</u> maj), 1.38 (1.95H, d, *J* = 7.0, C<u>H</u>$_3$

maj), 1.37 (1.05H, d, *J* = 7.0, C<u>H</u>$_3$ min); δ_C (100MHz, $CDCl_3$) 167.0, 163.7 (<u>C</u>=N), 147.6, 147.0, 135.2, 133.22 (quarternary), 131.1, 130.5, 129.8, 127.1, 126.9, 125.8, 125.5, 122.0 (Ar<u>C</u>), 38.21, 38.1 (<u>C</u>H$_2$), 36.3, 34.2 (<u>C</u>H), 20.0, 18.2 (<u>C</u>H$_3$); *m/z* (ES^+) 162.0 $[M+H]^+$, 184.0 $[M+Na]^+$.

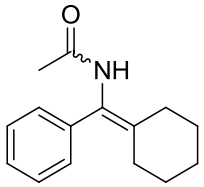
2,4-Dimethyl-3-pentanone oxime[241] (187)



187

The general procedure for the formation of oximes (6.2.2) was applied using 2,4-dimethyl-3-pentanone (5 g, 43.8 mmol), sodium acetate (4.31 g, 52.5 mmol), hydroxylamine hydrochloride (3.65 g, 52.5 mmol) and methanol (80 mL). The isolated product was a colourless crystalline solid (4.72g, 83%). R_f 0.46 (pet ether/EtOAc, 6:1); m.p. 34-36 ^oC, lit[242] 33-34 ^oC; υ_{max} 3264 (OH), 2964 (CH); δ_H (400MHz, $CDCl_3$) 9.35 (1H, s, O<u>H</u>), 3.21 (1H, hept, *J* = 7.0, C<u>H</u>), 2.56 (1H, hept, *J* = 7.0, C<u>H</u>), 1.16 (6H, d, *J* = 7.0, 1C<u>H</u>$_3$), 1.12 (6H, d, *J* = 7.0, C<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 168.6 (C=N), 30.6, 27.5 (<u>C</u>H), 21.2, 18.8 (<u>C</u>H$_3$); *m/z* (ES^+) 103.3 $[M+H]^+$, 152.2 $[M+Na]^+$.

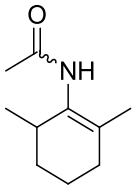
_N_-(cyclohexylidene(phenyl)methyl)-acetamide[169] (188)



188

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using cyclohexylphenylketoxime (1.60 g, 7.87 mmol), acetic acid (1.35 mL, 23.6 mmol), acetic anhydride (2.23 mL, 23.6 mmol), iron powder (879 mg, 15.7 mmol) and anhydrous toluene (12 mL). The crude product was purified by recrystallisation from petroleum ether /ethyl acetate 10:1 to give *N*-(cyclohexylidene(phenyl)methyl)-acetamide as a yellow crystalline solid (877 mg, 49%) and a mixture of rotamers in a 7:3 ratio. R_f 0.55 (pet ether/EtOAc, 1:1); m.p. 124-127 ^{o}C, lit[169] 130-131 ^{o}C; υ_{max} 3235 (NH), 2914 (CH), 1655 (C=O); δ_H (400MHz, $CDCl_3$) 7.17 – 7.49 (5H, m, 5 × Ar<u>H</u>), 6.68 (0.3H, br s, N<u>H</u> min), 6.47 (0.7H, br s, N<u>H</u> maj), 2.21 – 2.48 (4H, m, C=C(C<u>H</u>$_2$)$_2$), 2.08 (2.1H, s, C<u>H</u>$_3$ maj), 1.84 (0.9H, s, C<u>H</u>$_3$ min), 1.55 – 1.74 (6H, m, cy); δ_C (75MHz, $CDCl_3$) 173.4 (C=O), 168.3 (C=0), 138.8, 138.6, 138.1, 137.6 (Ar/N<u>C</u>=C quarternary), 129.1, 128.3, 128.1, 127.6, 127.2 (Ar<u>C</u>), 127.0, 124.9 (NC=<u>C</u>), 31.1, 31.0, 30.9, 30.6, 28.1, 27.6, 27.4, 26.5, 26.4 (cy), 23.5 (<u>C</u>H$_3$ maj), 20.7 (<u>C</u>H$_3$ min); *m/z* (ES$^+$) 252.1 [M+Na]$^+$.

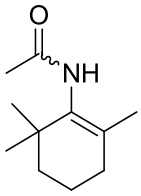
***N*-(2,6- dimethylcyclohexen-1-yl)-acetamide (189)**



189

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2,6-dimethycyclohexanone oxime (1.8 g, 12.6 mmol), acetic acid (2.19 mL, 38.3 mmol), acetic anhydride (3.61 mL, 38.3 mmol), iron powder (1.42 g, 25.5 mmol) and anhydrous toluene (18 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 6:1 to 1:1) to yield the pure product as an off white solid (490 mg, 23%). The isolated product was a mixture of isomers in a 2:1 ratio. R_f 0.36 (pet ether/EtOAc, 1:1); m.p. 125-127 ^{o}C; υ_{max} 3251 (NH), 2925 (CH), 1638 (C=O); δ_H (400MHz, $CDCl_3$) 6.25 (1H, s, N<u>H</u>), 2.36 – 2.50 (0.67H, m, C<u>H</u> maj), 2.15 (0.33H, m, C<u>H</u> min), 2.05 (2H, s, C(O)C<u>H</u>$_3$ maj), 2.00 – 2.07 (2H, m, CC<u>H</u>$_2$), 1.89 (1H, s, C(O)C<u>H</u>$_3$ min), 1.71 – 1.83 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.64 (1H, s, CC<u>H</u>$_3$ min), 1.52 – 1.68 (1H, m, CHC<u>H</u>H), 1.58 (2H, s, CC<u>H</u>$_3$ maj), 1.36 – 1.50 (1H, m, CHCH<u>H</u>), 1.03 (1H, d, *J* = 7.0, CHC<u>H</u>$_3$ min), 0.99 (2H, d, *J* = 7.0, CHC<u>H</u>$_3$ maj); δ_C (75MHz, $CDCl_3$) 168.3 (<u>C</u>=O), 130.5, 128.8 (<u>C</u>=<u>C</u>), 34.23 (<u>C</u>H), 32.14 (<u>C</u>H$_3$), 31.40, 31.28, 31.21, 31.01 (<u>C</u>H$_2$), 23.42, 19.73 (<u>C</u>H$_3$), 19.48 (<u>C</u>H$_2$), 18.97, 18.76, 18.57 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{10}H_{17}NNaO^+$ requires 190.1202, found 190.1207 $[M+Na]^+$.

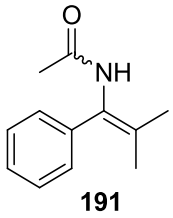
***N*-(2,2,6- trimethylcyclohexen-1-yl)-acetamide (190)**



190

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2,2,6-trimethylcyclohexanone oxime (2.40 g, 15.5 mmol), acetic acid (2.65 mL, 46.4 mmol), acetic anhydride (4.38 mL, 46.4 mmol), iron powder (1.73 g, 30.9 mmol) and anhydrous toluene (25 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1 to 1:1) to give *N*-(2,2,6-trimethylcyclohexen-1-yl)-acetamide as a yellow solid (403 mg, 14%). The product was a mixture isomers in a 2:1 ratio. R_f 0.50 (pet ether/EtOAc, 1:1); m.p. 122-124 ^{o}C; υ_{max} 3271 (NH), 2926 (CH), 1649 (C=O); δ_H (400MHz, $CDCl_3$) 6.41 (0.33H, s, N$\underline{H}$ min), 6.32 (0.67H, s, N$\underline{H}$ maj), 2.07 (2H, s, C(O)C$\underline{H}_3$ maj), 2.03 – 2.09 (2H, m, C=CC$\underline{H}_2$), 1.89 (1H, s, C(O)C$\underline{H}_3$ min), 1.62 (1H, s, C=CC$\underline{H}_3$ min), 1.48 – 1.68 (4H, m, C(CH$_3$)$_2$C$\underline{H}_2$C$\underline{H}_2$), 1.54 (2H, s, C=CC$\underline{H}_3$ maj), 1.01 (2H, s, C(C$\underline{H}_3$)$_2$ min), 1.00 (4H, s, C(C$\underline{H}_3$)$_2$ maj); δ_C (100MHz, $CDCl_3$) 173.6, 168.3 (C=0), 134.4, 131.8, 131.5, 130.3 (C=C), 38.83, 38.72, 35.61, 35.06 ($\underline{C}H_2$), 31.90, 31.69 (C=C$\underline{C}H_2$), 27.27, 27.11, 27.0, 26.42 (C($\underline{C}H_3$)$_2$), 23.32, 19.45 (CO$\underline{C}H_3$), 19.28, 19.19 (C=C$\underline{C}H_3$), 18.98, 18.88 ($\underline{C}$(CH$_3$)$_2$); *m/z* (ES$^+$) $C_{11}H_{19}NNaO^+$ requires 204.1364, found 204.1366 $[M+Na]^+$.

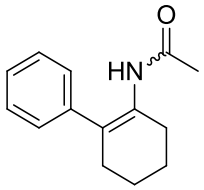
***N*-(1-phenyl-2-methylprop-1-en-1-yl)-acetamide[169] (191)**



191

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using isobutyrophenoxime (4.93 g, 30.2 mmol), acetic acid (5.19 mL, 90.6 mmol), acetic anhydride (8.55 mL, 90.6 mmol), iron powder (3.37 g, 60.4 mmol) and anhydrous toluene (120 mL). The crude product was purified by recrystallisation from hexane /ethyl acetate 10:1 to give *N*-(1-phenyl-2-methylprop-1-en-1-yl)-acetamide as a white solid (3.92 g, 69%) and as a mixture of isomers in a 7:3 ratio. R_f 0.43 (pet ether/EtOAc, 1:1); m.p. 84-86 ^oC, lit[31] 82-82 ^oC; υ_{max} 3271 (NH), 2907 (CH), 1648 (C=O); δ_H (300MHz, $CDCl_3$) 7.14 – 7.44 (5H, m, 5 × Ar<u>H</u>), 6.75 (0.3H, s, N<u>H</u> min), 6.63 (0.7H, s, N<u>H</u> maj), 2.04 (2.1H, s, C(O)C<u>H</u>$_3$ majo), 1.89 (0.9H, s, C(O)C<u>H</u>$_3$ min), 1.85 (0.9H, s, C=CC<u>H</u>$_3$ min), 1.80 (2.1H, s, C=CC<u>H</u>$_3$ maj), 1.79 (2.1H, s, C=CC<u>H</u>$_3$ maj), 1.76 (0.9H, s, C=CC<u>H</u>$_3$ min); δ_C (75MHz, $CDCl_3$) 173.5, 168.2 (<u>C</u>=O), 138.8, 138.2, 130.8, 130.2, 129.7 (quarternary), 129.1, 128.2, 128.0 (Ar<u>C</u>), 127.8 (quarternary), 127.6, 127.2 (Ar<u>C</u>), 23.3, 21.3, 21.1, 20.8, 20.7 (<u>C</u>H$_3$); *m/z* (ES^+) 212.2 $[M+H]^+$.

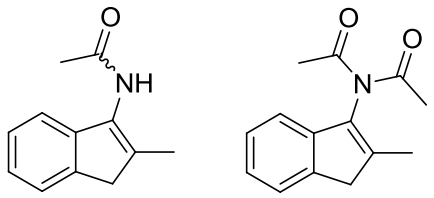
***N*-(2-phenylcyclohexene-1-yl)-acetamide[243] (192)**



192

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2-phenylcyclohexanone oxime (3.00 g, 15.8 mmol), acetic acid (2.72 mL, 47.6 mmol), acetic anhydride (4.49 mL, 47.6 mmol), iron powder (1.77 g, 31.7 mmol) and anhydrous toluene (25 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 6:1) to yield the pure product as an orange solid (640 mg, 19%). R_f 0.55 (pet ether/EtOAc, 1:1); m.p. 94-97 ^{o}C; υ_{max} 3259 (NH), 2922 (CH), 1636 (C=O); δ_H (300MHz, $CDCl_3$) 7.35 (2H, t, *J* = 7.5, Ar<u>H</u>), 7.26 (1H, t, *J* = 7.5, Ar<u>H</u>), 7.20 (2H, d, *J* = 7.5, Ar<u>H</u>), 6.43 (1H, s, N<u>H</u>), 2.9 – 2.69 (2H, m, CC<u>H</u>$_2$), 2.28 – 2.38 (2H, m, CC<u>H</u>$_2$), 1.83 (3H, s, C(O)C<u>H</u>$_3$), 1.69 – 1.81 (4H, m, C<u>H</u>$_2$); δ_C (75MHz, $CDCl_3$) 168.6 (<u>C</u>=O), 140.8, 130.7 (quarternary), 128.7, 128.1, 127.0 (Ar<u>C</u>), 126.2 (quarternary), 30.8, 27.7 (C=C<u>C</u>H$_2$), 23.9 (<u>C</u>H$_3$), 22.8, 22.7 (<u>C</u>H$_2$); *m/z* (ES$^+$) 238.0 $[M+Na]^+$.

_N_-(2-methylindene-1-yl)-acetamide[239] (193) and _N_-Acetyl-_N_-(2-methylindene-1-yl)-acetamide (193a)



193 **193a**

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2-methylindanone oxime (3.00 g, 18.6 mmol), acetic acid (3.20 mL, 55.8 mmol), acetic anhydride (5.27 mL, 55.8 mmol), iron powder (2.08 g, 37.2 mmol) and anhydrous toluene (30 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1 to 1:1) to give *N*-(2-methylindene-1-yl)-acetamide (1.72 g, 49%) as a brown solid and a mixture of isomers in a 2:1 ratio and by-product *N*-Acetyl-*N*-(2-methylindene-1-yl)-acetamide (412 mg, 10%) as an orange solid.

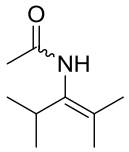
_N_-(2-methylindene-1-yl)-acetamide[239] (193)

R_f 0.50 (pet ether/EtOAc, 1:1); m.p. 126-128 ^oC; υ_{max} 3236 (NH), 2972 (CH), 1654 (C=O); δ_H (400MHz, $CDCl_3$) 7.06 – 7.49 (4H, m, Ar<u>H</u>), 6.69 (0.67H, s, N<u>H</u> maj), 6.52 (0.33H, s, N<u>H</u> min), 3.39 (0.67H, s, C<u>H</u>$_2$ min), 3.35 (1.33H, s, C<u>H</u>$_2$ maj), 2.24 (2H, s, C(O)C<u>H</u>$_3$ maj), 2.10 (1H, s, C(O)C<u>H</u>$_3$ min), 2.06 (2H, s, C=CC<u>H</u>$_3$ maj), 1.92 (1H, s, C=CC<u>H</u>$_3$ maj); δ_C (100MHz, $CDCl_3$) 168.9 (<u>C</u>=O), 142.8, 142.5, 141.0, 140.7, 139.7, 136.4, 131.6 (quarternary), 126.7, 126.1, 125.1, 124.5, 123.8, 123.4, 117.9, 117.6 (Ar<u>C</u>), 40.7, 40.6 (<u>C</u>H$_2$), 23.3, 20.2 (C(O)<u>C</u>H$_3$), 14.0, 13.5 (C=C<u>C</u>H$_3$); *m/z* (ES$^+$) 210.0 $[M+Na]^+$.

_N_-Acetyl-_N_-(2-methylindene-1-yl)-acetamide (193a)

R_f 0.41 (pet ether/EtOAc, 3:1); m.p. 77-79 ^oC; υ_{max} 2973 (CH), 1715, 1700 (C=O); δ_H (400MHz, $CDCl_3$) 7.41 (1H, d, *J* = 7.5, ArH), 7.27 (1H, t, *J* = 7.5, ArH), 7.19 (1H, t, *J* = 7.5, ArH), 7.01 (1H, d, *J* = 7.5, ArH), 3.47 (2H, s, CH_2), 2.36 (6H, s, C(O)CH_3), 2.01 (3H, s, C=CCH_3); δ_C (100MHz, $CDCl_3$) 172.36 (C=O), 141.70, 141.68, 140.75, 135.24 (quaternary), 126.75, 125.15, 124.04, 117.17 (ArC), 40.79 (CH_2), 25.91 (C(O)CH_3), 13.23 (C=CCH_3); *m/z* (ES^+) $C_{13}H_{15}NNaO_2^+$ requires 252.0995, found: 252.0994 $[M+Na]^+$.

_N_-(2,4-dimethylpent-2-en-3-yl)-acetamide (194)

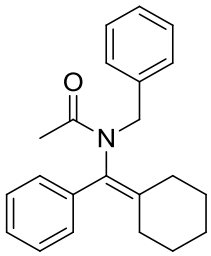


194

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2,4-dimethyl-3-pentanone oxime (4.72 g, 36.3 mmol), acetic acid (6.23 mL, 109 mmol), acetic anhydride (10.3 mL, 109 mmol), iron powder (4.06 g, 72.6 mmol) and anhydrous toluene (120 mL). The crude product was purified by recrystallisation from hexane to give *N*-(2,4-dimethylpent-2-en-3-yl)-acetamide as an pale yellow crystalline solid (3.17 g, 56%) and a mixture of isomers in a 5:3 ratio. R_f 0.60 (pet ether/EtOAc, 1:1); m.p. 64-66 ^oC; υ_{max} 3242 (NH), 2972 (CH), 1641 (C=O); δ_H (400MHz, $CDCl_3$); δ_C (100MHz, $CDCl_3$) 6.15 (0.37H, s, NH min), 6.07 (0.63H, s, NH maj), 2.87 – 3.01 (1H, m, CH), 2.07 (1.89H, s, C(O)CH_3 maj), 1.88 (1.11H, s, C(O)CH_3 min), 1.77 (3H, s, CCH_3), 1.67 (1.11H, s, CCH_3), 1.60 (1.89H, s,

C<u>H</u>$_3$), 0.96 (2.22H, d, *J* = 7.0, CHC(C<u>H</u>$_3$)$_2$ min), 0.95 (3.78H, d, *J* = 7.0, CHC(C<u>H</u>$_3$)$_2$ maj); δ_C (75MHz, $CDCl_3$) 168.6 (<u>C</u>=O), 131.2, 127.6 (quarternary), 29.6, 29.2 (<u>C</u>H), 23.3 (C(O)<u>C</u>H$_3$ maj), 20.5, 20.5, 20.0, 19.7, 19.5, 19.2, 19.2 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_9H_{17}NNaO^+$ requires 178.1202, found 178.1202 $[M+Na]^+$.

_N_-Benzyl-_N_-(cyclohexylidene(phenyl)methyl)-acetamide (195)

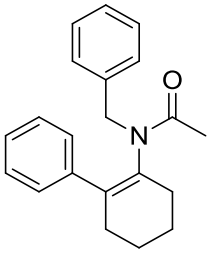


195

The general procedure for enamide alkylation (6.2.4) was applied using *N*-(cyclohexylidene(phenyl)methyl)-acetamide (600 mg, 2.62 mmol), sodium hydride (520 mg, 13.1 mmol) and benzyl bromide (0.33 mL, 2.75 mmol) and anhydrous THF (50 mL). The crude product was recrystallised from hexane to give *N*-Benzyl-*N*-(cyclohexylidene(phenyl)methyl)-acetamide as a pale orange crystalline solid (0.721 g, 86%). R_f 0.45 (pet ether/EtOAc, 4:1); m.p. 89-92 ^oC; υ_{max} 2925 (CH), 1646 (C=O); δ_H (400MHz, $CDCl_3$) 7.15 – 7.46 (10H, m, Ar<u>H</u>), 5.37 (1H, d, *J* = 14.0, ArC<u>H</u>H), 3.37 (1H, d, *J* = 14.0, ArCH<u>H</u>), 2.38 – 2.54 (1H, m, cy), 2.18 (3H, s, C(O)C<u>H</u>$_3$), 1.77 – 1.94 (2H, m, cy), 1.60 – 1.74 (2H, m, cy), 1.43 – 1.54 (1H, m, cy), 1.22 – 1.42 (3H, m, cy), 0.42 – 0.56 (1H, m, cy); δ_C (100MHz, $CDCl_3$) 170.68 (<u>C</u>=O), 140.69, 137.33, 136.42, 130.68 (quarternary), 129.96, 129.25, 128.41, 128.18, 127.91, 127.36 (Ar<u>C</u>), 47.94 (Ar<u>C</u>H$_2$), 31.32, 31.24, 27.94, 26.59, 26.30 (cy

$\underline{C}H_2$), 21.39 (C(O)$\underline{C}H_3$); *m/z* (ES^+) $C_{22}H_{26}NO^+$ requires 320.2009, found 320.2005 $[M+H]^+$.

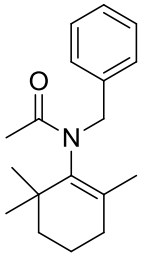
_N_-Benzyl-_N_-(2-phenylcyclohexene-1-yl)-acetamide[244] (196)



196

The general procedure for enamide alkylation (6.2.4) was applied using *N*-Benzyl-*N*-(2-phenylcyclohexene-1-yl)-acetamide (300 mg, 1.39 mmol), sodium hydride (279 mg, 6.97 mmol) and benzyl bromide (0.17 mL, 1.46 mmol) and anhydrous THF (30 mL). Crude product was purified by column chromatography (pet ether/EtOAc 2:1) to give the product as a pale yellow oil (293 mg, 69%). R_f 0.48 (pet ether/EtOAc, 2:1); υ_{max} 2928 (CH), 1638 (C=O); δ_H (400MHz, $CDCl_3$) 7.01 – 7.42 (10H, m, Ar$\underline{H}$), 5.11 (1H, d, *J* = 14.5, ArC$\underline{H}$H), 3.52 (1H, d, *J* = 14.5, ArCH$\underline{H}$), 2.33 – 2.61 (2H, m, C=CC$\underline{H}_2$), 2.11 (3H, s, C(O)C$\underline{H}_3$), 1.94 – 2.07 (2H, m, C=CC$\underline{H}_2$), 1.55 – 1.79 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$); δ_C (75MHz, $CDCl_3$) 169.5 (C=O), 140.0, 137.5, 135.6, 134.8 (quarternary), 128.1, 127.9, 127.6, 126.6, 126.5, 126.3 (Ar$\underline{C}$), 49.9 (Ar$\underline{C}H_2$), 31.0, 30.6, 22.3, 21.9 (CH_2), 21.4 (CH_3); *m/z* (ES^+) 306.1 $[M+H]^+$, 328.1$[M+Na]^+$.

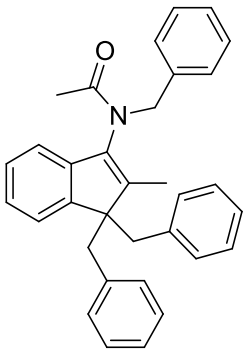
_N_-Benzyl-_N_-(2,2,6- trimethylcyclohexen-1-yl)-acetamide (197)



197

The general procedure for enamide alkylation (6.2.4) was applied using *N*-(2,2,6-trimethylcyclohexen-1-yl)-acetamide (300 mg, 1.65 mmol), sodium hydride (331 mg, 8.27 mmol) and benzyl bromide (0.21 mL, 1.73 mmol) and anhydrous THF (30 mL). The crude product was purified by column chromatography (pet ether/EtOAc 3:1) to give *N*-Benzyl-*N*-(2,2,6- trimethylcyclohexen-1-yl)-acetamide as a pale yellow oil (0.331 g, 74%). R_f 0.52 (pet ether/EtOAc, 3:1); υ_{max} 2931 (CH), 1641 (C=O); δ_H (400MHz, $CDCl_3$) 7.11 – 7.49 (5H, m, Ar<u>H</u>), 5.00 (1H, d, *J* = 14.5, ArC<u>H</u>H), 4.35 (1H, d, *J* = 14.5, ArCH<u>H</u>), 1.99 – 2.07 (2H, m, C=CC<u>H</u>$_2$), 1.97 (3H, s, C(O)C<u>H</u>$_3$), 1.50 – 1.83 (4H, m, C=CCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.17 (3H, s, C=CC<u>H</u>$_3$), 1.07 (3H, s, C(C<u>H</u>$_3$)(CH$_3$)), 1.06 (3H, s, C(CH$_3$)(C<u>H</u>$_3$)); δ_C (100MHz, $CDCl_3$) 172.1 (<u>C</u>=O), 139.4, 137.8, 133.8 (quarternary), 129.4, 128.1, 127.0 (Ar<u>C</u>), 51.6 (Ar<u>C</u>H$_2$), 41.1 (<u>C</u>H$_2$), 35.9 (<u>C</u>H), 31.7 (C=C<u>C</u>H$_2$), 30.4 (C=C<u>C</u>H$_3$), 27.6 (C(<u>C</u>H$_3$)(CH$_3$)), 21.8 (C(O)<u>C</u>H$_3$), 19.3 (C(CH$_3$)(<u>C</u>H$_3$), 18.5 (<u>C</u>H$_2$); *m/z* (ES$^+$) $C_{18}H_{25}NNaO^+$ requires 294.1828, found 294.1829 $[M+Na]^+$.

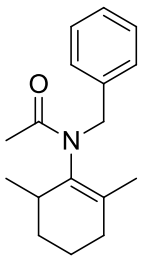
_N_-Benzyl-_N_-(2-methyl-3,3-dibenzylindene-1-yl)-acetamide (198)



198

The general procedure for enamide alkylation (6.2.4) was applied using *N*-(2-methylindene-1-yl)-acetamide (1.00 g, 5.34 mmol), sodium hydride (1.07 g, 26.7 mmol) and benzyl bromide (0.67 mL, 5.61 mmol) and anhydrous THF (100 mL). The crude product was purified by column chromatography (pet ether/EtOAc 4:1) to give *N*-Benzyl-*N*-(2-methyl-3,3-dibenzylindene-1-yl)-acetamide as an orange solid (376 mg, 44%). R_f 0.43 (pet ether/EtOAc, 4:1); m.p. 151-153 ^{o}C; υ_{max} 2921 (CH), 1645 (C=O); δ_H (400MHz, $CDCl_3$) 7.50 (1H, d, *J* = 7.5, Ar<u>H</u>), 7.25 (1H, t, *J* = 7.5, Ar<u>H</u>), 7.01 – 7.16 (7H, m, Ar<u>H</u>), 6.86 – 6.99 (3H, m, Ar<u>H</u>), 6.76 (2H, d, *J* = 6.5, Ar<u>H</u>), 6.66 (2H, d, *J* = 7.5, Ar<u>H</u>), 6.60 (2Hm d, *J* = 7.0, Ar<u>H</u>), 6.37 (1H, d, *J* = 7.5, Ar<u>H</u>), 4.37 (1H, d, *J* = 13.5, ArC<u>H</u>HN), 4.16 (1H, d, *J* = 13.5, ArCH<u>H</u>N), 3.48 (1H, d, *J* = 13.5, ArC<u>H</u>HC), 3.41 (1H, d, *J* = 13.5, ArC<u>H</u>HC), 3.07 (1H, d, *J* = 13.5, ArCH<u>H</u>C), 2.99 (1H, d, *J* = 13.5, ArCH<u>H</u>C), 1.75 (3H, s, C(O)C<u>H</u>$_3$), 0.87 (C=CC<u>H</u>$_3$, s, 3H); δ_C (75MHz, $CDCl_3$) 170.98 (C=O), 146.49, 144.18, 142.01, 140.32, 137.89, 136.78, 136.60 (quarternary), 129.75, 129.59, 129.24, 127.92, 127.78, 127.75, 127.14, 127.11, 126.64, 126.58, 124.75, 123.53, 118.17 (Ar<u>C</u>), 58.40 (<u>C</u>(Bn)$_2$), 50.87 (Ar<u>C</u>H$_2$N), 43.54, 43.16 (Ar<u>C</u>H$_2$C), 20.26 (C=C<u>C</u>H$_3$), 11.04 (C(O)<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{33}H_{32}NO^+$ requires 458.2478, found 458.2480 $[M+H]^+$.

_N_-Benzyl-_N_-(2,6- dimethylcyclohexen-1-yl)-acetamide[157] (199)



199

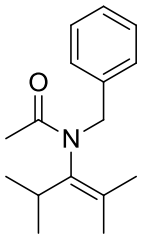
The general procedure for enamide alkylation (6.2.4) was applied using *N*-(2,6-dimethylcyclohexen-1-yl)-acetamide (250 mg, 1.49 mmol), sodium hydride (299 mg, 7.47 mmol) and benzyl bromide (0.19 mL, 1.57 mmol) and anhydrous THF (30 mL). The crude product was purified by column chromatography (pet ether/EtOAc 9:1) to give *N*-Benzyl-*N*-(2,6- dimethylcyclohexen-1-yl)-acetamide as a yellow oil (313 mg, 81%).

Discernible data for the major diastereomer; *Rf* 0.25 (3:1 pet ether/EtOAc); υ_{max} 2930 (CH), 1641 (C=O); δ_H (300 MHz, $CDCl_3$) 7.22 - 7.33 (5H, m Ar), 5.13 (1H, d, *J* = 14.0 Hz, Ar-C$\underline{H}_a$H$_b$), 4.05 (1H, d, *J* = 14.0 Hz, Ar-CH$_a$$\underline{H}_b$), 2.43 (1H, m, C$\underline{H}$(CH$_3$)), 1.41 - 2.02 (6H, m, 3 x C$\underline{H}_2$), 1.97 (3H, s, CO(C$\underline{H}_3$)), 1.08 (3H, br s, C=C(C$\underline{H}_3$)), 0.95 (3H, d, *J* = 7.0 Hz, CH(C$\underline{H}_3$)); δ_C (75 MHz, CDCl3) 170.9 ($\underline{C}$=O), 138.0 (N-$\underline{C}$), 135.1 (Ar, quaternary), 133.3 (C=$\underline{C}$CH$_3$), 128.9, 128.1, 127.3 ($\underline{Ar}$), 48.1 (Ar-$\underline{C}$H$_2$), 31.6, 31.4, 25.6 ($\underline{C}$H$_2$), 29.9 (CO($\underline{C}$H$_3$)), 27.6 ($\underline{C}$HCH$_3$), 18.8 (C=C$\underline{C}$H$_3$), 18.4 (CH$\underline{C}$H$_3$); *m/z* (ESI) 280.2 $[M+Na]^+$.

Discernible data for the minor diastereomer: *Rf* 0.25 (3:1 pet ether/EtOAc) 0.25; υ_{max} 2930 (CH), 1641 (C=O); δ_H (300 MHz, $CDCl_3$) 7.22 - 7.33 (5H, m Ar), 5.40 (1H, d, *J* = 14.5 Hz, Ar-C$\underline{H}_a$H$_b$), 3.96 (1H, d, *J* = 14.5 Hz, Ar-CH$_a$$\underline{H}_b$), 2.41 (1H, m, C$\underline{H}$(CH$_3$)), 1.41 - 2.02 (6H, m, C$\underline{H}_2$), 2.04 (3H, s, C$\underline{H}_3$), 1.19 (3H, br s, C=C(C$\underline{H}_3$)),

1.03 (3H, br d, CH(C<u>H</u>$_3$)); δ_C (75 MHz CDCl3) 171.6 (<u>C</u>=O), 137.9 (N-<u>C</u>), 135.0 (Ar, quaternary), 133.3 (C=<u>C</u>CH$_3$), 130.1, 128.9, 127.0 (Ar), 50.8 (Ar-<u>C</u>H$_2$), 31.6, 31.4, 25.6 (<u>C</u>H$_2$), 29.9 (CO(<u>C</u>H$_3$)), 27.6 (<u>C</u>HCH$_3$), 18.8 (C=C<u>C</u>H$_3$), 18.4 (CH<u>C</u>H$_3$); *m/z* (ESI) 280.2 $[M+Na]^+$.

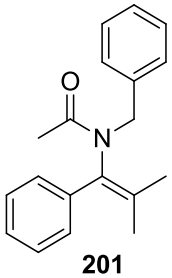
_N_-Benzyl-_N_-(2,4-dimethylpent-2-en-3-yl)-acetamide[157] (200)



200

The general procedure for enamide alkylation (6.2.4) was applied using *N*-(2,4-dimethylpent-2-en-3-yl)-acetamide (2.73 g, 17.6 mmol), sodium hydride (3.52 mg, 87.9 mmol) and benzyl bromide (2.19 mL, 18.5 mmol) and anhydrous THF (300 mL). The crude product was purified by column chromatography (pet ether/EtOAc 4:1) to give *N*-Benzyl-*N*-(2,6- dimethylcyclohexen-1-yl)-acetamide as a yellow oil (2.63 g mg, 61%). R_f 0.36 (pet ether/EtOAc, 3:1); υ_{max} 2965 (CH), 1642 (C=O); δ_H (400MHz, $CDCl_3$) 7.38 (2H, dd, *J* = 7.5, 2.0 Hz, 2 x Ar<u>H</u>), 7.18 – 7.34 (3H, m, 3 x Ar<u>H</u>), 5.27 (1H, d, *J* = 14.0 Hz, ArC<u>H</u>$_a$H$_b$N), 3.99 (1H, d, *J* = 14.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.98 (1H, hept, *J* = 7.0 Hz, C<u>H</u>(CH$_3$)$_2$), 1.96 (3H, s, COC<u>H</u>$_3$), 1.72 (3H, s, C=CC<u>H</u>$_3$), 1.27 (3H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 1.05 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)(C<u>H</u>$_3$)), 1.04 (3H, s, C=CC<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 171.2 (C=O), 137.6 (Ar quaternary), 137.6 (N<u>C</u>=C), 131.7 (NC=<u>C</u>), 130.0, 128.2, 127.4 (Ar<u>C</u>H), 50.7 (Ar<u>C</u>H$_2$N), 30.2 (<u>C</u>H(CH$_3$)$_2$), 23.9 (CH(<u>C</u>H$_3$)(CH$_3$)), 21.7 (CO<u>C</u>H$_3$), 20.5 (C=C<u>C</u>H$_3$), 19.5 (C=C<u>C</u>H$_3$), 19.4 ((CH(CH$_3$)(<u>C</u>H$_3$)); *m/z* (ES^+) 268.2 $[M+Na]^+$.

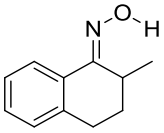
_N_-Benzyl-_N_-(1-phenyl-2-methylprop-1-en-1-yl)-acetamide[154] (201)



201

The general procedure for enamide alkylation was applied using *N*-(1-phenyl-2-methylprop-1-en-1-yl)-acetamide (3.50 g, 18.5 mmol), sodium hydride (3.70 mg, 92.5 mmol) and benzyl bromide (2.30 mL, 19.4 mmol) and anhydrous THF (300 mL). The crude product was purified by column chromatography (pet ether/EtOAc 9:1) to give *N*-Benzyl-*N*-(1-phenyl-2-methylprop-1-en-1-yl)-acetamide as a yellow oil (3.67 g, 71%). R_f 0.18 (pet ether/EtOAc, 6:1); υ_{max} 2991, 2929 (CH), 1642 (C=O); δ_H (400MHz, $CDCl_3$) 7.28 – 7.42 (3H, m, 3 x Ar<u>H</u>), 7.19 – 7.28 (7H, m, 7 x Ar<u>H</u>), 5.27 (1H, d, *J* = 14.0 Hz, ArC<u>H</u>$_a$H$_b$N), 3.48 (1H, d, *J* = 14.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.16 (3H, s, COC<u>H</u>$_3$), 1.76 (3H, s, C=CC<u>H</u>$_3$), 1.28 (3H, s, C=CC<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 170.7 (C=O), 137.18, 136.51 (Ar quarternary), 133.70, 133.46 (C=C), 129.82, 129.33, 128.36, 128.11, 127.87, 127.31 (Ar<u>C</u>), 48.46 (Ar<u>C</u>H$_2$N), 21.38 (CO<u>C</u>H$_3$), 21.30 (C=C<u>C</u>H$_3$), 20.81 (C=C<u>C</u>H$_3$); *m/z* (ES$^+$) 280.2 $[M+H]^+$.

2-Methyl-1-tetralone oxime[170] (209a)

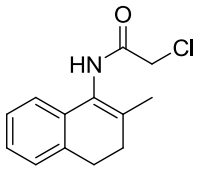


209a

The genereal procedure for the synthesis of oximes was applied using 2-methyl-1-tetralone (3.17 g, 19.7 mmol, 1 eq.), hydroxylamine hydrochloride (1.65 g, 23.7

mmol, 1.2 eq.), sodium acetate (1.95 g, 23.7 mmol, 1.2 eq.) and methanol (32 mL). The product was isolated as a pale brown crystalline solid (3.38 g, 97%) which was taken on without further purification. R_f 0.30 (pet/EtOAc, 9:1); m.p. 97-99 ^{o}C, lit[245] 95-96 ^{o}C; υ_{max} 3187 (O-H), 2933 (C-H); δ_H (300MHz, $CDCl_3$) 8.89 (1H, br s, O<u>H</u>), 7.88 (1H, d, *J* = 9.0, Ar<u>H</u>), 7.11 - 7.31 (3H, m, Ar<u>H</u>), 3.61 - 3.73 (1H, m, C(O)C<u>H</u>), 2.97 (1H, ddd, *J* = 16.5, 12.5, 4.5, ArC<u>H</u>H), 2.67 (1H, ddd, *J* = 16.5, 4.5, 4.0, ArCH<u>H</u>), 1.92 - 2.05 (1H, m, C(O)CHC<u>H</u>H), 1.75 (1H, ddd, *J* = 12.5, 4.5, 4.0, C(O)CHCH<u>H</u>), 1.23 (3H, d, *J* = 7.0, C<u>H</u>$_3$); δ_C (75MHz, $CDCl_3$) 159.0 (<u>C</u>=N), 138.9 (quarternary), 129.8 (quarternary), 129.2 (Ar<u>C</u>), 128.8 (Ar<u>C</u>), 126.4 (Ar<u>C</u>), 124.5 (Ar<u>C</u>), 28.4 (C(O)CH<u>C</u>H$_2$), 26.8 (C(O)<u>C</u>H), 25.2 (Ar<u>C</u>H$_2$), 15.3 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{11}H_{14}NO^+$ requires 176.1070, found: $[M+H]^+$ 176.1065.

_N_-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide[157] (209b)

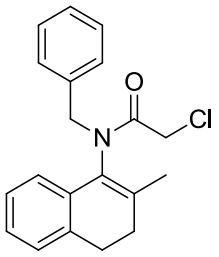


209b

2-Methyl-1-tetralone oxime (2.94 g, 16.8 mmol, 1 eq.) as a mixture with 2,2-dimethy-1-tetralone oxime (74% 2-methyl-1-tetralone) was dissolved in toluene (100 mL). 2-Chloroacetic acid (4.76 g, 50.4 mmol, 3 eq.), 2-chloroacetic anhydride (8.61 g, 50.4 mmol, 3 eq.) and iron powder (1.88 g, 33.6 mmol, 2 eq.) were then added and the reaction mixture heated to 70 ^{o}C for 36 h. The reaction mixture was then cooled and filtered through celite and washed with 2M NaOH (2 × 80 mL) and $NaCl_{(aq)}$ (80 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow solid (5.05 g). The crude product

was then purified by recrystallisation from hexane/EtOAc 10:1 to give the product as pale brown needles (2.09 g, 53%). R_f 0.23 (pet ether/EtOAc, 3:1); m.p. 139-141 ^oC; υ_{max} 3229 (NH), 2933(CH), 1650 (C=O); δ_H (400MHz, $CDCl_3$) 7.59 (1H, s, N<u>H</u>), 7.22 – 7.09 (3H, m, 3 × Ar<u>H</u>), 7.06 (1H, d, *J* = 7.5, Ar<u>H</u>), 4.25 (2H, s, C(O)C<u>H</u>$_2$), 2.84 (2H, t, *J* = 8.0, ArC<u>H</u>$_2$), 2.42 (2H, t, *J* = 8.0, NC=CC<u>H</u>$_2$), 1.88 (3H, s, C<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 164.6 (<u>C</u>=O), 135.2, 134.9, 132.4 (quarternary), 127.5, 126.9, 126.5 (Ar<u>C</u>), 125.1 (quarternary), 121.2 (Ar<u>C</u>), 42.8 (C(O)<u>C</u>H$_2$), 29.7 (NC=C<u>C</u>H$_2$), 27.4 (Ar<u>C</u>H$_2$), 19.5 (<u>C</u>H$_3$); *m/z* (ES^+) $C_{13}H_{14}ClNNaO^+$ requires 258.0656, found: 258.0656 $[M+Na]^+$.

_N_-benzyl-_N_-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide[157] (209)

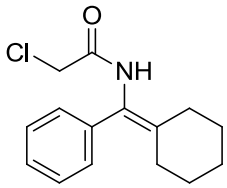


209

The general procedure for enamide alkylation (6.2.4) was applied using *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (1.9 g, 8.06 mmol, 1 eq.), sodium hydride (520 mg, 13.1 mmol) sodium hydride (1.61 g, 40.3 mmol, 5 eq.) and benzyl bromide (1.01 mL, 8.46 mmol, 1.05 eq.) and anhydrous THF (150 mL). The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 9:1) yielded the product as a white solid (960 mg, 37%). R_f 0.18 (pet ether/EtOAc, 9:1); m.p. 99-101 ^oC; υ_{max} 2925 (CH), 1666(C=O); δ_H (400MHz, $CDCl_3$) 7.09 – 7.42 (8H, m, 8 × Ar<u>H</u>), 6.95 (1H, d, *J* = 4.0, Ar<u>H</u>), 5.45 (1H, d, *J* = 13.5, ArC<u>H</u>HN), 3.94 (2H,

s, C(O)C$\underline{H}_2$), 3.90 (1H, d, *J* = 13.5, ArCH$\underline{H}$N), 2.70 – 2.89 (2H, m, ArC$\underline{H}_2$C), 2.32 – 2.47 (1H, m, C=CC$\underline{H}$H), 2.24 – 2.14 (1H, m, C=CCH$\underline{H}$), 1.28 (3H, s, C$\underline{H}_3$); δ_C (75MHz, $CDCl_3$) 166.2 ($\underline{C}$=O), 137.6, 137.5, 135.7, 135.5, 130.6 (quarternary), 129.7, 127.7, 127.3, 127.2, 127.1, 126.5, 121.1 (Ar$\underline{C}$), 50.1 (Ar$\underline{C}H_2$N), 41.6 (C(O)$\underline{C}H_2$), 28.9 (C=C$\underline{C}H_2$), 26.7 (Ar$\underline{C}H_2CH_2$), 18.6 ($\underline{C}H_3$); *m/z* (ES^+) 326.2 $[M+H]^+$, 348.1 $[M+Na]^+$.

2-Chloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide (210a)

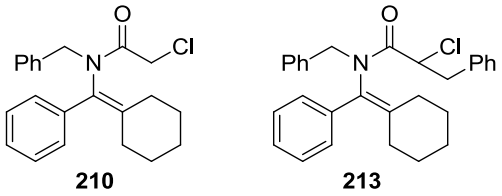


210a

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using cyclohexyl(phenyl)methanone oxime (4 g, 19.7 mmol), chloroacetic acid (5.58 g, 59.1 mmol), chloroacetic anhydride (10.1 g, 59.1 mmol), iron powder (2.20 g, 39.4 mmol) and anhydrous toluene (80 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 4:1) to give the product as a yellow crystalline solid (2.26 g, 48%). R_f 0.64 (pet ether/EtOAc, 1:1); m.p. 128-130 ^oC; υ_{max} 3232 (NH), 2917 (CH), 1654 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.56 (1H, s, N$\underline{H}$), 7.12 – 7.39 (5H, m, 5 x Ar$\underline{H}$), 4.09 (2H, s, C=O$\underline{C}H_3$), 2.17 – 2.26 (4H, m, C=C(C$\underline{H}_2$)$_2$), 1.51 – 1.69 (6H, m, 3 x $CH_2C\underline{H}_2CH_2$); δ_C (100MHz, $CDCl_3$) δ 164.2 ($\underline{C}$=O), 138.4 (C=$\underline{C}$(N)Ar), 137.8 (Ar$\underline{C}$), 129.1 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 124.0 (ArC=$\underline{C}$(CH$_2$)$_2$), 42.8 (C=O$\underline{C}H_2$), 31.0 (C=C($\underline{C}H_2$)(CH$_2$)), 30.7 (C=C(CH$_2$)($\underline{C}H_2$)),

28.0 ($CH_2\underline{C}H_2CH_2$), 27.4 ($CH_2\underline{C}H_2CH_2$), 26.4 ($CH_2\underline{C}H_2CH_2$); *m/z* (ES^+) $C_{15}H_{18}ClNNaO$ requires 286.0969, found: 286.0977 $[M+Na]^+$.

_N_-Benzyl-2-chloro-_N_-(cyclohexylidene(phenyl)methyl)acetamide (210) and _N_-Benzyl-2-chloro-_N_-(cyclohexylidene(phenyl)methyl)-3-phenylpropanamide (213a)



210 **213**

The general procedure for the alkylation of enamides (6.2.4) was applied using *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (1.9 g, 8.06 mmol), sodium hydride (1.61 g, 40.3 mmol) and benzyl bromide (1.01 mL, 8.46 mmol) and anhydrous THF (150 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to give the product as an off white solid (1.1 g, 46%), and the side product *N*-benzyl-2-chloro-*N*-(cyclohexylidene(phenyl)methyl)-3-phenylpropanamide as a yellow oil (370 mg, 12%) as a 1:0.85 mixture of diastereomers.

_N_-Benzyl-2-chloro-_N_-(cyclohexylidene(phenyl)methyl)acetamide (210)

R_f 0.4 (pet ether/EtOAc, 9:1); m.p. 111-113 ^oC; υ_{max} 2928 (CH), 1663 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.28 (4H, m, 4 x Ar$\underline{H}$), 5.25 (1H, d, *J* = 14.0 Hz, ArC$\underline{H}_aH_bN$), 4.28 (1H, d, *J* = 13.5 Hz, C=OC$\underline{H}_aH_bCl$), 4.03 (1H, d, *J* = 13.5 Hz, C=OC$H_a\underline{H}_bCl$), 3.38 (1H, d, *J* = 14.0 Hz, ArC$H_a\underline{H}_bN$), 2.39 (1H, d, *J* = 13.4 Hz, cy$\underline{H}$), 1.75 – 1.87 (1H, m, cy$\underline{H}$), 1.64 – 1.74 (1H, m, cy$\underline{H}$), 1.49 – 1.62 (2H, m, cy$\underline{H}$), 1.35 – 1.44 (1H,

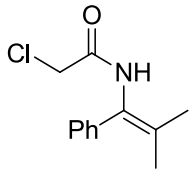
m, cyH), 1.09 – 1.36 (3H, m, cyH), 0.28 – 0.48 (1H, m, cyH); δ_C (100MHz, $CDCl_3$) δ 166.5 (C=O), 142.0 (NC=C$(CH_2)_2$), 136.4 (ArCC=C), 135.5 (ArCCH_2N), 130.1 (ArCH), 129.8 (NC=C$(CH_2)_2$), 129.5 (ArCH), 129.3 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 127.7 (ArCH), 49.0 (ArCH_2N), 41.8 (C=OCH_2Cl), 31.4 (C=CCH_2), 31.3 (C=CCH_2), 27.9 ($CH_2CH_2CH_2$), 26.7 ($CH_2CH_2CH_2$), 26.2 ($CH_2CH_2CH_2$); *m/z* (ES^+) $C_{22}H_{24}ClNaO$ requires 376.1439, found: 376.1435 $[M+Na]^+$.

_N_-Benzyl-2-chloro-_N_-(cyclohexylidene(phenyl)methyl)-3-phenylpropanamide (213)

R_f 0.6 (pet ether/EtOAc, 9:1); υ_{max} 2927 (CH), 1660 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.18 – 7.46 (14H maj and 14 min, m, ArH maj and min), 6.72 (1H maj and 1H min, d, *J* = 7.5 Hz, ArH), 5.42 (1H maj, d, *J* = 14.0 Hz, ArCH_aH_bN maj), 5.12 (1H min, d, *J* = 14.0 Hz, ArCH_aH_bN min), 4.94 (1H maj, dd, *J* = 8.5, 5.5 Hz, C=OCHCl maj), 4.83 (1H min, t, *J* = 7.0 Hz, C=OCHCl min), 3.82 (1H min, d, *J* = 14.0 Hz, ArCH_aH_bN min), 3.52 – 3.61 (1H maj and 1H min, m, ArCH_aH_bN maj and ClCHCH_aH_bPh min), 3.33 – 3.47 (2H maj, m, ClCHCH_2Ph maj), 3.25 (1H min, dd, *J* = 13.5, 7.0 Hz, ClCHCH_aH_bPh min), 2.61 (1H maj, d, *J* = 14.0 Hz, C=CCH_aH_b maj), 2.50 (1H min, d, *J* = 13.5 Hz, C=CCH_aH_b min), 1.18 – 2.18 (8H maj and 8H min, m, cyH maj and min), 0.48 – 0.64 (1H min, m, C=C$CH_2CH_aH_b$ min), 0.27 (q, *J* = 12.0 Hz, C=CCH2CH_aH_b maj); δ_C (100MHz, $CDCl_3$) δ (ppm) 169.4, 169.3 (2 x C=O maj and min), 143.1, 141.2, 136.9, 136.7, 136.1, 135.8, 130.6 (7 x quaternary C), 130.1, 130.0, 130.0, 129.7 (4 x ArCH), 129.6 (quaternary C), 129.2, 128.7, 128.5, 128.5, 128.3, 128.3, 127.9, 127.7, 127.6, 127.3, 127.1 (11 x ArCH), 55.6 (C=OCHCl min) , 55.0 (C=OCHCl maj), 50.3 (ArCH_2N min), 49.1 (ArCH_2N maj), 42.6 (ArCH_2CHCl min), 40.9 (ArCH_2CHCl maj), 32.8, 31.9, 31.8, 31.7, 28.3, 28.1, 27.3, 27.1, 26.2,

26.2 (10 x cyC) (2 quaternary carbons missing); *m/z* (ES^+) $C_{29}H_{30}ClNNaO$ requires 466.1908, found: 466.1915 $[M+Na]^+$.

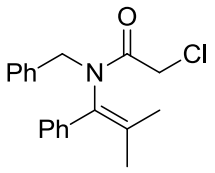
2-Chloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide[246] (211a)



211a

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using 2-methyl-1-phenylpropan-1-one oxime (2 g, 12.2 mmol), chloroacetic acid (3.47 g, 36.8 mmol), chloroacetic anhydride (6.28 g, 36.8 mmol), iron powder (1.37 g, 24.5 mmol) and anhydrous toluene (20 mL). The crude product (1.58 g) was purified by recrystallisation (pet ether/EtOAc, 6:1) to give the product as an off white solid (676 mg, 25%). R_f 0.48 (pet ether/EtOAc, 4:1); m.p. 104-107 ^oC; υ_{max} 3138 (NH), 2988 (CH), 1648 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.63 (1H, s, NH), 7.24 – 7.36 (5H, m, 5 x ArH), 4.10 (2H, s, C=OCH_2Cl), 1.82 (6H, s, 2 x CH_3); δ_C (100MHz, $CDCl_3$) δ 163.9 (C=O), 137.8 (ArC), 131.0 (NC=C$(CH_3)_2$), 129.1 (ArCH), 128.1 (ArCH), 127.5 (ArCH), 126.8 (NC=C$(CH_3)_2$), 42.7 (C=OCH_2Cl), 21.2 (CH_3), 20.6 (CH_3); *m/z* (ES^+) 246.1 $[M+Na]^+$.

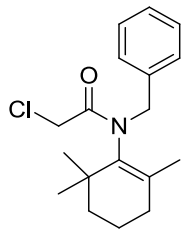
_N_-Benzyl-2-chloro-_N_-(2-methyl-1-phenylprop-1-enyl)acetamide (211)



211

The general procedure for the alkylation of enamides (6.2.4) was applied using 2-chloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (500 mg, 2.24 mmol), sodium hydride (447 mg, 11.2 mmol) and benzyl bromide (278 μL, 2.35 mmol) and anhydrous THF (40 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to give the product as a yellow oil (x g, 42%). R_f 0.28 (pet ether/EtOAc, 6:1); υ_{max} 3028, 2933 (CH), 1659 (C=O) ; δ_H (400 MHz, CDCl3) 7.30 – 7.43 (3H, m, Ar<u>H</u>), 7.22 – 7.30 (7H, m, Ar<u>H</u>), 5.24 (1H, d, *J* = 14.0 Hz, ArC<u>H</u>$_a$H$_b$), 4.34 (1H, d, *J* = 13.5 Hz, COC<u>H</u>$_a$H$_b$Cl), 4.10 (1H, d, *J* = 13.5 Hz, COCH$_a$<u>H</u>$_b$Cl), 3.60 (1H, d, *J* = 14.0 Hz, ArCH$_a$<u>H</u>$_b$), 1.80 (3H, s, C<u>H</u>$_3$), 1.29 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, CDCl3) 166.5 (C=O), 136.3 (<u>Ar</u>-CH$_2$ quarternary), 135.6 (<u>Ar</u>-C=C quarternary), 135.1 (NC=<u>C</u>), 132.5 (N<u>C</u>=C), 129.9, 129.5, 128.6, 128.3, 127.7 (<u>Ar</u>), 49.6 (NC<u>H</u>$_2$), 41.8 (COC<u>H</u>$_2$Cl), 21.5 (C<u>H</u>$_3$), 20.9 (C<u>H</u>$_3$); *m/z* (ES$^+$) $C_{19}H_{20}ClNNaO$ requires 336.1131, found: 336.1126 $[M+Na]^+$.

***N*-Benzyl-2-chloro-*N*-(2,2,6- trimethylcyclohexen-1-yl)-acetamide (212)**

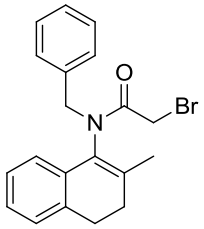


212

2,2,6-Trimethylcyclohexanone oxime (750 mg, 4.83 mmol), chloroacetic acid (1.37 g, 14.5 mmol), chloroacetic anhydride (2.48 g, 14.5 mmol) and iron powder (0.54 g, 9.65 mmol) in anhydrous toluene (25 mL) were heated to reflux under an inert atmosphere for 14 hours. The mixture was then filtered through celite, diluted with DCM (25 mL) and washed with 2M NaOH (2 x 50 mL) and brine (50 mL). The organic phase was then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give a brown solid (390 mg). This solid was then added to sodium hydride (145 mg, 1.81 mmol) in anhydrous THF (18 mL) and cooled to 0 ^oC. Benzyl bromide (0.226 mL, 1.90 mmol) was then added and the reaction heated to reflux under an inert atmosphere for 16 hours. The reaction mixture was then added to water (50 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product as a brown oil (515 mg). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to give the product as a yellow oil (250 mg, 17%). R_f 0.26 (pet ether/EtOAc, 6:1); υ_{max} 2932 (CH), 1658 (C=O); δ_H (300 MHz, CDCl3) 7.30 – 7.39 (2H, m, Ar$\underline{H}$), 7.18 – 7.30 (3H, m, Ar$\underline{H}$), 5.09 (1H, d, *J* = 14.0 Hz, ArC$\underline{H}_aH_b$), 4.31 (1H, d, *J* = 14.0 Hz, ArC$H_a\underline{H}_b$), 4.10 (1H, d, *J* = 13.5 Hz, CO$\underline{H}_aH_b$Cl), 3.92 (1H, d, *J* = 13.5 Hz, CO$H_a\underline{H}_b$Cl), 2.02 (2H, t, *J* = 6.0 Hz, C=CC$\underline{H}_2$), 1.47 – 1.82 (4H, m, 2 x C$\underline{H}_2$), 1.20 (3H, s, C=CC$\underline{H}_3$), 1.04 (3H, s, C(C$\underline{H}_3$)(CH$_3$)), 1.02 (3H, s,

$C(CH_3)(C\underline{H}_3)$); δ_C (75 MHz, $CDCl_3$) 167.0 ($\underline{C}$=O), 137.3 (NC=$\underline{C}$), 136.2 (Ar quarternary), 135.1 (N$\underline{C}$=C), 129.0, 127.7, 126.9 (Ar), 51.7 (N$\underline{C}H_2$), 41.3 (CO$\underline{C}H_2$Cl), 40.3 ($\underline{C}H_2$), 35.2 ($\underline{C}(CH_3)_2$), 31.1 (C=C$\underline{C}H_2$), 29.8 (C=C$\underline{C}H_3$), 27.1 ($\underline{C}H_3$), 18.8 ($\underline{C}H_3$), 17.7 ($\underline{C}H_2$); *m/z* (ES^+) $[M+Na]^+$ $C_{18}H_{25}ClNO$ requires 306.1625, found: 306.1622 $[M+H]^+$.

_N_-benzyl-_N_-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide (214)

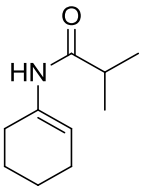


214

N-benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (540 mg, 1.66 mmol, 1 eq.) in acetone (35 mL) was cooled to 0 ^oC and lithium bromide (1.43 g, 16.6 mmol, 10 eq.). The resulting mixture was then stirred at room temperature for 60 h. The raction mixture was then concentrated *in vacuo* to give a white solid which was taken up in water (30ml) and extracted with DCM (3 × 20 mL). The combined organic extracts were then washed with cold water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid. The crude product was then purified by recyrstallisation from hexane to give *N*-benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide as a orange crystalline solid (519 mg, 84%). R_f 0.19 (pet ether/EtOAc, 9:1); m.p. 94-96 ^oC; υ_{max} 2926 (CH), 1660 (C=O); δ_H (300MHz, $CDCl_3$) 7.09 – 7.85 (8H, m, Ar$\underline{H}$), 6.94 (1H, dt, *J* = 7.5, 2.0, Ar$\underline{H}$), 5.40 (1H, d, *J* = 13.5, ArC$\underline{H}$HN), 3.92 (1H, d, *J* = 13.5, ArCH$\underline{H}$N), 3.77 (2H, s, C(O)C$\underline{H}_2$), 2.72 – 2.84 (2H, m, ArC$\underline{H}_2$CH_2), 2.47 – 2.28 (1H, m, ArCH_2C$\underline{H}$H), 2.26

– 2.11 (1H, m, $ArCH_2CH\underline{H}$), 1.28 (3H, s, $C\underline{H}_3$); δ_C (75MHz, $CDCl_3$) 166.3 ($\underline{C}$=O), 137.4, 135.7, 135.5, 130.7, 130.3 (quarternary), 129.7, 127.6, 127.2, 127.0, 126.4, 121.3 (Ar$\underline{C}$), 50.2 (Ar$\underline{C}H_2$N), 29.0 ($\underline{C}H_2$), 27.4 (C(O)$\underline{C}H_2$), 26.7 (CH_2), 18.8 ($\underline{C}H_3$); *m/z* (ES^+) $C_{20}H_{20}BrNNaO^+$ requires 392.0620, found 392.0626 $[M+Na]^+$.

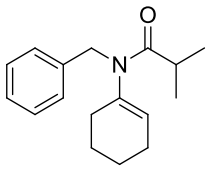
_N_-(cyclohexene-1-yl)isobutryamide (217)



217

The general procedure for the iron mediated synthesis of enamides (6.2.3) was applied using cyclohexanone oxime (5 g, 44 mmol, 1 eq.), isobutyric acid (12.3 mL, 133 mmol, 3 eq.), isobutyric anhydride (22.0 mL, 133 mmol, 3 eq.), iron powder (4.94 g, 88 mmol, 2 eq.) and anhydrous toluene (200 mL). The crude product was purified by column chromatography (pet ether/EtOAc 9:1 to 3:1) to give the product as an orange solid (2.13 g, 29%). R_f 0.23 (pet ether/EtOAc, 9:1); m.p. 59-61 ^oC; υ_{max} 3291 (N-H), 2928 (C-H), 1658 (C=O); δ_H (300MHz, $CDCl_3$) 6.28 (1H, br s, N$\underline{H}$), 6.05 - 6.11 (1H, m, C=C$\underline{H}$), 2.22 - 2.37 (1H, m, C(O)C$\underline{H}$), 2.02 - 2.14 (4H, m, C=CC$\underline{H}_2$), 1.61 - 1.71 (2H, m, $NCCH_2C\underline{H}_2$), 1.49 - 1.59 (2H, m, $NCCH_2CH_2C\underline{H}_2$), 1.14 (6H, d, *J* = 7.0, 2 × $C\underline{H}_3$); δ_C (75MHz, $CDCl_3$) 175.3 ($\underline{C}$=O), 132.5 (N$\underline{C}$=C), 112.8 (NC=$\underline{C}$H), 36.6 (C(O)$\underline{C}$H), 28.2 (NC$\underline{C}H_2$), 24.0 (NC=C$\underline{C}H_2$), 22.6 ($NCCH_2\underline{C}H_2$), 22.0 ($NCCH_2CH_2\underline{C}H_2$), 19.7 ($\underline{C}H_3$); *m/z* ($ES^+$) $C_{10}H_{17}NNaO^+$ requires 190.1202, found: 190.1210 $[M+Na]^+$

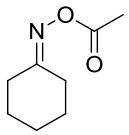
_N_-benzyl-_N_-(cyclohexene-1-yl)isobutryamide (215)



215

The general procedure for enamide alkylation (6.2.4) was applied using 1-isobutyramido-1-cyclohexene (1.6 g, 9.6 mmol, 1 eq.), sodium hydride (1.91 g, 47.9 mmol, 5 eq.) benzyl bromide (1.19 mL, 10.0 mmol, 1.05 eq.) and anhydrous THF (200 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 6:1) to give the product as a yellow crystalline solid (2.21 g, 89%). R_f 0.6 (pet ether/EtOAc, 6:1); υ_{max} 2926 (C-H), 1636 (C=O); δ_H (400MHz, $CDCl_3$) 7.23 - 7.34 (5H, m, 5 × Ar<u>H</u>), 5.42 (1H, m, NC=C<u>H</u>), 4.63 (2H, br s, ArC<u>H</u>$_2$), 2.84 (1H, hept, *J* = 6.5, C(O)C<u>H</u>), 2.02 - 2.07 (2H, m, NC=CHC<u>H</u>$_2$), 1.94 - 2.02 (2H, m, NCC<u>H</u>$_2$), 1.65 - 1.73 (2H, m, NCCH$_2$C<u>H</u>$_2$), 1.52 - 1.60 (2H, m, NCCH$_2$CH$_2$C<u>H</u>$_2$), 1.16 (6H, d, *J* = 6.5, 2 × C(O)CHC<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$) 177.0 (<u>C</u>=O), 138.6 (Ar<u>C</u>), 128.7, 128.2, (Ar<u>C</u>H), 127.5 (NC=<u>C</u>H), 127.0 (Ar<u>C</u>H), 60.4 (N<u>C</u>=C), 49.7 (Ar<u>C</u>H$_2$), 31.4 (C(O)<u>C</u>H), 28.8 (NC=C<u>C</u>H$_2$), 24.8 (NC<u>C</u>H$_2$), 22.87 (NCCH$_2$<u>C</u>H$_2$), 21.51 (NCCH$_2$CH$_2$<u>C</u>H$_2$), 20.27 (C(O)CH<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{17}H_{24}NO^+$ requires 258.1852, found: 258.1846 $[M+H]^+$.

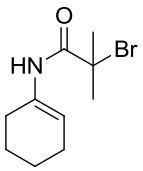
Cyclohexanone oxime acetate[247] (221)



221

Cyclohexanone oxime (300 mg, 2.65 mmol, 1 eq.), acetic anhydride (0.75 ml, 7.95 mmol, 3 eq.), acetic acid (0.46 ml, 7.95 mmol, 3 eq.) and iron acetate (922 mg, 5.30 mmol, 2 eq.) in toluene (4 mL) were heated to reflux under and inert atmosphere for 3 h. The reaction mixture was then cooled, filtered through celite, diluted with DCM (10 mL) and washed with 2M NaOH (3 × 15 mL). The organic phase was then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the product as a brown oil (307 mg, 70%). R_f 0.39 (pet ether/EtOAc, 1:1); υ_{max} 2927 (C-H), 1763 (C=N), 1623 (C=O) 1560 (N-O); δ_H (300MHz, $CDCl_3$) 2.46 – 2.53 (2H, m, C=NC$\underline{H}_2$), 2.27 – 2.36 (2H, m, C=NC$\underline{H}_2$), 2.11 (3H, s, C$\underline{H}_3$), 1.53 – 1.76 (6H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$); δ_C (75MHz, $CDCl_3$) 175.1 (<u>C</u>=O), 168.0 (<u>C</u>=N), 31.5, 26.2, 26.2, 25.2, 24.8 (<u>C</u>H_2), 19.0 (<u>C</u>H_3); *m/z* (ES^+) 178.1 $[M+H]^+$.

2-Bromo-*N*-cyclohexenyl-2-methylpropanamide (223)

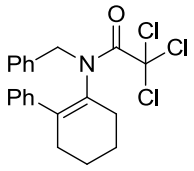


223

Cyclohexanone oxime (5 g, 44.2 mmol), copper iodide (842 mg, 4.42 mmol), sodium bisulphite (13.9 g, 133 mmol) and 2-bromoisobutyric anhydride (27.9 g, 88.4 mmol) in DCE (200 mL) were heated to reflux for 4 hours. The reaction mixture was

then cooled, diluted with EtOAc (100 mL) and washed with 2M NaOH (2 x 100 mL) and brine (100 mL). The organice layer was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a dark brown solid. This was then purified by column chromatography (pet ether/EtOAc 14:1) to give the desired product as a light brown solid (970 mg, 9%). R_f 0.37 (pet ether/EtOAc, 14:1); m.p. 84-86 ^oC; υ_{max} 3384, 3187 (NH), 2925 (CH), 1654 (C=O); δ_H (400MHz, $CDCl_3$) 7.59 (1H, br s, N<u>H</u>), 6.15 (1H, t, *J* = 4.0 Hz, C=C<u>H</u>), 2.17 – 2.25 (2H, m, C<u>H</u>$_2$C(N)=C), 2.12 – 2.17 (2H, m, NC=CC<u>H</u>$_2$), 2.00 (6H, s, 2 x C<u>H</u>$_3$), 1.69 – 1.79 (2H, m, NC=CCH$_2$C<u>H</u>$_2$), 1.57 – 1.67 (2H, m, C<u>H</u>$_2$CH$_2$C(N)=C); δ_C (100MHz, $CDCl_3$) 169.9 (C=O), 132.3 (N<u>C</u>=C), 114.1 (NC=<u>C</u>), 63.5 (C=O<u>C</u>(CH$_3$)$_2$Br, 32.6 (<u>C</u>H$_3$), 27.8 (<u>C</u>H$_2$C(N)=C), 24.0 (NC=C<u>C</u>H$_2$), 22.5 (<u>C</u>H$_2$CH$_2$C(N)=C), 21.9 (NC=CCH$_2$<u>C</u>H$_2$); *m/z* (ES^+) $C_{10}H_{16}BrNNaO$ requires 268.0307, found: 268.0305 $[M+Na]^+$.

_N_-Benzyl-2,2,2-trichloro-_N_-(2-phenylcyclohex-1-enyl)acetamide[248] (229)

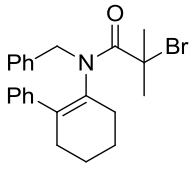


229

The general procedure for the formation of enamides *via* imines (6.2.1) was applied using 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzylamine (1.52 mL, 13.9 mmol), toluene (15 mL, 25 mL), triethylamine (2.32 mL, 16.7 mmol) and trichloroacetyl chloride (1.71 mL, 15.3 mmol). The crude product was purified by column chromatography (pet ether/EtOAc, 14:1) to yield *N*-benzyl-2,2,2-trichloro-

N-(2-phenylcyclohex-1-enyl)acetamide as a colourless crystalline solid (1.18 g, 21%). R_f 0.52 (pet ether/EtOAc, 14:1); m.p. 116-118 ^{o}C; υ_{max} 2924 (CH), 1671 (C=O); δ_H (700MHz, $CDCl_3$) 7.37 (2H, t, *J* = 7.5 Hz, Ar<u>H</u>), 7.34 – 7.33 (6H, m, Ar<u>H</u>), 7.22 (2H, d, *J* = 7.5 Hz, Ar<u>H</u>), 5.17 (1H, d, *J* = 14.0 Hz, ArC<u>H</u>$_a$H$_b$N), 3.55 (1H, d, *J* = 14.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.44 (1H, apparent d, *J* = 18.0 Hz, NC=C(Ph)C<u>H</u>$_a$H$_b$), 2.34 (1H, apparent d, *J* = 17.0 Hz, PhC=C(N)C<u>H</u>$_a$H$_b$), 2.17 – 2.26 (1H, m, NC=C(Ph)CH$_a$<u>H</u>$_b$), 1.64 – 1.73 (1H, m, NC=C(Ph)CH$_2$C<u>H</u>$_a$H$_b$), 1.49 – 1.59 (m, PhC=C(N)CH$_2$C<u>H</u>$_a$H$_b$), 1.31 – 1.41 (1H, m, PhC=C(N)CH$_2$CH$_a$<u>H</u>$_b$), 1.20 – 1.30 (1H, m, NC=C(Ph)CH$_2$CH$_a$<u>H</u>$_b$), 1.06 – 1.16 (1H, m, PhC=C(N)CH$_a$<u>H</u>$_b$); δ_C (176MHz, $CDCl_3$) 159.3 (<u>C</u>=O), 140.2 (Ar<u>C</u>C=C), 135.2 (<u>C</u>=C), 135.1 (C=<u>C</u>), 134.7 (Ar<u>C</u>CH$_2$N), 129.4 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 93.5 (C=O<u>C</u>Cl$_3$), 53.3 (Ar<u>C</u>H$_2$N), 31.2 (NC=C(Ph)<u>C</u>H$_2$), 28.9 (PhC=C(N)<u>C</u>H$_2$), 22.5 (CH$_2$<u>C</u>H$_2$CH$_2$), 22.4 (CH$_2$<u>C</u>H$_2$CH$_2$); *m/z* (ES$^+$) 408.0 [M+H]$^+$, 430.0 [M+Na]$^+$.

_N_-benzyl-2-bromo-2-methyl-_N_-(2-phenylcyclohex-1-enyl)propanamide (231)



231

The general procedure for the formation of enamides *via* imines (6.2.1) was applied using 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzylamine (1.52 mL, 13.9 mmol), toluene (15 mL, 25 mL), triethylamine (2.32 mL, 16.7 mmol) and 2-bromoisobutyryl bromide (1.89 mL, 15.3 mmol). The crude product was purified by

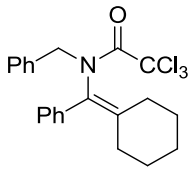
column chromatography (pet ether/EtOAc, 14:1) to yield the product as a colourless solid (716 mg, 13%). R_f 0.33 (pet ether/EtOAc, 14:1); m.p. 83-86 ^oC; υ_{max} 2940 (CH), 1626 (C=O); δ_H (700MHz, $CDCl_3$) 7.10 – 7.51 (10H, m, Ar$\underline{H}$), 5.33 (1H, d, *J* = 14.0 Hz, ArC$\underline{H}_a$H$_b$N), 3.47 (1H, d, *J* = 14.0 Hz, ArCH$_a\underline{H}_b$N), 2.39 (1H, apparent d, *J* = 17.5 Hz, NC=C(Ph)C$\underline{H}_a$H$_b$), 2.32 (1H, apparent d, *J* = 17.0 Hz, PhC=C(N)C$\underline{H}_a$H$_b$), 2.12 – 2.23 (1H, m, NC=C(Ph)CH$_a\underline{H}_b$), 2.07 (3H, s, C=OC(C$\underline{H}_3$)(CH$_3$)Br), 1.82 (3H, s, C=OC(CH$_3$)(C$\underline{H}_3$)Br), 1.62 – 1.71 (1H, m, PhC=C(N)CH$_2$C$\underline{H}_a$H$_b$), 1.48 – 1.60 (1H, m, NC=C(Ph)CH$_2$C$\underline{H}_a$H$_b$), 1.28 – 1.39 (1H, m, NC=C(Ph)CH$_2$CH$_a\underline{H}_b$), 1.17 – 1.27 (m, PhC=C(N)CH$_2$CH$_a\underline{H}_b$), 1.05 – 1.16 (1H, m, PhC=C(N)CH$_a\underline{H}_b$); δ_C (100MHz, $CDCl_3$) 169.6 (C=O), 141.1, 136.2, 135.9, 133.9, 129.4 (Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 127.3 (Ar$\underline{C}$H), 52.7 (Ar$\underline{C}$H$_2$N), 33.8 ($\underline{C}$H$_3$), 31.5 ($\underline{C}$H$_3$), 31.2 (NC=C(Ph)$\underline{C}$H$_2$), 29.5 (PhC=C(N)$\underline{C}$H$_2$), 22.7 (PhC=C(N)CH$_2\underline{C}$H$_2$), 22.5 (NC=C(Ph)CH$_2\underline{C}$H$_2$); *m/z* (ES$^+$) $C_{23}H_{26}BrNNaO$ requires 434.1090, found: 434.1087 $[M+Na]^+$.

6.2.5 General Procedure for the Synthesis of Enamides 232-236.

Ketone (1 eq.), benzylamine (1.0 eq.) and TsOH, were dissolved in dry toluene and heated to reflux under Dean-Stark conditions for 4-16 hours. The reaction mixture was then cooled and concentrated *in vacuo* and a crude NMR of the imine intermediate taken, before redisolving in toluene and cooling to 0 ^oC. Triethylamine (1.2 eq.) was then added slowly followed by the dropwise addition of the appropriate acid halide (1.1 eq.). The reaction mixture was then allowed to warm to room temperature and stirred for 12 hours. $NaHCO_3$ (~50 mL) was then added and the layers separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to

give the crude product. Products were purified by column chromatography or recrystallisation.

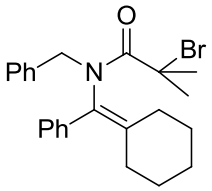
_N_-Benzyl-2,2,2-trichloro-_N_-(cyclohexylidene(phenyl)methyl)acetamide (232)



232

The general procedure for the formation of enamides (6.2.5) was applied using cyclohexylphenylketone (1.5 g, 7.97 mmol), benzylamine (0.87 mL, 7.97 mmol), TsOH (3.03 g, 1.60 mmol), toluene (9 mL, 15 mL), triethylamine (1.33 mL, 9.56 mmol) and trichloroacetyl chloride (0.978 mL, 8.76 mmol). The crude product was recrystallised from 14:1 pet ether/EtOAc to yield the product as a cream solid in a 4:1 ratio of amide rotamers (1.46 g, 43%). R_f 0.54 (pet ether/EtOAc, 6:1); m.p. 128-129 ^{o}C; υ_{max} 2972, 2932 (CH), 1671 (C=O); δ_H (400 MHz, CDCl3) 7.24 – 7.46 (2H, m, ArH), 7.20 (2H, d, *J* = 4.0 Hz, ArH), 7.06 (2H, d, *J* = 7.0 Hz, ArH), 5.45 (1H maj, d, *J* = 14.5 Hz, ArCH_aH_b maj), 5.14 (1H min, d, *J* = 14.5 Hz, ArCH_aH_b min), 4.06 (1H maj, d, *J* = 14.5 Hz, ArCH_aH_b maj), 3.77 (1H, d, *J* = 13.5 Hz, ArCH_aH_b min), 2.52 – 2.65 (1H min, m, cy CH_aH_b min), 2.12 – 2.24 (1H, m, cy CH_aH_b maj), 1.11 – 2.07 (7H maj + 8H min, m, cy), 0.81 – 0.98 (2H maj, m, cy CH_2 maj), 0.37 – 0.52 (1H min, m, cy CH_aH_b min); δ_C (100 MHz, CDCl3) 167.6 (C=O min), 159.6 (C=O maj), 152.3, 141.0, 136.2, 135.5, 135.4, 134.9, 130.5, 130.3 (quarternary), 129.7, 129.3, 128.4, 128.2, 128.2, 128.1, 127.6, 127.0 (ArCH), 94.4, 94.1 (CCl_3), 54.1, 53.2 (NCH_2), 32.2, 31.8, 30.9, 27.6, 27.3, 26.5, 26.3, 26.2 (cy); *m/z* (ES^+) $C_{22}H_{22}Cl_3NNaO$ requires 444.0665, found: 444.0659 $[M+Na]^+$.

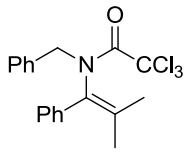
_N_-Benzyl-2-bromo-_N_-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (233)



233

The general procedure for the formation of enamides (6.2.5) was applied using cyclohexylphenylketone (1.5 g, 7.97 mmol), benzylamine (0.87 mL, 7.97 mmol), TsOH (3.03 g, 1.60 mmol), toluene (9 mL, 15 mL), triethylamine (1.33 mL, 9.56 mmol) and 2-bromoisobutyryl bromide (1.08 mL, 8.76 mmol). The crude product was recrystallised from 14:1 pet ether/EtOAc to yield the product as a brown solid in a 1:0.62 ratio of amide rotamers (2.02 g, 59%). R_f 0.43 (pet ether/EtOAc, 6:1); m.p. 102-104 ^oC; υ_{max} 2973, 2929, 2852 (CH), 1656 (C=O); δ_H (400 MHz, $CDCl_3$) 7.14 – 7.58 (8H maj + 10H min, m, Ar<u>H</u>), 7.01 (2H maj, d, *J* = 7.0 Hz, Ar<u>H</u>), 5.52 (1H maj, d, *J* = 14.5 Hz, NC<u>H</u>$_a$H$_b$), 5.16 (1H min, d, *J* = 13.5 Hz, NC<u>H</u>$_a$H$_b$), 4.02 (1H maj, d, *J* = 14.5 Hz, NCH$_a$<u>H</u>$_b$), 3.63 (1H min, d, *J* = 13.5 Hz, NCH$_a$<u>H</u>$_b$), 2.69 (1H min, d, *J* = 12.5 Hz, cy), 2.19 (3H maj, s, C<u>H</u>$_3$), 2.10 (3H maj, s, C<u>H</u>$_3$), 2.06 (6H min, s, C<u>H</u>$_3$), 1.08 – 2.12 (9H maj + 8H min, m, cy), 0.80 – 1.03 (1H maj, m, cy), 0.30 (1H min, d, *J* = 12.5 Hz, cy); δ_C (75 MHz, $CDCl_3$) 172.2, 169.3 (C=O), 141.2, 140.4, 137.2, 136.6, 136.3, 136.0, 131.3, 131.3 (quarternary), 130.4, 130.0, 129.7, 129.0, 128.5, 128.2, 128.1, 128.0, 127.6, 127.1 (Ar), 62.8, 57.8 (<u>C</u>(CH$_3$)$_2$Br), 52.7, 52.7 (N<u>C</u>H$_2$), 33.6, 33.5, 32.7 (<u>C</u>H$_3$), 32.2, 31.6, 30.9, 27.7, 27.5, 26.6, 26.4, 26.3 (cy); *m/z* (ES^+) $C_{22}H_{22}Cl_3NNaO$ requires 448.1252, found: 448.1246 $[M+Na]^+$.

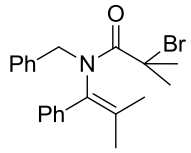
_N_-Benzyl-2,2,2-trichloro-_N_-(2-methyl-1-phenylprop-1-enyl)acetamide (234)



234

The general procedure for the formation of enamides (6.2.5) was applied using isobutyrophenone (5.06 mL, 33.8 mmol), benzylamine (3.69 mL, 33.8 mmol), TsOH (1.92 g, 10.12 mmol), toluene (35 mL, 15 mL), triethylamine (1.40 mL, 10.1 mmol) and trichloroacetyl chloride (1.03 mL, 9.27 mmol). The crude product was purified by column chromatography (pet ether/EtOAc, 19:1) to yield the product as a mixture with isobutyrophenone. Pet ether (5 mL) was added to the solid and the mixture filtered to give the product as a colourless solid in a 1:0.26 ratio of amide rotamers (1.21 g, 38%). R_f 0.51 (pet ether/EtOAc, 6:1); m.p. 68-69 ^{o}C; υ_{max} 3003, 2913 (CH), 1680 (C=O); δ_H (300 MHz, CDCl3) 7.08 – 7.51 (10H min + 8H min, m, Ar<u>H</u>), 7.02 (2H maj, dd, *J* = 8.0, 1.5 Hz, Ar<u>H</u>), 5.41 (1H maj, d, *J* = 14.5 Hz, ArC<u>H</u>$_a$H$_b$), 5.05 (1H min, d, *J* = 13.5 Hz, ArC<u>H</u>$_a$H$_b$), 4.13 (1H maj, d, *J* = 14.5 Hz, ArCH$_a$<u>H</u>$_b$), 3.85 (1H min, d, *J* = 13.5 Hz, ArCH$_a$<u>H</u>$_b$), 1.80 (3H min, s, C<u>H</u>$_3$), 1.60 (3H maj, s, C<u>H</u>$_3$), 1.55 (3H maj, s, C<u>H</u>$_3$), 1.29 (3H min, s, C<u>H</u>$_3$); δ_C (75 MHz, $CDCl_3$) 158.7 (C=O maj), 135.7, 134.0, 134.0, 130.2 (<u>C</u> - quarternary), 129.8, 129.7, 129.0, 128.5, 127.7, 127.5, 127.5, 127.4, 126.9 (Ar<u>C</u>), 93.4 (<u>C</u>Cl$_3$ maj), 53.9 (Ar<u>C</u>H$_2$ min), 52.8 (Ar<u>C</u>H$_2$ maj), 21.4 (<u>C</u>H$_3$ min), 20.3(<u>C</u>H$_3$ maj); *m/z* (ES$^+$) $C_{19}H_{18}Cl_3NNaO$ requires 404.0352, found: 404.0346 $[M+Na]^+$.

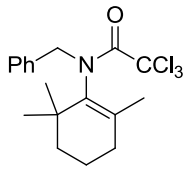
_N_-Benzyl-2-bromo-2-methyl-_N_-(2-methyl-1-phenylprop-1-enyl)propanamide (235)



235

The general procedure for the formation of enamides (6.2.5) was applied using isobutyrophenone (5.06 mL, 33.8 mmol), benzylamine (3.69 mL, 33.8 mmol), TsOH (1.92 g, 10.12 mmol), toluene (35 mL, 15 mL), triethylamine (1.40 mL, 10.1 mmol) and 2-bromoisobutyryl bromide (1.15 mL, 9.27 mmol). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to yield the product as a pale yellow solid in a 1:0.65 ratio of amide rotamers (2.39 g, 74%). R_f 0.37 (pet ether/EtOAc, 6:1); m.p. 74-76 ^oC; υ_{max} 2989, 2910 (CH), 1639 (C=O); δ_H (400 MHz, CDCl3) 7.10 – 7.56 (10H min + 8H maj, m, Ar<u>H</u>), 7.00 (2H maj, d, *J* = 7.0 Hz, Ar<u>H</u>), 5.49 (1H maj, d, *J* = 15.0 Hz, ArC<u>H</u>$_a$H$_b$), 5.07 (1H min, d, *J* = 13.5 Hz, ArC<u>H</u>$_a$H$_b$), 4.14 (1H maj, d, *J* = 15.0 Hz, ArCH$_a$<u>H</u>$_b$), 3.76 (1H min, d, *J* = 13.5 Hz, ArCH$_a$<u>H</u>$_b$), 2.18 (s, J = 4.5 Hz, 1H), 2.10 (s, 1H), 2.04 (s, 1H), 2.02 (s, 1H), 1.83 (s, 1H), 1.60 (s, J = 6.2 Hz, 1H), 1.58 (s, J = 2.9 Hz, 1H), 1.25 (s, J = 12.8 Hz, 1H); δ_C (75 MHz, CDCl3) 171.3 (C=O min), 168.6 (C=O maj), 136.8, 135.8, 135.2, 133.8, 133.4, 132.7, 130.9 (<u>C</u>-quarternary), 129.6, 129.5, 129.1, 128.3, 127.8, 127.5, 127.3, 127.0, 126.9, 126.5 (Ar<u>C</u>), 61.8 (<u>C</u>(CH$_3$)$_2$Br min), 57.2 (<u>C</u>(CH$_3$)$_2$Br maj), 52.5, 52.5 (Ar<u>C</u>H$_2$), 33.3, 32.9, 32.7, 32.1 (C(<u>C</u>H$_3$)$_2$Br), 21.2, 21.2, 20.4, 20.2 (C=C(<u>C</u>H$_3$)$_2$); *m/z* (ES$^+$) $C_{21}H_{24}BrNNaO$ requires 408.0939, found: 408.0933 $[M+Na]^+$.

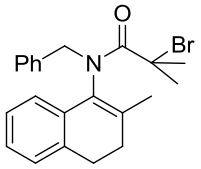
_N_-Benzyl-2,2,2-trichloro-_N_-(2,6,6-trimethylcyclohex-1-enyl)acetamide (236)



236

The general procedure for the formation of enamides (6.2.5) was applied using 2,2,6-trimethylcyclohexanone (1.00 g, 7.13 mmol), benzylamine (0.779 mL, 7.13 mmol), TsOH (271 mg, 1.45 mmol), toluene (15 mL, 15 mL), triethylamine (1.19 mL, 8.58 mmol) and trichloroacetyl chloride (0.876 mL, 7.8 mmol). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to yield the product as a colourless oil (1.18 g, 44%). R_f 0.54 (pet ether/EtOAc, 6:1); υ_{max} 2934 (CH), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 7.36 – 7.50 (2H, m, Ar<u>H</u>), 7.21 – 7.36 (3H, m, Ar<u>H</u>), 5.60 (1H maj, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 5.09 (1H min, d, *J* = 14.0 Hz, NC<u>H</u>$_a$H$_b$), 4.59 (1H maj, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 4.45 (1H min, d, *J* = 14.0 Hz, NCH$_a$<u>H</u>$_b$), 1.44 – 2.12 (6H, m, cy), 1.33 (3H min, s, C=C<u>C</u>H$_3$), 1.24 (3H maj, s, C=C<u>C</u>H$_3$), 1.20 (3H min, s, C(C<u>H</u>$_3$)(CH$_3$)), 1.18 (3H min, s, C(CH$_3$)(C<u>H</u>$_3$)), 1.11 (3H maj, s, C(C<u>H</u>$_3$)(CH$_3$)), 0.97 (3H maj, s, C(CH$_3$)(C<u>H</u>$_3$)); δ_C (100 MHz, $CDCl_3$) 159.6, 158.5 (C=O), 135.8, 135.2, 135.1, 134.6, 134.0, 133.5 (Ar<u>C</u>), 130.7, 130.1, 129.5, 128.5, 128.1, 127.9 (Ar<u>C</u>H), 94.5, 92.2 (CO<u>C</u>Cl$_3$), 56.8, 54.21 (N<u>C</u>H$_2$), 41.1, 40.0, 38.7, 37.6, 36.7 (cy), 34.1 (<u>C</u>H$_3$), 32.1, 31.7 (cy), 31.4, 30.0, 27.7, 26.8, 19.7 (<u>C</u>H$_3$), 18.5 (cy), 12.6 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{18}H_{22}Cl_3NNaO$ requires 396.0665, found: 396.0659 $[M+Na]^+$.

_N_-Benzyl-2-bromo-2-methyl-_N_-(2-methyl-3,4-dihydronaphthalen-1-yl)propanamide (237)



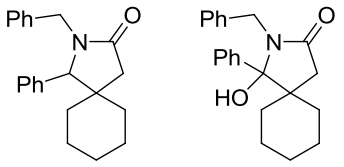
237

2-Methyl-1-tetralone (1.00 g, 6.24 mmol), benzylamine (0.818 mL, 7.49 mmol) and titanium isopropoxide (2.77 mL, 9.36 mmol) were heated to 80 ^{o}C for 48 hours. The reaction mixture was then cooled to room temperature and tolune (12 mL) was added. The resulting solution was then cooled further to 0 ^{o}C added triethylamine (1.30 mL, 9.36 mmol) was added followed by the dropwise addition of 2-bromoisobutyryl bromide (0.93 mL, 7.49 mmol), and the reaction mixture stirred at room temperature for 14 hours. Saturated ammonium chloride (15 mL) was then added and the phases separated. The organic phase was diluted with toluene (20 mL) and washed with 2M HCl (3 x 30 mL), then dried over MgSO4, filtered and concentrated in vacuo to give the crude product as a brown oil (1.26 g). The crude product was purified by column chromatography (14:1, pet ether/EtOAc) to give the product as a light brown oil (144 mg, 6%). R_f 0.17 (pet ether/EtOAc, 14:1); δ_H (600 MHz, $CDCl_3$) 7.33 – 7.40 (2H maj, m, Ar$\underline{H}$), 7.25 – 7.29 (3H maj, m, Ar$\underline{H}$), 7.16 – 7.25 (3H maj + 6H min, m, Ar$\underline{H}$), 7.07 – 7.14 (1H maj + 2H min, m, Ar$\underline{H}$), 6.98 (1H min, d, J = 7.5 Hz, Ar$\underline{H}$), 5.65 (1H min, d, J = 13.5 Hz, NC$\underline{H}_a$H$_b$), 5.50 (1H maj, d, J = 13.5 Hz, NC$\underline{H}_a$H$_b$), 4.56 (1H min, d, J = 13.5 Hz, NCH$_a\underline{H}_b$), 3.90 (1H maj, d, J = 13.5 Hz, NCH$_a\underline{H}_b$), 2.75 – 2.89 (2H maj, m, ArC$\underline{H}_2$CH$_2$), 2.52 – 2.59 (1H min, m, ArC$\underline{H}_a$H$_b$CH$_a$H$_b$), 2.35 – 2.45 (2H min, m, ArCH$_a\underline{H}_b$C$\underline{H}_a$H$_b$), 2.20 – 2.33 (2H maj + 6H min, m, ArCH$_2$C$\underline{H}_2$ maj + C(C$\underline{H}_3$)$_2$ min), 1.97 (3H, s, C(C$\underline{H}_3$)(CH$_3$)), 1.89 (1H

min, dd, *J* = 10.0, 2.5 Hz, $ArCH_2CH_a\underline{H}_b$), 1.86 (3H, s, $C(CH_3)(C\underline{H}_3)$), 1.45 (3H min, s, $C{=}CC\underline{H}_3$), 1.29 (3H maj, s, $C{=}CC\underline{H}_3$); δ_C (150 MHz, CDCl3) 171.9 (C=O maj), 169.2 (C=O min), 137.4 ($C{=}\underline{C}CH_3$ maj), 136.8 ($NCH_2\underline{C}$(Ar) maj), 136.3 ($C{=}\underline{C}CH_3$ min), 136.1 ($NC\underline{C}$(Ar) min), 135.9 ($NC\underline{C}$(Ar) maj), 135.2 ($NCH_2\underline{C}$(Ar) min), 132.9 ($CH_2CH_2\underline{C}$(Ar) maj), 132.1 ($N\underline{C}{=}C$ maj), 131.7 ($CH_2CH_2\underline{C}$(Ar) min), 130.7 (ArH), 130.2 (($N\underline{C}{=}C$ min), 129.9, 128.1, 127.9, 127.8, 127.7, 127.7, 127.4, 127.2, 126.8, 126.5, 126.3, 122.9, 121.5 (ArH), 60.2 ($\underline{C}(CH_3)_2Br$ maj), 57.7 ($\underline{C}(CH_3)_2Br$ min), 53.9 ($N\underline{C}H_2$ maj), 53.2 ($N\underline{C}H_2$ min), 34.2 ($C(\underline{C}H_3)(CH_3)Br$ maj), 33.3 ($C(\underline{C}H_3)(CH_3)Br$ min), 32.8 ($C(CH_3)(\underline{C}H_3)Br$ maj + min), 29.7 ($C{=}C\underline{C}H_2$ maj), 29.4 ($C{=}C\underline{C}H_2$ min), 27.5 ($C{=}CCH_2\underline{C}H_2$ min), 27.2 ($C{=}CCH_2\underline{C}H_2$ maj), 20.8 ($C{=}C\underline{C}H_3$ maj), 19.3 ($C{=}C\underline{C}H_3$ maj); *m/z* (ES^+) $C_{22}H_{24}BrNNaO$ requires 420.0933, found: 408.0930 $[M+Na]^+$.

6.3 Compounds Synthesised in Chapter Three

2-Benzyl-1-phenyl-2-azaspiro[4.5]decan-3-one (264) and 2-benzyl-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (265)



264 **265**

N-Benzyl-2-chloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide **(210)** (500 mg, 1.49 mmol), Bu_3SnH (0.600 mL, 2.23 mmol) and ACN (72.7 mg, 0.298 mmol) in toluene (75 mL) were heated to reflux for 26 hours. The reaction mixture was then cooled and concentrated *in vacuo*. The residue was then partitioned between

acetonitrile (50 mL) and hexane (50 mL), and the acetonitrile phase concentrated *in vacuo* to give the crude product as a brown oil (434 mg). Purification of the crude mixture (14:1 to 9:1, pet ether/EtOAC) led to the identification of two products, 2-benzyl-1-phenyl-2-azaspiro[4.5]decan-3-one and 2-benzyl-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one.

Dicernable data for 2-benzyl-1-phenyl-2-azaspiro[4.5]decan-3-one **(264):** R_f 0.17 (pet ether/EtOAc, 6:1); δ_H (400 MHz, $CDCl_3$) 6.93 – 7.45 (10H, m, Ar<u>H</u>), 5.15 (1H, d, *J* = 14.5 Hz, NC<u>H</u>$_a$H$_b$), 3.92 (1H, s, NC<u>H</u>), 3.41 (1H, d, *J* = 14.5 Hz, NCH$_a$<u>H</u>$_b$), 2.43 (2H, q, *J* = 17.0 Hz, COC<u>H</u>$_2$), 0.73 – 1.79 (10H, m, cy); δ_C (100 MHz, $CDCl_3$) 174.3 (C=O), 137.1, 136.4 (quarternary), 130.0, 129.6, 129.3, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4 (Ar<u>C</u>H), 72.1 (N<u>C</u>H), 44.6 (N<u>C</u>H$_2$), 37.8, 34.5, 25.7, 23.0, 22.5 (cy); *m/z* (ES^+) $C_{22}H_{25}NNaO$ requires 342.1834, found: 342.1825 $[M+Na]^+$.

Discernable data for 2-Benzyl-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one **(265):** R_f 0.15 (pet ether/EtOAc, 6:1); δ_H (400 MHz, $CDCl_3$) 6.93 – 7.45 (10H, m, Ar<u>H</u>), 4.86 (1H, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 3.90 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 2.95 (1H, br s, OH), 2.61 (1H, d, *J* = 17.0 Hz, COC<u>H</u>$_a$H$_b$), 2.35 (1H, d, *J* = 17.0 Hz, COCH$_a$<u>H</u>$_b$), 0.73 – 1.79 (10H, m, cy); δ_C (100 MHz, $CDCl_3$) 175.0 (C=O), 138.9, 138.7 (quarternary), 128.6, 128.5, 128.1, 128.1, 127.5, 127.2 (Ar<u>C</u>H), 98.2 (N<u>C</u>(OH)) 45.7 (N<u>C</u>H$_2$), 39.5, 33.7, 25.5, 23.1, 22.8 (cy); *m/z* (ES^+) $C_{22}H_{25}NNaO_2$ requires 358.1783, found: 358.1778 $[M+Na]^+$.

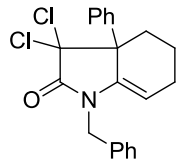
6.3.1 General Procedure for Cyclisation of Trichloroenamides

Enamide (1 eq.), CuCl (1 eq.) and TPA (1 eq.) were heated to reflux in toluene (0.12 M) for 2-16 hours. The reaction mixture was then cooled to room temperature and filtered through a silica plug with EtOAc (15 mL). The filtrate was then concentrated *in vacuo* to give the crude product. The products were purified by column chromatography.

6.3.2 General Procedure for Cyclisation of Bromoenamides.

Enamide (1 eq.), CuBr (0.6 eq.) and TPA (0.6 eq.) were heated to reflux in toluene (0.12 M) for 2-15 hours. The reaction mixture was then cooled to room temperature and filtered through a silica plug with EtOAc. The filtrate was then concentrated *in vacuo* to give the crude product. The products were purified by column chromatography.

1-Benzyl-3,3-dichloro-3a-phenyl-3a,4,5,6-tetrahydro-1H-indol-2(3H)-one (269)

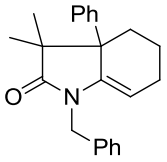


269

The general procedure for the cyclisation of trichloroenamides (6.3.1) was applied using *N*-benzyl-2,2,2-trichloro-*N*-(2-phenylcyclohex-1-enyl)acetamide (200 mg, 0.49 mmol), CuCl (48.5 mg, 0.49 mmol), TPA (142 mg, 0.49 mmol) and toluene (4.2 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 9:1) to give the product as a colourless oil (123 mg, 70%). R_f 0.37 (pet ether/EtOAc, 9:1); δ_H (400MHz, $CDCl_3$) δ 7.24 – 7.33 (5H, m, Ar<u>H</u>), 7.07 – 7.15 (3H, m, Ar<u>H</u>),

6.99 – 7.03 (2H, m, Ar<u>H</u>), 5.25 (1H, t, *J* = 3.5 Hz, C=C<u>H</u>), 4.86 (1H, d, *J* = 15.0 Hz, ArC<u>H</u>$_a$H$_b$N), 4.69 (1H, d, *J* = 15.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.40 – 2.49 (2H, m, C=CHC<u>H</u>$_2$), 1.93 – 2.13 (3H, m, C(Ph)C<u>H</u>$_2$), 1.59 – 1.68 (1H, m, CH$_2$C<u>H</u>$_a$H$_b$CH$_2$), 0.97 – 1.11 (1H, m, CH$_2$CH$_a$<u>H</u>$_b$CH$_2$); δ_C (100MHz, $CDCl_3$) δ 166.3 (C=O), 139.1 , 138.2, 135.1 (quarternary) 129.0, 128.8, 128.1, 128.1, 128.1, 127.8 (Ar<u>C</u>H), 105.4 (C=<u>C</u>H), 89.1 (C=O<u>C</u>Cl$_2$), 56.8 (CCl$_2$<u>C</u>(Ph)CH$_2$), 45.2 (Ar<u>C</u>H$_2$N), 29.3 (C=C<u>C</u>H$_2$), 23.1 (C(Ph)<u>C</u>H$_2$), 18.1 (CH$_2$<u>C</u>H$_2$CH$_2$); *m/z* (ES$^+$) $C_{21}H_{19}Cl_2NNaO$ requires 394.0736, found: 394.0732 $[M+Na]^+$.

1-Benzyl-3,3,3a-trimethyl-3a,4,5,6-tetrahydro-1H-indol-2(3H)-one (270)

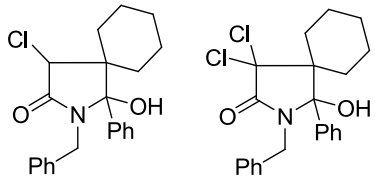


270

The general procedure for the cyclisation of bromoenamides (6.3.2) was apllied using *N*-benzyl-2-bromo-2-methyl-*N*-(2-phenylcyclohex-1-enyl)propanamide (150 mg, 0.36 mmol), CuBr (15.6 mg, 0.11 mmol), TPA (31.9 mg, 0.11 mmol) and toluene (3 mL). The crude product was purified by column chromatography (8:1, pet ether/EtOAc) to give the product as a yellow oil (49 mg, 41%). R_f 0.37 (pet ether/EtOAc, 6:1); δ_H (400MHz, $CDCl_3$) 6.98 – 7.39 (8H, m, Ar<u>H</u>), 6.8 – 6.88 (2H, m, Ar<u>H</u>), 5.01 (1H, t, *J* = 3.5 Hz, C=C<u>H</u>), 4.74 (1H, d, *J* = 15.0 Hz, ArC<u>H</u>$_a$H$_b$N), 4.56 (1H, d, *J* = 15.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.14 (1H, dt, *J* = 12.5, 3.5 Hz, C(Ph)C<u>H</u>$_a$H$_b$), 2.06 – 1.81 (2H, m, C=CHC<u>H</u>$_2$), 1.81 – 1.66 (1H, m, C(Ph)CH$_a$<u>H</u>$_b$), 1.40 – 1.56 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.15 (3H, s, C<u>H</u>$_3$), 0.75 (3H, s, C<u>H</u>$_3$); δ_C (75 MHz, $CDCl_3$) 178.8 (<u>C</u>=O), 142.7 (Ar<u>C</u>-CC=C), 142.1 (<u>C</u>=CH), 136.1 (Ar<u>C</u>-CH$_2$N), 128.0, 127.5, 127.3,

127.2, 126.9, 125.7 (Ar<u>C</u>H), 100.9 (C=<u>C</u>H), 51.2 (CH=C<u>C</u>Ph), 47.9 (<u>C</u>(CH_3)$_2$), 43.4 (N<u>C</u>H_2), 26.8 (CH_2), 23.8 (<u>C</u>H_3), 22.6 (C=CH<u>C</u>H_2), 20.1 (CH_2), 17.9 (<u>C</u>H_3); *m/z* (ES^+) $C_{23}H_{25}NNaO$ requires 354.1834, found: 354.1828 $[M+Na]^+$.

2-Benzyl-4-chloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (272) and 2-Benzyl-4,4-dichloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (273)



272 **273**

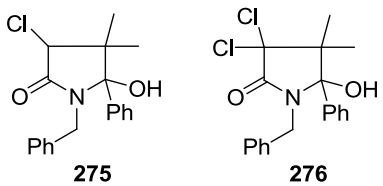
The general procedure for the cyclisation of trichloroenamides (6.3.1) was applied using *N*-Benzyl-2,2,2-trichloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide (**232**) (150 mg, 0.355 mmol), CuCl (35.1 mg, 0.355 mmol), TPA (103 mg, 0.355 mmol) and toluene (3.3 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 10:1) to give 2-benzyl-4-chloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one as a colourless solid (21 mg, 16%) and 2-benzyl-4,4-dichloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one as a colourless solid (33 mg, 23%).

2-Benzyl-4-chloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (272): R_f 0.18 (pet ether/EtOAc, 6:1); m.p. 183-185 ^oC; υ_{max} 3213 (OH), 2929, 2861 (CH), 1687 (C=O); δ_H (400 MHz, $CDCl_3$) 6.76 – 7.81 (10H, m, Ar<u>H</u>), 4.84 (1H, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 4.47 (1H, s, C<u>H</u>Cl), 4.19 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 2.58 (1H, s, O<u>H</u>), 2.26 (1H, dd, *J* = 13.5, 2.5 Hz, cy), 1.48 – 1.77 (3H, m, cy), 1.13 – 1.42 (4H, m, cy), 0.79 – 0.96 (1H, m, cy), 0.69 (1H, td, *J* = 13.0, 4.0 Hz, cy); δ_C (100 MHz, $CDCl_3$)

172.2 (C=O), 137.5, 136.0 (quarternary), 129.0, 128.7, 128.6, 128.6, 128.2, 127.6 (ArCH), 98.5 (NC(OH)Ph), 60.4 (CHCl) 48.2 (CH(Cl)CC(OH)), 45.2 (NCH_2Ph), 33.62, 26.45, 24.71, 22.65, 22.41 (cy); *m/z* (ES^+) $C_{22}H_{24}ClNNaO_2$ requires 392.1393, found: 392.1388 $[M+Na]^+$.

2-Benzyl-4,4-dichloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (273): R_f 0.21 (pet ether/EtOAc, 6:1); m.p. 178-180 ^oC; υ_{max} 3517 (OH), 2932, 2869 (CH), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 6.86 – 7.86 (10H, m, ArH), 4.82 (1H, d, *J* = 15.0 Hz, NCH_aH_b), 4.03 (1H, d, *J* = 15.0 Hz, NCH_aH_b), 2.80 (1H, br s, OH), 1.94 - 2.09 (1H, m, cy), 1.72 – 1.87 (1H, m, cy), 1.41 – 1.70 (4H, m, cy), 1.23 – 1.41 (1H, m, cy), 1.10 – 1.23 (1H, m, cy), 0.91 – 1.10 (1H, m, cy), 0.54 – 0.76 (1H, m, cy); δ_C (100 MHz, $CDCl_3$) 166.7 (C=O), 136.1, 135.7 (quarternary), 128.1, 127.9, 127.5, 126.8 (ArCH), 95.5 (NC(OH)Ph), 90.8 (CCl_2), 52.6 ($C(Cl)_2CC(OH)$), 45.1 (NCH_2Ph), 31.7, 27.5, 23.8, 21.0, 20.6 (cy), (Only four aromatic CH observed, overlap of peaks is presumed); *m/z* (ES^+) $C_{22}H_{23}Cl_2NNaO_2$ requires 426.1004, found: 426.0998 $[M+Na]^+$.

1-Benzyl-3-chloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (275) and 1-Benzyl-3,3-dichloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (276)



275 **276**

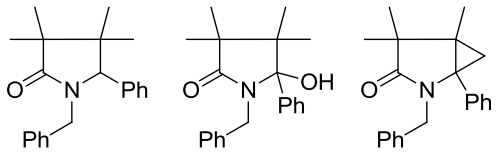
The general procedure for the cyclisation of trichloroenamides (6.3.1) was applied using *N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (**234**)

(150 mg, 0.39 mmol), CuCl (38.8 mg, 0.39 mmol), TPA (114 mg, 0.39 mmol) and toluene (3.5 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 10:1) to give 1-benzyl-3-chloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one as a colourless solid (17 mg, 13%) and 2-benzyl-4,4-dichloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one as a colourless solid (68 mg, 48%).

1-Benzyl-3-chloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (275): R_f 0.10 (pet ether/EtOAc, 6:1); m.p. 183-185 ^oC; υ_{max} 3376 (OH), 2972, 2935 (CH), 1677 (C=O); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.48 (3H, m, Ar<u>H</u>), 7.29 – 7.37 (2H, m, Ar<u>H</u>), 7.17 – 7.28 (3H, m, Ar<u>H</u>), 6.96 – 7.04 (2H, m, Ar<u>H</u>), 5.16 (1H, d, *J* = 14.5 Hz, NC<u>H</u>$_a$H$_b$), 4.73 (1H, s, C<u>H</u>Cl), 4.13 (1H, d, *J* = 14.5 Hz, NCH$_a$<u>H</u>$_b$), 2.08 (1H, s, OH), 1.10 (3H, s, C<u>H</u>$_3$), 0.77 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 172.1 (<u>C</u>=O), 137.2, 136.6 (quarternary), 129.1, 129.0, 128.7, 128.3, 128.0 (Ar<u>C</u>H), 95.9 (N<u>C</u>(OH)Ph), 65.7 (<u>C</u>HCl), 48.3 (<u>C</u>(CH$_3$)$_2$), 44.5 (N<u>C</u>H$_2$Ph), 22.0 (<u>C</u>H$_3$), 19.1(<u>C</u>H$_3$) (Only five aromatic CH observed, overlap of peaks is presumed); *m/z* (ES$^+$) $C_{19}H_{21}ClNO_2$ requires 330.1261, found: 330.1255 $[M+H]^+$.

1-Benzyl-3,3-dichloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (276): R_f 0.18 (pet ether/EtOAc, 6:1); m.p. 171-172 ^oC; υ_{max} 3520 (OH), 2933, 2866 (CH), 1676 (C=O); δ_H (400 MHz, $CDCl_3$) 7.31 – 7.55 (4H, m, Ar<u>H</u>), 7.16 – 7.31 (6H, m, Ar<u>H</u>), 4.96 (1H, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 4.22 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 2.88 (1H, s, O<u>H</u>), 1.33 (3H, s, C<u>H</u>$_3$), 0.87 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 167.8 (<u>C</u>=O), 136.7, 136.4 (quarternary), 129.1, 128.9, 128.6, 128.0, 127.9 (Ar<u>C</u>H), 96.0 (N<u>C</u>(OH)Ph), 90.7 (<u>C</u>Cl$_2$), 52.6 (<u>C</u>(CH$_3$)$_2$), 46.0 (N<u>C</u>H$_2$Ph), 26.6 (<u>C</u>H$_3$), 18.0 (<u>C</u>H$_3$) (Only five aromatic CH observed, overlap of peaks is presumed); *m/z* (ES$^+$) $C_{19}H_{19}Cl_2NNaO_2$ requires 386.0691, found: 386.0691 $[M+Na]^+$.

1-Benzyl-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (278), 1-Benzyl-5-hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (279) and 2-Benzyl-4,4,5-trimethyl-1-phenyl-2-azabicyclo[3.1.0]hexan-3-one (280)



278 **279** **280**

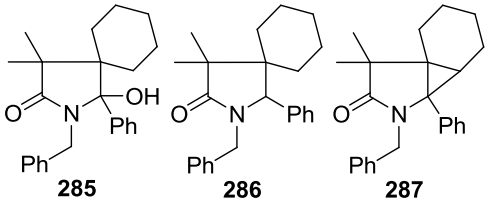
The general procedure for the cyclisation of bromoenamides (6.3.2) was applied using *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-1-phenylprop-1-enyl)propanamide (**235**) (200 mg, 0.518 mmol), CuBr (44.6 mg, 0.311 mmol), TPA (90.2 mg, 0.311 mmol) and toluene (5 mL). The crude product was purified by column chromatography (6:1, pet ether/EtOAc) to yielding 1-benzyl-5-hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (**279**) as a white solid (61 mg, 36%) and a colourless oil (30 mg) that was found to be a 4:1 mixture of 1-benzyl-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (**278**) (15%) and 2-benzyl-4,4,5-trimethyl-1-phenyl-2-azabicyclo[3.1.0]hexan-3-one (**280**) (4%).

1-Benzyl-5-hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (279): R_f 0.16 (pet ether/EtOAc, 6:1); m.p. 117-119 ^{o}C; υ_{max} 3217 (OH), 2912 (CH), 1666 (C=O); δ_H (400 MHz, $CDCl_3$) 7.14 – 7.48 (8H, m, Ar<u>H</u>), 7.01 – 7.14 (2H, m, Ar<u>H</u>), 5.20 (1H, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 4.03 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 1.95 (1H, s, O<u>H</u>), 1.35 (3H, s, C<u>H</u>$_3$), 1.09 (3H, s, C<u>H</u>$_3$), 0.95 (3H, s, C<u>H</u>$_3$), 0.53 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 182.1 (<u>C</u>=O), 139.2, 138.5 (quarternary), 128.9, 128.5, 128.3, 128.0, 127.7 (Ar<u>C</u>H), 96.9 (N<u>C</u>(OH)Ph), 46.7 (<u>C</u>(CH$_3$)$_2$), 46.0 (<u>C</u>(CH$_3$)$_2$), 44.0 (N<u>C</u>H$_2$), 25.4 (<u>C</u>H$_3$), 24.9 (<u>C</u>H$_3$), 20.4 (<u>C</u>H$_3$), 17.0 (<u>C</u>H$_3$), (Only five aromatic CH observed,

overlap of peaks is presumed); *m/z* (ES^+) $C_{21}H_{25}NNaO_2$ requires 346.1783, found: 346.1781 $[M+Na]^+$.

1-Benzyl-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (278) and 2-Benzyl-4,4,5-trimethyl-1-phenyl-2-azabicyclo[3.1.0]hexan-3-one (280) (4:1): R_f 0.19 (pet ether/EtOAc, 6:1); δ_H (400 MHz, $CDCl_3$) 6.87 – 7.44 (10H maj + 10 H min, m, Ar<u>H</u>), 5.24 (1H maj, d, *J* = 14.0 Hz, NC<u>H</u>$_a$H$_b$), 4.83 (1H min, d, *J* = 14.0 Hz, NC<u>H</u>$_a$H$_b$), 3.97 (1H maj, s, NC<u>H</u>), 3.72 (1H min, d, *J* = 14.0 Hz, NCH$_a$<u>H</u>$_b$), 3.66 (1H maj, d, *J* = 14.0 Hz, NCH$_a$<u>H</u>$_b$), 1.32 (3H min, s, COC(C<u>H</u>$_3$)(CH$_3$)), 1.18 (3H min, s, COC(CH$_3$)(C<u>H</u>$_3$)), 1.08 (3H maj, s, COC(C<u>H</u>$_3$)(CH$_3$)), 1.00 (1H min, d, *J* = 6.0 Hz, NCC<u>H</u>$_a$H$_b$), 0.96 (3H maj, s, COC(CH$_3$)(C<u>H</u>$_3$)), 0.85 (3H maj, s, C<u>H</u>$_3$), 0.79 (3H min, s, C<u>H</u>$_3$), 0.59 (3H maj, s, C<u>H</u>$_3$), 0.30 (1H min, d, *J* = 6.0 Hz, NCCH$_a$<u>H</u>$_b$); δ_C (150 MHz, $CDCl_3$) 181.2 (<u>C</u>=O maj), 179.5 (<u>C</u>=O min), 137.1 (Ar quaternary min), 136.3 (Ar quaternary maj), 135.4 (Ar quaternary maj), 134.2 (Ar quaternary min), 129.5, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.8, 127.5, 127.3 (Ar<u>C</u>H), 68.6 (N<u>C</u>H maj), 51.6 (N<u>C</u>(Ph)CH$_2$), 46.7 (CO<u>C</u>(CH$_3$)$_2$ maj), 45.3 (N<u>C</u>H$_2$Ph min), 45.3 (CO<u>C</u>(CH$_3$)$_2$ min), 44.8 (N<u>C</u>H$_2$Ph maj), 42.4 (NCH<u>C</u>(CH$_3$)$_2$ maj), 28.8 (NC(Ph)<u>C</u>(CH$_3$) min), 25.0 (NC<u>C</u>H$_2$ min), 24.2 (COC(<u>C</u>H$_3$)(CH$_3$) min), 21.6 (COC(CH$_3$)(<u>C</u>H$_3$) min), 21.3 (NCHC(<u>C</u>H$_3$)(CH$_3$) maj), 21.1 (NCHC(CH$_3$)(<u>C</u>H$_3$) maj), 20.7 (COC(<u>C</u>H$_3$)(CH$_3$) maj), 19.2 (COC(CH$_3$)(<u>C</u>H$_3$) maj), 14.1 (NCC(<u>C</u>H$_3$) min); *m/z* (ES^+) $C_{21}H_{25}NNaO$ requires 330.1834, found: 330.1832 $[M+Na]^+$ **(278)**. *m/z* (ES^+) 306.2 $[M+H]^+$, 328.2 $[M+Na]^+$ **(280)**.

2-Benzyl-1-hydroxy-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (285), 2-Benzyl-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (286) and (287) (0.22:1).



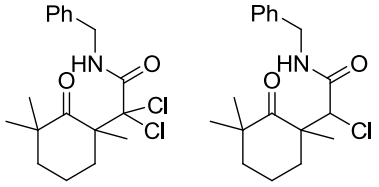
The general procedure for the cyclisation of bromoenamides (6.3.2) was applied using *N*-Benzyl-2-bromo-*N*-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (**233**) (200 mg, 0.469 mmol), CuBr (40.1 mg, 0.281 mmol), TPA (81.7 mg, 0.281 mmol) and toluene (5 mL). The crude product was purified by column chromatography (9:1:0.2, hexane/diethyl ether/triethylamine) yielding 2-benzyl-1-hydroxy-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (**285**) as a white solid (56 mg, 33%) and 0.22:1 mixture (41 mg) of 2-benzyl-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (**286**) (5%) and (**287**) (21%).

2-Benzyl-1-hydroxy-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (285): R_f 0.18 (pet ether/EtOAc, 6:1); m.p. 169-170 ^{o}C; υ_{max} 3165 (OH), 2919 (CH), 1664 (C=O); δ_H (400 MHz, $CDCl_3$) 7.30 – 7.66 (4H, m, Ar<u>H</u>), 7.06 – 7.30 (4H, m, Ar<u>H</u>), 6.98 – 7.05 (2H, m, Ar<u>H</u>), 5.14 (1H, d, *J* = 15.0 Hz, NC<u>H</u>$_a$H$_b$), 3.91 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>H</u>$_b$), 1.93 (1H, s, O<u>H</u>), 1.78 (1H, dd, *J* = 13.5, 6.0 Hz, cy), 1.47 – 1.58 (2H, m, cy), 1.39 (3H, s, C<u>H</u>$_3$), 1.24 – 1.45 (4H, m, cy), 1.31 (3H, s, C<u>H</u>$_3$), 0.97 – 1.07 (1H, m, cy), 0.87 – 0.97 (1H, m, cy), 0.77 – 0.87 (1H, m, cy); δ_C (100 MHz, $CDCl_3$) 182.1 (C=O), 140.0, 138.4 (quarternary), 128.9, 128.5, 128.4, 127.8 (Ar<u>C</u>), 97.3 (<u>C</u>OH), 48.7 (COH<u>C</u>(cy)), 47.1 (<u>C</u>(CH$_3$)$_2$), 44.2 (NC<u>H</u>$_2$), 32.4 (cy), 30.5 (cy), 27.5

(cy), 25.5 (cy), 25.2 (C$\underline{H}_3$), 23.5 (C$\underline{H}_3$), 22.7 (cy); *m/z* (ES^+) $C_{24}H_{39}NNaO_2$ requires 386.2096, found: 386.2096 $[M+Na]^+$.

2-Benzyl-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (286) and (287): R_f 0.21 (pet ether/EtOAc, 6:1); υ_{max} 2933, 2866 (CH), 1676 (C=O); δ_H (400 MHz, $CDCl_3$) 7.16 – 7.39 (8H maj + 8H min, m, Ar$\underline{H}$), 7.02 – 7.06 (2H maj, m, Ar$\underline{H}$), 6.99 – 7.02 (2H min, m, Ar$\underline{H}$), 5.22 (1H min, d, *J* = 14.5 Hz, NC$\underline{H}_a$H$_b$), 4.61 (1H maj, d, *J* = 14.5 Hz, NC$\underline{H}_a$H$_b$), 4.08 (1H min, s, $\underline{C}$H), 3.74 (1H maj, d, *J* = 14.5 Hz, NCH$_a\underline{H}_b$), 3.46 (1H min, d, *J* = 14.5 Hz, NCH$_a\underline{H}_b$), 1.83 – 1.93 (1H maj + 1H min, m, cy), 1.78 (1H maj, td, *J* = 14.5, 6.5 Hz, cy), 1.57 – 1.70 (2H maj, m, cy), 1.46 – 1.54 (2H min, m, cy), 1.39 (3H maj, s, C$\underline{H}_3$), 1.34 – 1.41 (3H min, m, cy), 1.15 – 1.30 (3H min, m, cy), 1.27 (3H min, s, C$\underline{H}_3$), 1.23 (3H maj, s, C$\underline{H}_3$), 1.11 (3H maj, s, C$\underline{H}_3$), 1.04 – 1.15 (1H maj + 1H min, m, cy), 0.95 – 1.04 (1H maj, m, cy), 0.85 (1H maj, dd, *J* = 8.5, 2.5 Hz, cy), 0.74 – 0.82 (1H maj, m, cy), 0.57 – 0.69 (1H maj, m, cy).; δ_C (100 MHz, $CDCl_3$) 180.1 (C=O min), 178.8 (C=O maj), 137.7 (NCH$_2\underline{C}$ maj), 136.7 (Ar$\underline{C}$CN min), 136.3 (NCH$_2\underline{C}$ min), 132.7 (Ar$\underline{C}$CN maj), 132.3, 128.7, 128.7, 128.6, 128.4, 128.2, 128.2, 128.0, 127.9, 127.5, 126.9 (Ar$\underline{C}$H), 68.5 (N$\underline{C}$HPh min), 52.6 (C(O)N$\underline{C}$Ph), 47.6, 46.5, 44.9, 44.8 (quarternary), 34.0 (cy), 31.1 ($\underline{C}$H maj), 29.7 (cy), 28.4 (cy), 25.6 (cy), 23.9 ($\underline{C}H_3$ maj), 23.8 ($\underline{C}H_3$ min), 23.0 (cy), 22.5 (cy), 21.8 ($\underline{C}H_3$ min), 21.6 (cy), 21.2 (cy), 21.2 ($\underline{C}H_3$ maj), 20.1 (cy); *m/z* (ES^+) $C_{24}H_{30}NO$ requires 348.2327, found: 348.2323 $[M+H]^+$ (**286**), $C_{24}H_{28}NO$ requires 346.2171, found: 346.2175 $[M+H]^+$ (**287**).

***N*-benzyl-2,2-dichloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide (292) and *N*-benzyl-2-chloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide (293)**



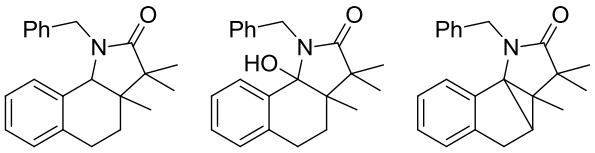
292 **293**

The general procedure for the cyclisation of trichloroenamides (6.3.1) was applied using *N*-benzyl-2,2,2-trichloro-*N*-(2,6,6-trimethylcyclohex-1-enyl)acetamide (**236**) (150 mg, 0.39 mmol), CuCl (38.8 mg, 0.39 mmol), TPA (114 mg, 0.39 mmol) and toluene (3.5 mL). The crude product was purified by column chromatography (pet ether/EtOAc, 10:1) to give *N*-benzyl-2,2-dichloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide as a colourless oil (23 mg, 12%) and *N*-benzyl-2-chloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide as a colourless solid (65 mg, 38%).

***N*-benzyl-2,2-dichloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide (292):** R_f 0.37 (pet ether/EtOAc, 6:1); δ_H (300 MHz, $CDCl_3$) 7.06 – 7.35 (5H, m, Ar<u>H</u>), 6.99 (1H, br s, N<u>H</u>), 4.41 (2H, qd, *J* = 15.0, 5.5 Hz, NC<u>H</u>$_2$Ph), 2.28 (1H, dd, *J* = 15.0, 10.5 Hz, cy), 1.88 - 2.03 (1H, m, cy), 1.40 - 1.88 (4H, m, cy), 1.51 (3H, s, C<u>H</u>$_3$), 1.06 (3H, s, C<u>H</u>$_3$), 1.03 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 216.1 (ketone <u>C</u>=O), 166.4 (amide <u>C</u>=O), 137.3 (Ar quarternary), 128.8, 127.7, 127.6 (Ar<u>C</u>H), 94.3 (<u>C</u>Cl$_2$), 45.2 (cy quarternary), 44.6 (cy), 37.8 (cy), 36.8 (cy quarternary), 27.9 (<u>C</u>H$_3$), 27.7 (<u>C</u>H$_3$), 23.4 (<u>C</u>H$_3$), 18.2 (cy); *m/z* (ES$^+$) $C_{18}H_{24}Cl_2NO_2$ requires 356.1184, found: 356.1186 $[M+NH]^+$.

***N*-benzyl-2-chloro-2-(1,3,3-trimethyl-2-oxocyclohexyl)acetamide (293):** R_f 0.32 (pet ether/EtOAc, 6:1); m.p. 129- 131 ^oC; υ_{max} 3356 (NH), 2968, 2924 (CH), 1728 (C=O), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 7.09 – 7.48 (5H, m, Ar<u>H</u>), 6.71 (1H, br s, N<u>H</u>), 5.12 (1H, s, C<u>H</u>Cl), 4.41 (2H, qd, *J* = 145.0, 5.5 Hz, NC<u>H</u>$_2$Ph), 1.54 – 1.95 (6H, m, cy), 1.27 (3H, s, C<u>H</u>$_3$), 1.22 (3H, s, C<u>H</u>$_3$), 1.15 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 217.7 (Ketone <u>C</u>=O), 167.1 (amide <u>C</u>=O), 136.8 (Ar quaternary), 128.2, 127.2, 127.1 (Ar<u>C</u>H), 68.8 (<u>C</u>HCl), 49.6, 43.8 (cy quarternary), 43.4 (N<u>C</u>H$_2$), 37.2 (cy), 32.1 (cy), 27.8 (<u>C</u>H$_3$), 27.3 (<u>C</u>H$_3$), 24.7 (<u>C</u>H$_3$), 16.9 (cy); *m/z* (ES^+) $C_{18}H_{24}ClNNaO_2$ requires 344.1393, found: 344.1379 $[M+Na]^+$.

1-Benzyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one (294), 1-Benzyl-9b-hydroxy-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one (295) and (296)



294 **295** **296**

The general procedure for the cyclisation of bromoenamides (6.3.2) was applied using *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)propanamide (**237**) (132 mg, 0.331 mmol), CuBr (28.5 mg, 0.199 mmol), TPA (57.7 mg, 0.199 mmol) and toluene (3.3 mL). The crude product was purified by column chromatography (10:1 to 5:1, pet ether/EtOAc) to give the 1-benzyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one (**294**) (33 mg, 31%), 1-benzyl-9b-hydroxy-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one

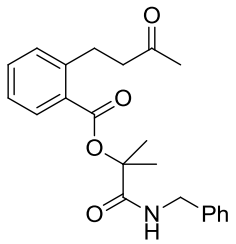
(**295**) (21 mg, 19%) and 1-benzyl-[3,9b]cyclopropyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9b*H*)-one (**296**) (7 mg, 7%)

1-Benzyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one (294): R_f 0.15 (pet ether/EtOAc, 8:1); δ_H (600 MHz, $CDCl_3$) 7.30 (2H, t, *J* = 7.5 Hz, Ar<u>H</u>), 7.21 – 7.28 (2H, m, Ar<u>H</u>), 7.15 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 7.12 (1H, t, *J* = 7.5 Hz, Ar<u>H</u>), 7.09 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 6.92 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 4.95 (1H, d, *J* = 15.5 Hz, NC<u>H</u>$_a$H$_b$), 4.24 (1H, s, NC<u>H</u>), 3.62 (1H, d, *J* = 15.5 Hz, NCH$_a$<u>H</u>$_b$), 2.79 (2H, dt, *J* = 12.0, 6.0 Hz, ArC<u>H</u>$_2$), 1.68 – 1.75 (1H, m, ArCH$_2$C<u>H</u>$_a$H$_b$), 1.54 (1H, m, ArCH$_2$C<u>H</u>$_a$H$_b$), 1.24 (3H, s, C<u>H</u>$_3$), 1.13 (3H, s, C<u>H</u>$_3$), 0.94 (3H, s, C<u>H</u>$_3$); δ_C (600 MHz, $CDCl_3$) 179.9 (<u>C</u>=O), 137.7 (Ar<u>C</u>CH$_2$N), 137.2 (Ar<u>C</u>CH$_2$CH$_2$), 132.8 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>CH), 129.1, 128.6, 128.5, 127.4, 127.0, 125.4 (Ar<u>C</u>H), 61.5 (N<u>C</u>H), 47.0 (CO<u>C</u>(CH$_3$)$_2$), 43.2 (Ar<u>C</u>H$_2$N), 41.0 (COC(CH$_3$)$_2$<u>C</u>), 27.3 (Ar<u>C</u>H$_2$CH$_2$), 25.8 (Ar<u>C</u>H$_2$CH$_2$), 20.8, 17.2, 14.6 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{22}H_{25}NNaO$ requires 342.1834, found: 342.1828 $[M+Na]^+$.

1-Benzyl-9b-hydroxy-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9bH)-one (295): R_f 0.05 (pet ether/EtOAc, 8:1); δ_H (400 MHz, $CDCl_3$) 7.21 – 7.29 (1H, m, Ar<u>H</u>), 6.59 – 6.91 (8H, m, Ar<u>H</u>), 4.30 (1H, d, *J* = 15.5 Hz, NC<u>H</u>$_a$H$_b$), 3.80 (1H, d, *J* = 15.5 Hz, NCH$_a$<u>H</u>$_b$), 2.47 (1H, ddd, *J* = 17.5, 11.0, 6.5 Hz, ArC<u>H</u>$_a$H$_b$CH$_2$), 2.27 (1H, dt, *J* = 17.5, 4.5 Hz, ArC<u>H</u>$_a$H$_b$CH$_2$), 1.95 (1H, s, O<u>H</u>), 1.17 – 1.48 (2H, m, ArCH$_2$C<u>H</u>$_2$), 1.14 (3H, s, C<u>H</u>$_3$), 0.77 (3H, s, C<u>H</u>$_3$), 0.72 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 180.7 (C=O), 137.9, 136.1, 134.6 (Ar<u>C</u>), 128.1, 128.0, 127.6, 127.5, 126.8, 126.0, 125.6 (Ar<u>C</u>H), 90.8 (N<u>C</u>OH), 45.4 (CO<u>C</u>(CH$_3$)$_2$), 44.6 (NC(OH)<u>C</u>(CH$_3$)), 42.5 (N<u>C</u>H$_2$), 30.9 (C(CH$_3$)<u>C</u>H$_2$), 25.1 (Ar<u>C</u>H$_2$CH$_2$), 24.8 (COC(<u>C</u>H$_3$)(CH$_3$)), 18.8 (COC(CH$_3$)(<u>C</u>H$_3$)), 12.3 (NC(OH)C(<u>C</u>H$_3$)); *m/z* (ES$^+$) $C_{22}H_{25}NNaO_2$ requires 358.1738: found: 358.1778 $[M+Na]^+$.

1-Benzyl-[3,9b]cyclopropyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1H-benzoindol-2(9b*H*)-one (296): R_f 0.26 (pet ether/EtOAc, 8:1); δ_H (600 MHz, $CDCl_3$) 7.08 – 7.54 (7H, m, ArH), 7.00 – 7.07 (2H, m, ArH), 4.92 (1H, d, *J* = 14.5 Hz, NCH$_a$H$_b$), 4.30 (1H, d, *J* = 14.5 Hz, NCH$_a$H$_b$), 2.89 (1H, dd, *J* = 17.5, 7.5 Hz, ArCH$_a$H$_b$CH), 2.54 (1H, d, *J* = 17.5 Hz, ArCH$_a$H$_b$CH), 1.33 (3H, s, CH$_3$), 1.13 (3H, s, CH$_3$), 0.90 (1H, d, *J* = 7.5 Hz, CH$_2$CH), 0.64 (3H, s, CH$_3$); δ_C (150 MHz, $CDCl_3$) 180.1 (C=O), 143.1, 137.3, 137.0 (ArC), 128.8, 128.2, 127.3, 126.7, 126.4, 124.9, 123.4 (ArCH), 59.3, 52.8 (quarternary), 45.7 (NCH$_2$), 44.4 (quarternary), 32.4 (CH$_3$), 30.8 (ArCH2), 25.0 (CH$_3$), 21.3 (CH$_3$), 6.5 (CH); *m/z* (ES$^+$) $C_{22}H_{24}NO$ requires 318.1858, found: 318.1860 $[M+H]^+$.

1-(Benzylamino)-2-methyl-1-oxopropan-2-yl 2-(3-oxobutyl)benzoate (297)



297

R_f 0.14 (pet ether/EtOAc, 6:1); δ_H (600 MHz, $CDCl_3$) 7.76 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.40 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.27 – 7.34 (4H, m, ArH), 7.21 – 7.27 (3H, m, ArH), 6.64 (1H, br t, *J* = 7.5 Hz, NH), 4.50 (2H, d, *J* = 7.5 Hz, NCH$_2$), 3.10 (2H, t, *J* = 7.5 Hz, CH$_2$CH$_2$), 2.73 (2H, t, *J* = 7.5 Hz, CH$_2$CH$_2$), 2.04 (3H, s, COCH$_3$), 1.77 (6H, s, C(CH$_3$)$_2$); δ_C (150 MHz, $CDCl_3$) 208.2 (C=O ketone), 172.9 (C=O amide), 166.1 (C=O ester), 142.8 (ArC), 138.3 (ArC), 132.2, 131.0, 130.3, 128.6, 127.7, 127.4, 126.2 (ArC), 81.6 (COC(CH$_3$)), 45.1 (CH$_2$CH$_2$CO), 43.5

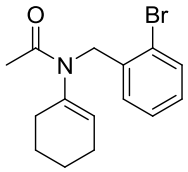
(N<u>C</u>H_2), 29.9 (CO<u>C</u>H_3), 27.9 (Ar<u>C</u>$H_2$$CH_2$), 24.9 (C(<u>C</u>$H_3$)); *m/z* ($ES^+$) $C_{22}H_{26}NO_4$ requires 368.1862, found: 368.1856 $[M+H]^+$.

6.4 Compounds Synthesised in Chapter Four

6.4.1. General Procedure for synthesis of *N*-bromobenzyl enamides

Oxime (1 eq.), acetic acid (3 eq.), acetic anhydride (3 eq.) and iron powder (2 eq.) in anhydrous toluene were heated to reflux under an inert atmosphere for 6-16 hours. The mixture was then filtered through celite, diluted with DCM and washed with 2M NaOH and $NaCl_{(aq)}$. The organic phase was then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. The crude enamide (1 eq.) was added to sodium hydride (5 eq., 60% w/w dispersion in mineral oil) in anhydrous THF and cooled to 0 ^oC. 2-Bromobenzyl bromide (1.05 eq.) was then added and the reaction heated to reflux under an inert atmosphere for 10-16 hours. The reaction mixture was then added to water and extracted with ethyl acetate. The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. Products were purified by column chromatography or recrystallisation as stated below.

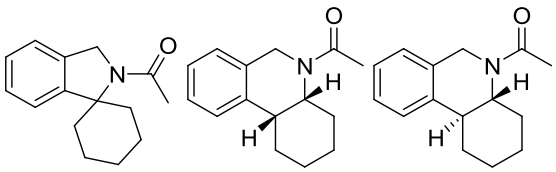
_N_-(2-Bromobenzyl)-_N_-cyclohexenylacetamide (320)



320

Cyclohexanone oxime (4 g, 35.3 mmol), copper iodide (0.673 g, 3.53 mmol), acetic anhydride (6.67 mL, 70.7 mmol) and sodium bisulfite (11.1 g, 106 mmol) in DCE (156 mL) were heated to 120 ^{o}C for 16 hours. The reaction mixture was then cooled, diluted with EtOAc (100 mL), washed with NaOH (2 M, 2 x 200 mL), dried over $MgSO_4$ and concentrated in vacuo to give a brown oil (3.73 g). The oil was added to sodium hydride (5.36 g, 134 mmol) in THF (250 mL) at 0 ^{o}C, and the reaction then heated to reflux for 18 hours. After cooling, water (150 mL) was added and the mixture was extracted with EtOAc (3 x 150 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product as a brown oil (9.25 g). The crude product was purified by column chromatography (pet ether/ EtOAc, 6:1) to give the product as a pale yellow oil (3.71 g, 34%). R_f 0.15 (pet ether/EtOAc, 6:1); υ_{max} 2931 (CH), 1651 (C=O); δ_H (400 MHz, $CDCl_3$) 7.50 (1H, dd, *J* = 8.0, 1.0 Hz, ArH), 7.38 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.22 – 7.28 (1H, m, ArH), 7.09 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 5.40 – 5.45 (1H, m, C=CH), 4.78 (2H, s, NCH_2), 2.10 (3H, s, CH_3), 1.96 – 2.06 (4H, m, cy), 1.63 – 1.71 (2H, m, cy), 1.49 – 1.57 (2H, m, cy); δ_C (100 MHz, $CDCl_3$) 170.2 (C=O), 138.7 (C=CN), 137.2 (ArC), 132.5 (ArCH), 130.4 (C=CH), 128.7 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 124.0 (ArCBr), 48.8 (NCH_2), 28.0, 24.8, 22.7, 21.6 (cy), 21.4 ($COCH_3$); *m/z* (ES^+) $C_{15}H_{18}BrNONa$ requires 330.0472, found 330.0464 $[M+Na]^+$.

1-(Spiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (326), *cis*-1-(1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (327a) and *trans*-1-(1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (327b)



326 **327a** **327b**

N-(2-Bromobenzyl)-*N*-cyclohexenylacetamide (1 g, 3.24 mmol) was dissolved in toluene (225 mL) and heated to reflux. A mixture of Bu3SnH (1.31 mL, 4.87 mmol) and ACN (159 mg, 0.649 mmol) in toluene (225 mL) was added by syringe pump over 7 hours and the reaction heated at reflux for a further 10 hours before cooling to room temperature. The reaction mixture was then concentrated *in vacuo* to give a yellow oil which was taken up in acetonitirile (100 mL) and washed with hexane (3 x 100 mL). The acetonitrile phase was then concentrated *in vacuo* to give the crude product as a yellow oil (813 mg). The mixture was purified by column chromatography (14:1 to 6:1 pet ether/EtOAc) which led to the isolation of 1-(spiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (81 mg, 11%), *cis*-1-(1,2,3,4,4a,10b-hexahydrophenanthridin-5(6H)-yl)ethanone (209 mg, 28%) and *trans*-1-(1,2,3,4,4a,10b-hexahydrophenanthridin-5(6H)-yl)ethanone (153 mg, 21%)

1-(Spiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (326): υ_{max} 2925 (CH), 1644 (C=O); δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* = 15.0, 12.5 Hz, Ar<u>H</u>), 6.82 – 7.42 (3Hz, m, Ar<u>H</u>), 4.76 (2H, s, NC<u>H</u>$_2$), 3.08 (2H, td, *J* = 13.0, 5.5 Hz, 1H), 2.13 (3H, s, COC<u>H</u>$_3$), 1.67 – 1.87 (4H, m, cy), 1.43 – 1.61 (4H, m, cy); δ_C (100 MHz, $CDCl_3$) 169.4 (C=O), 147.0, 134.0 (Ar<u>C</u>), 127.3, 127.2, 124.0, 122.4 (Ar<u>C</u>H), 70.7

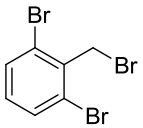
(N<u>C</u> quarternary), 53.8 (N<u>C</u>H_2), 32.1, 27.8 (cy), 25.3 (<u>C</u>H_3), 24.3, 22.4 (cy); *m/z* (ES^+) requires 252.1364, found 252.1359 $[M+H]^+$.

***cis*-1-(1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (327a) (1:0.7 ratio of amide rotamers):** δ_H (400 MHz, $CDCl_3$) 7.36 (1H maj + 1H min, dd, *J* = 16.5, 7.5 Hz, Ar<u>H</u>), 7.06 – 7.31 (3H maj + 3H min, m, Ar<u>H</u>), 5.03 (1H maj, d, *J* = 18.0 Hz, NC<u>H</u>$_a$H$_b$), 4.82 (1H min, dt, *J* = 12.0, 4.5 Hz, NC<u>H</u>), 4.65 (1H min, d, *J* = 16.5 Hz, NC<u>H</u>$_a$H$_b$), 4.55 (1H, d, *J* = 16.5 Hz, NCH$_a$<u>H</u>$_b$), 4.34 (1H, d, *J* = 18.0 Hz, NCH$_a$<u>H</u>$_b$), 3.95 (1H maj, dt, *J* = 11.5, 4.5 Hz, NC<u>H</u>), 3.24 (1H maj, br s, NCHC<u>H</u>), 3.12 (1H min, br s, NCHC<u>H</u>), 2.58 (1H maj, ddt, *J* = 14.0, 5.5, 3.0 Hz, cy), 2.45 – 2.54 (1H min, m, cy), 2.21 (3H maj, s, C<u>H</u>$_3$), 2.17 (3H min, s, C<u>H</u>$_3$), 1.08 – 1.84 (5H maj + 5H min, m, cy); δ_C (100 MHz, $CDCl_3$) 169.4 (C=O maj), 169.3 (C=O min), 135.9, 134.4, 133.2, 132.5 (Ar<u>C</u>, quarternary), 127.2, 126.8, 126.7, 126.4, 126.2, 126.1, 126.0, 125.9 (Ar<u>C</u>H), 55.7 (N<u>C</u>H maj), 49.9 (N<u>C</u>H min), 45.9 (N<u>C</u>H_2 min), 42.6 (N<u>C</u>H_2 maj), 37.2 (NCH<u>C</u>H maj), 36.4 (NCH<u>C</u>H min), 27.6, 27.3, 27.2, 25.7, 25.6, 25.4 (cy), 22.4, 21.7 (CO<u>C</u>H_3), 19.8, 19.5 (cy); *m/z* (ES^+) requires 252.1364, found 252.1351 $[M+H]^+$.

***Trans*-1-(1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (327b) (1:1.7 ratio of amide rotamers):** υ_{max} 2931 (CH), 1625 (C=O); δ_H (400 MHz, $CDCl_3$) 7.04 – 7.38 (4H maj + 4H min, m, Ar<u>H</u>), 5.55 (1H min, d, *J* = 13.5 Hz, NC<u>H</u>$_a$H$_b$), 4.44 (1H maj, d, *J* = 14.5 Hz, NC<u>H</u>$_a$H$_b$), 4.27 (1H maj, d, *J* = 14.5 Hz, NCH$_a$<u>H</u>$_b$), 3.73 (1H, d, *J* = 13.5 Hz, 1H), 3.36 (1H maj, t, *J* = 12.5 Hz, NC<u>H</u>), 3.08 (1H min, td, *J* = 12.0, 5.5 Hz, NC<u>H</u>), 1.28 - 2.69 (9H maj + 9H min, m, cy), 2.13 (3H, s, CH_3), 2.03 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 170.6 (C=O min), 169.8

(C=O maj), 139.9, 139.2, 137.7, 136.3 (Ar<u>C</u> quarternary), 127.9, 127.5, 126.3, 126.2, 125.6, 124.4, 123.1, 122.6 (Ar<u>C</u>H), 60.2, 58.3 (N<u>C</u>H min), 53.8 (N<u>C</u>H maj), 47.1 (N<u>C</u>H min), 43.2 (N<u>C</u>H_2 maj), 42.1 (N<u>C</u>H_2 maj), 41.8 (NCH<u>C</u>H), 33.9, 31.0, 27.8, 26.0, 25.8, 25.3, 25.2 (cy), 22.9 (<u>C</u>H_3), 22.5, 22.4 (cy), 21.8 (<u>C</u>H_3); *m/z* (ES^+) requires 252.1364, found 252.1359 $[M+H]^+$.

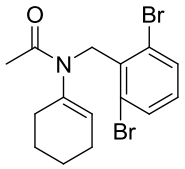
1,3-Dibromo-2-(bromomethyl)benzene[202] (339)



339

2,6-Dibromotoluene (1 g, 4.00 mmol), *N*-bromosuccinimide (783 mg, 4.40 mmol) and benzoyl peroxide (64.6 mg, 0.2 mmol) in CCl_4 (10 mL) were heated to reflux for 16 hours. The reaction mixture was then cooled, diluted with DCM (30 mL) and washed with water (3 x 50 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product as a brown solid. The product was recrystallised from 10:1, hexane/EtOAc to give a brown crystalline solid (1.152 g, 87%). R_f 0.59 (pet ether/EtOAc, 6:1); υ_{max} 2930 (CH); δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 8.0 Hz, Ar<u>H</u>), 6.72 (1H, t, *J* = 8.0 Hz, Ar<u>H</u>), 4.54 (2H, s, C<u>H</u>$_2$); δ_C (100 MHz, $CDCl_3$) 135.7 (Ar<u>C</u>), 132.1 (Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 125.1 (Ar<u>C</u>), 33.4 (<u>C</u>H_2). ; *m/z* (ES^+) 326.8 $[M+H]^+$.

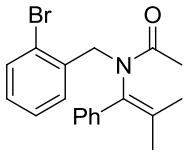
_N_-Cyclohexenyl-_N_-(2,6-dibromobenzyl)acetamide (340)



340

_N_-Cyclohexenylacetamide (253 mg, 1.82 mmol) in THF (10 mL) was added to sodium hydride (367 mg, 9.09 mmol) in THF (15 mL) and the reaction mixture was cooled to 0 ^{o}C. 2,6-dibromobenzyl bromide (627 mg, 1.91 mmol) was then added and the reaction heated to reflux for 12 hours. The reaction mixture was then cooled and added to water (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography (pet ether/ EtOAc, 9:1) to give the product as a pale yellow oil (353 mg, 50%). R_f 0.15 (pet ether/EtOAc, 6:1); υ_{max} 2928 (CH), 1649 (C=O) ; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* = 8.0 Hz, Ar<u>H</u>), 6.98 (1H, t, *J* = 8.0 Hz, Ar<u>H</u>), 5.26 – 5.50 (1H, m, C=C<u>H</u>), 5.10 (2H, s, C<u>H</u>$_2$), 2.05 (3H, s, C<u>H</u>$_3$), 1.80 – 2.00 (4H, m, 5.0 Hz, C=CC<u>H</u>$_2$), 1.50 – 1.64 (2H, m, C<u>H</u>$_2$), 1.32 – 1.50 (2H, m, C<u>H</u>$_2$); δ_C (100 MHz, $CDCl_3$) 169.6 (C=O), 137.3 (C=<u>C</u>N), 135.7 (Ar<u>C</u>), 132.4 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>H), 129.4 (C=<u>C</u>H), 127.0 (Ar<u>C</u>Br), 48.7 (N<u>C</u>H$_2$), 28.6, 24.8, 22.7, 21.4 (cy), 21.3 (CO<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{15}H_{17}Br_2NNaO$ requires 407.9569, found 407.9569 $[M+Na]^+$.

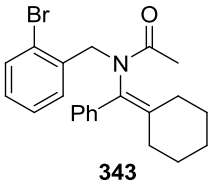
_N_-(2-Bromobenzyl)-_N_-(2-methyl-1-phenylprop-1-enyl)acetamide (342)



342

The general procedure for the synthesis of *N*-bromobenzyl enamides (6.2.1) was applied using 2-methyl-1-phenylpropan-1-one oxime (2 g, 12.2 mmol), acetic acid (2.10 mL, 36.8 mmol), acetic anhydride (3.47 mL, 36.8 mmol) and iron powder (1.37 g, 24.5 mmol) in toluene (50 mL) to give the crude enamide as an yellow oil (1.82 g). This was reacted with sodium hydride (1.92 g, 48.1 mmol) and 2-bromobenzyl bromide (2.52 g, 10.1 mmol) in anhydrous THF (140 mL) to give the crude product as a yellow oil (3.82 g). The crude product was purified by column chromatography (pet ether/ EtOAc, 4:1) to give the product as a pale yellow crystalline solid (1.88 g, 55%). R_f 0.43 (pet ether/EtOAc, 4:1); m.p. 92-94 ^{o}C; υ_{max} 2922 (CH), 1640 (C=O); δ_H (400MHz, $CDCl_3$) 7.53 (1H, d, *J* = 7.5 Hz, ArC(Br)C<u>H</u>), 7.46 (1H, d, *J* = 8.0 Hz, ArC(CH_2)C<u>H</u>), 7.25 – 7.40 (5H, m, 5 x Ar), 7.21 (1H, t, *J* = 7.5 Hz, ArC(Br)CHC<u>H</u>), 7.08 (1H, t, *J* = 7.5 Hz, ArC(CH_2)CHC<u>H</u>), 5.22 (1H, d, *J* = 14.5 Hz, ArC<u>H</u>$_a$H$_b$N), 4.13 (1H, d, *J* = 14.5 Hz, ArCH$_a$<u>H</u>$_b$N), 2.21 (3H, s, C=OC<u>H</u>$_3$), 1.82 (3H, s, C=C(C<u>H</u>$_3$)(CH_3)), 1.51 (3H, s, C=C(CH_3)(C<u>H</u>$_3$)); δ_C (100MHz, $CDCl_3$) 171.2 (C=O), 137.0 (Ar<u>C</u>CH_2N), 136.4, 134.1, 134.1 (quaternary), 132.5 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 124.3 (Ar<u>C</u>Br), 48.6 (Ar<u>C</u>H_2N), 21.4 (<u>C</u>H_3), 21.4 (<u>C</u>H_3), 21.0 (C=C<u>C</u>H_3); *m/z* (ES^+) $C_{19}H_{21}BrNO$ requires 358.0801, found: 358.0800 $[M+H]^+$.

_N_-(2-Bromobenzyl)-_N_-(cyclohexylidene(phenyl)methyl)acetamide (343)

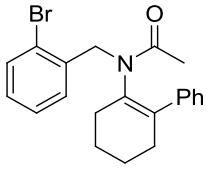


343

The general procedure for the synthesis of *N*-bromobenzyl enamides (6.2.1) was applied using cyclohexyl(phenyl)methanone oxime (2 g, 9.84 mmol), acetic acid (1.69 mL, 29.5 mmol), acetic anhydride (2.78 mL, 29.5 mmol) and iron powder (1.10 g, 19.7 mmol) in toluene (40 mL) to give the crude enamide as an orange/brown solid (2.2 g). This was reacted with sodium hydride (1.92 g, 47.9 mmol) and 2-bromobenzyl bromide (2.52 g, 10.1 mmol) in anhydrous THF (140 mL) to give the crude product as a brown solid (2.72 g). The crude product was purified by recrystallisation from hexane to give the product as an orange/brown solid (1.76 g, 46%). R_f 0.5 (pet ether/EtOAc, 4:1); m.p. 116-118 ^oC; υ_{max} 2936 (CH), 1641 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 7.5 Hz, ArCBrC<u>H</u>CH), 7.49 (1H, d, *J* = 7.5 Hz, ArC(CH_2)C<u>H</u>CH), 7.30 – 7.41 (3H, m, Ar<u>H</u>), 7.28 (2H, d, *J* = 7.0 Hz, Ar<u>H</u>), 7.24 (1H, t, *J* = 7.5 Hz, Br-Ar<u>H</u>), 7.11 (1H, t, *J* = 7.5 Hz, Br-Ar<u>H</u>), 5.36 (1H, d, *J* = 14.0 Hz, ArC<u>H</u>$_a$H$_b$N), 3.98 (1H, d, *J* = 14.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.54 (1H, dd, *J* = 14.0, 5.0 Hz, C=C(C<u>H</u>$_a$H$_b$)(CH$_a$H$_b$)), 2.22 (3H, s, C<u>H</u>$_3$), 2.08 (1H, dt, *J* = 9.0, 4.5 Hz, C=C(CH$_a$H$_b$)(C<u>H</u>$_a$H$_b$)), 1.97 (1H, ddd, *J* = 14.0, 10.5, 4.0 Hz, C=C(CH$_a$<u>H</u>$_b$)(CH$_a$H$_b$)), 1.81 (1H, ddd, *J* = 13.5, 10.5, 4.0 Hz, C=C(CH$_a$H$_b$)(CH$_a$<u>H</u>$_b$)), 1.65 – 1.73 (1H, m, cy<u>H</u>), 1.54 – 1.62 (1H, m, cy<u>H</u>), 1.36 – 1.54 (3H, m, cy<u>H</u>), 0.69 – 0.85 (1H, m, C=CCH$_2$C<u>H</u>$_a$H$_b$); δ_C (100MHz, $CDCl_3$) δ 171.1 (<u>C</u>=O), 141.2 (C=<u>C</u>(CH_2)$_2$), 137.1 (Ar<u>C</u>CH$_2$N), 136.2 (Ar<u>C</u>C=C), 132.7 (Ar<u>C</u>H), 132.6 (Ar<u>C</u>H), 131.1 (N<u>C</u>=C(CH_2)$_2$), 129.3 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 124.5 (Ar<u>C</u>Br), 48.0 (Ar<u>C</u>H$_2$N), 31.4

(C=C(<u>C</u>H$_2$)(CH$_2$), 31.4 (C=C(<u>C</u>H$_2$)(CH$_2$), 27.8 (CH$_2$<u>C</u>H$_2$CH$_2$), 27.0 (CH$_2$<u>C</u>H$_2$CH$_2$), 26.4 (CH$_2$<u>C</u>H$_2$CH$_2$), 21.4 (<u>C</u>H$_3$); *m/z* (ES$^+$) $C_{22}H_{24}BrNNaO$ requires 420.0933, found: 420.0936 $[M+Na]^+$.

_N_-(2-Bromobenzyl)-_N_-(2-phenylcyclohex-1-enyl)acetamide (344)

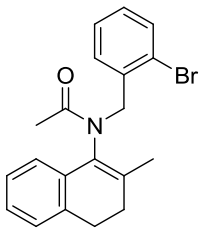


344

The general procedure for the synthesis of *N*-bromobenzyl enamides (6.2.1) was applied using 2-phenylcyclohexanone oxime (800 mg, 4.23 mmol), acetic acid (0.73 mL, 12.7 mmol), acetic anhydride (1.20 mL, 12.7 mmol) and iron powder (472 mg, 8.45 mmol) in toluene (20 mL) to give the crude enamide as an orange solid (880 mg). This was reacted with sodium hydride (817 mg, 20.4 mmol) and 2-bromobenzyl bromide (1.07 g, 4.29 mmol) in anhydrous THF (60 mL) to give the crude product as a brown solid (2.72 g). The crude product was purified by column chromatography (pet ether/EtOAc 4:1) to give the product as a yellow oil (690 mg, 43%). R_f 0.36 (pet ether/EtOAc, 4:1); υ_{max} 2930 (CH), 1638 (C=O); δ_H (400MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 8.0, 1.5 Hz, Ar<u>H</u>), 7.02 – 7.37 (9H, m, Ar<u>H</u>), 5.02 (1H, d, *J* = 15.0 Hz, ArC<u>H</u>$_a$H$_b$N), 3.94 (1H, d, *J* = 15.0 Hz, ArCH$_a$<u>H</u>$_b$N), 2.30 – 2.50 (2H, m, C=C<u>C</u>H$_2$), 2.13 (3H, s, C=OC<u>H</u>$_3$), 1.99 – 2.10 (2H, m, C=CC<u>H</u>$_2$), 1.59 – 1.75 (4H, m, CH$_2$C<u>H</u>$_2$CH$_2$); δ_C (100MHz, $CDCl_3$) δ 170.3 (C=O), 140.5 (Ar<u>C</u>C=C), 137.3 (Ar<u>C</u>CH$_2$N), 136.7 (N<u>C</u>=CPh), 135.2 (NC=<u>C</u>Ph), 132.5 (Ar<u>C</u>H), 130.8 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>Br), 50.2 (N<u>C</u>H$_2$Ar), 31.8 (C=C<u>C</u>H$_2$), 30.8 (C=C<u>C</u>H$_2$), 23.0 (CH$_2$<u>C</u>H$_2$CH$_2$),

22.5 ($CH_2\underline{C}H_2CH_2$), 21.8 ($\underline{C}H_3$); *m/z* (ES^+) $C_{21}H_{22}BrNNaO$ requires 406.06777, found: 406.0771 $[M+Na]^+$.

_N_-(2-bromobenzyl)-_N_-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (345)

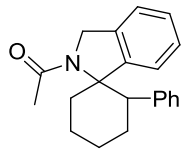


345

Methytetralone oxime (1 g, 5.71 mmol), copper iodide (109 mg, 0.571 mmol), acetic anhydride (1.08 mL, 11.4 mmol) and sodium bisulfite (1.79 g, 17.1 mmol) were heated to rflux in DCE (29 mL) fro 4 hours. The reaction mixture was then cooled and diluted with EtOAc (30 mL) before washing with NaOH (2M, 2 x 70 mL) an dbrine (70 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange solid (366 mg). The solid was added to sodium hydride (497 mg, 12.4 mmol) in THF (25 mL). The reaction mixture was then cooled to 0 ^oC and 2-bromobenzyl bromide (652 mg, 2.6 mmol) followed by heating to reflux for 14 hours. Water (40 mL) was then added and the mixture and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo* to give the crude product. The crude product was purified by recrystallisation from hexane to give the product as an pale yellow crystalline solid (1.76 g, 46%). *Rf* 0.46 (3:1, pet ether/EtOAc); υ_{max} 2927, 2881, 2824 (CH), 1654 (C=O); δ_H 7.59 (1H, dd, J = 7.5, 1.5 Hz, Ar$\underline{H}$), 7.43 (1H, dd, *J* = 8.0, 1.0 Hz, Ar$\underline{H}$), 7.11 – 7.25 (3H, m, Ar$\underline{H}$), 7.04 – 7.11 (1H, m, Ar$\underline{H}$), 6.91 – 6.98 (1H, m, Ar$\underline{H}$), 5.52 (1H, d, *J* = 14.0 Hz, NC$\underline{H}_aH_b$), 4.29 (1H, d, *J* = 14.0

Hz, $NCH_a\underline{H}_b$), 2.88 (1H, td, *J* = 15.0, 7.0 Hz, $C\underline{H}_aH_bCH_2$), 2.70 (1H, ddd, *J* = 15.5, 6.5, 4.0 Hz, $CH_a\underline{H}_bCH_2$), 2.35 (1H, tdd, *J* = 15.0, 6.5, 1.0 Hz, $CH_2C\underline{H}_aH_b$), 2.15 (1H, ddd, *J* = 16.5, 7.0, 7.0 Hz, $CH_2CH_a\underline{H}_b$), 1.92 (3H, s, $COC\underline{H}_3$), 1.35 (3H, s, $C{=}CC\underline{H}_3$); δ_C (100 MHz $CDCl_3$) 171.6, 137.0, 136.5, 136.2, 133.1, 132.5, 132.4, 132.0, 129.1, 127.6, 127.4, 127.1, 126.8, 125.0, 121.6, 48.1, 29.5, 27.2, 21.1, 18.8; *m/z* (ES^+) $C_{20}H_{20}BrNNaO$ requires 392.0626, found: 392.0627 $[M+Na]^+$.

1-(2-Phenylspiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (347)



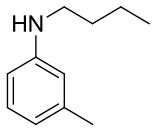
347

N-(2-Bromobenzyl)-*N*-(2-phenylcyclohex-1-enyl)acetamide (**344**) (670 mg, 1.74 mmol), Bu_3SnH (0.703 mL, 2.62 mmol) and ACN (85.2 mg, 0.349 mmol) in toluene (87.2 mL) were heated to reflux for 26 hours. The reaction mixture was then cooled and concentrated *in vacuo*. The residue was then partitioned between acetonitrile (50 mL) and hexane (50 mL), and the acetonitrile phase concentrated *in vacuo* to give the crude product as a brown oil (561 mg). The crude product was purified by column chromatography (9:1, pet ether/EtOAC) to give 1-(2-phenylspiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (111 mg, 21%). R_f 0.17 (6:1 pet ether/EtOAC); δ_H (400 MHz) 7.33 – 7.44 (2H, m, Ar$\underline{H}$), 7.17 – 7.23 (1H, m, Ar$\underline{H}$), 6.98 – 7.10 (3H, m, Ar$\underline{H}$), 6.87 (1H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 6.64 – 6.70 (2H, m, Ar$\underline{H}$), 4.30 (1H, d, *J* = 13.5 Hz, $NC\underline{H}_aH_b$), 3.21 (1H, d, *J* = 13.5 Hz, $NC\underline{H}_aH_b$), 2.82 – 3.02 (2H, m, cy), 2.63 – 2.78 (1H, m, cy), 2.41 – 2.51 (1H, m, cy), 2.16 – 2.27 (1H, m, cy), 2.07 – 2.16 (1H, m, cy), 1.98 (3H, s, $C\underline{H}_3$), 1.47 – 1.83 (3H, m, cy); δ_C (100

MHz, $CDCl_3$)170.3 (C=O), 147.8, 141.9, 135.3 (Ar<u>C</u>), 128.5, 127.7, 127.5, 127.3, 126.2, 123.0, 121.1 (Ar<u>C</u>H), 74.1 (N<u>C</u> quarternary), 56.4 (<u>C</u>H), 55.1 (N<u>C</u>H_2), 38.7, 28.2, 25.8 (cy), 25.1 (CO<u>C</u>H_3), 22.8(cy); *m/z* (ES^+) $C_{21}H_{23}NNaO$ requires 328.2677, found: 328.1673 $[M+Na]^+$.

6.5 Compounds Synthesised in Chapter Five

N-Butyl-3-methylaniline[249] (392)

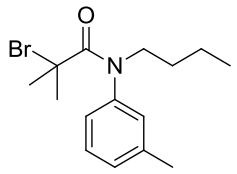


392

Sodium hydride (1.87 g, 46.6 mmol) was added to 3-methylaniline (5.00 g, 46.6 mmol) in DMF (35 mL) and the mixture was stirred for 1 h. Iodobutane (5.31 mL, 46.6 mmol) was then added and the reaction stirred at room temperature for 14 h. the reaction was then quenched with ethanol (25 mL) followed by saturated ammonium chloride (40 mL). Diethyl ether (100 mL) was then added and the organic layer was washed with water (2 x 100 mL) and brine (2 x 100 mL). The organic phase was then dried over MgSO4, filtered, and concentrated *in vacuo* to give the crude product as an orange oil (6.79 g). The crude product was purified by column chromatography (16:1 pet ether/EtOAC) to give the product as a yellow oil (1.96 g, 26%). R_f 0.35 (16:1 pet ether/EtOAC); υ_{max} 3403 (NH), 2955, 2926, 2860 (CH); δ_H (300 MHz) 7.10 – 7.02 (1H, m, Ar<u>H</u>), 6.51 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 6.45 – 6.39 (2H, m, 2 x Ar<u>H</u>), 3.52 (1H, br s, N<u>H</u>), 3.10 (2H, t, *J* = 7.0 Hz, NHC<u>H_2</u>CH_2), 2.28 (3H, s, ArC<u>H_3</u>), 1.66 – 1.52 (2H, m, $NHCH_2C$<u>H_2</u>), 1.43 (2H, sextuplet, *J* = 7.0 Hz, CH_2C<u>H_2</u>CH_3), 0.96 (3H, t, *J* = 7.0 Hz, CH_2C<u>H_3</u>); δ_C 148.7 (Ar<u>C</u>N), 139.0 (Ar<u>C</u>), 129.1, 118.1, 113.5,

109.9 (Ar<u>C</u>H), 43.7 (N<u>C</u>H$_2$), 31.8 (CH$_2$<u>C</u>H$_2$CH$_2$), 21.7 (Ar-<u>C</u>H$_3$), 20.4 (<u>C</u>H$_2$CH$_3$), 14.0 (CH$_2$<u>C</u>H$_3$); *m/z* (ES$^+$) 164.1 [M+H]$^+$.

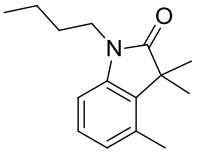
2-Bromo-*N*-butyl-2-methyl-*N*-*m*-tolylpropanamide[223] (394)



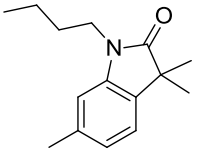
394

N-Butyl-3-methylaniline was dissolved in diethyl ether and the solution cooled to 0 ^{o}C. Triethylamine (1.02 mL, 7.35 mmol) was then added followed by the dropwise addition of 2-bromoisobutyryl bromide (0.909 mL, 7.35 mmol). The reaction was then allowed to warm to room temperature and stirred for 24 h. The reaction was then quenched by the addition of water and the phases separated. The organic phase was washed with 2M HCl, dried over MgSO4, filtered and concentrated *in vacuo* to give the product as an orange oil (1.67 g, 85%). R_f 0.44 (pet ether/EtOAC, 6:1); υ_{max} 2965 (C-H), 1719 (C=O), 833 (C-Br); δ_H (300 MHz) 7.28 (1H, t, *J* = 7.5 Hz, Ar<u>H</u>), 7.21 – 7.10 (3H, m, 3 x Ar<u>H</u>), 3.65 (2H, t, *J* = 7.5 Hz, NC<u>H</u>$_2$), 2.38 (3H, s, ArC<u>H</u>$_3$), 1.71 (6H, s, C(C<u>H</u>$_3$)$_2$Br), 1.56 (2H, quintet, *J* = 7.5 Hz, NCH$_2$C<u>H</u>$_2$), 1.31 (2H, sextuplet, *J* = 7.5 Hz, C<u>H</u>$_2$CH$_3$), 0.90 (3H, t, *J* = 7.5 Hz, CH$_2$C<u>H</u>$_3$); δ_C (75 MHz) 169.7 (<u>C</u>=O), 142.6 (Ar<u>C</u>-N), 139.0, 132.3 (Ar<u>C</u>), 130.2, 128.9, 128.8, 126.6 (Ar<u>C</u>H), 58.6 (<u>C</u>(CH$_3$)$_2$Br), 53.4 (N<u>C</u>H$_2$), 33.4 (C(<u>C</u>H$_3$)$_2$Br), 29.2 (NCH$_2$<u>C</u>H$_2$), 21.4 (Ar-<u>C</u>H$_3$), 20.1 (<u>C</u>H$_2$CH$_3$), 14.9 (CH$_2$<u>C</u>H$_3$); *m/z* (ES$^+$) 312.0 [M+H]$^+$.

1-Butyl-3,3,4-trimethylindolin-2-one[223] (395) and 1-butyl-3,3,6-trimethylindolin-2-one[223] (396)



395



396

Intramolecular Friedel-Crafts Method.

2-Bromo-*N*-butyl-2-methyl-*N*-*m*-tolylpropanamide (500 mg, 1.60 mmol) was added to anhydrous aluminium chloride (5.34 mg, 4.00 mmol) under nitrogen and the mixture heated to 50 ^{o}C for 10 min and then 160 ^{o}C for 1 h. Upon cooling a purple/brown solid was obtained. This was taken up in diethyl ether (50 mL) and washed with water (3 x 50 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product as a yellow oil (351 mg).

Bu_3SnH / AIBN Radical Cyclisation Method

A solution of Bu_3SnH (0.948 mL, 3.52 mmol) and AIBN (97.8 mg, 0.400 mmol) in toluene (30 mL) was added over 2 hours *via* syringe pump to a refluxing solution of 2-bromo-*N*-butyl-2-methyl-*N*-*m*-tolylpropanamide (500 mg, 1.60 mmol) in toluene (50 mL). The reaction mixture was then heated a reflux for a further 14 hours. The reaction was then concentrated *in vacuo* and the residue taken up in acetonitrile (50 mL) and washed with hexane (5 x 30 mL). The acetonitrile phase was then concentrated *in vacuo* to give the crude product as a yellow oil (535 mg).

Copper Mediated Radical Cyclisation Method

2-Bromo-*N*-butyl-2-methyl-*N*-*m*-tolylpropanamide (500 mg, 1.60 mL), CuBr (68.9 mg, 0.48 mmol) and TPA (139 mg, 0.48 mmol) were dissolved in methanol (13.3

mL) and the mixture stirred for 5 mins. KBH_4 (259 mg, 4.80 mmol) was then added and the reaction stirred at 50 ^oC for 24 h. The reaction mixture was then cooled and filtered through a silica plug with DCM (50 mL). The solvent was then evaporated and the residue was taken up in diethyl ether (50 mL) and washed with water (3 x 50 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (347 mg).

In all three reactions 1-butyl-3,3,4-trimethylindolin-2-one (**395**) and 1-butyl-3,3,6-trimethylindolin-2-one (**396**) were identified in the crude ^1H NMR by comparison with previous literature data.[223]

1-Butyl-3,3,4-trimethylindolin-2-one (395)

δ_H (400 MHz) 7.14 (1H, t, J = 8.0 Hz, Ar$\underline{H}$), 6.81 (1H, d, J = 8.0 MHz, Ar$\underline{H}$), 6.71 (1H, d, J = 8.0 MHz, Ar$\underline{H}$), 3.70 (2H, t, J = 7.5 Hz, NC$\underline{H}_2$), 2.40 (3H, s, Ar-C$\underline{H}_3$), 1.65 (2H, quintet, J = 7.5 Hz, NCH$_2$C$\underline{H}_2$), 1.45 (6H, s, C(C$\underline{H}_3$)$_2$), 1.38 – 1.34 (2H, m, C$\underline{H}_2$CH$_3$), 0.95 (3H, t, J = 7.5 Hz, CH$_2$C$\underline{H}_3$).

1-Butyl-3,3,6-trimethylindolin-2-one (396)

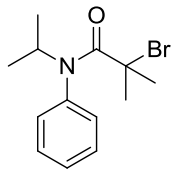
δ_H (400 MHz) 7.08 (1H, d, J = 7.5 Hz, Ar$\underline{H}$), 6.86 (1H, d, J = 7.5 Hz, Ar$\underline{H}$), 6.68 (1H, s, Ar$\underline{H}$), 3.69 (2H, t, J = 7.5 Hz, NC$\underline{H}_2$), 2.38 (3H, s, Ar-C$\underline{H}_3$), 1.65 (2H, quintet, J = 7.5 Hz, NCH$_2$C$\underline{H}_2$), 1.38 – 1.34 (2H, m, C$\underline{H}_2$CH$_3$), 1.34 (6H, s, C(C$\underline{H}_3$)$_2$), 0.95 (3H, t, J = 7.5 Hz, CH$_2$C$\underline{H}_3$).

6.5.1 General Procedure of the Synthesis of Anilides

Amine (1.0 eq.) was dissolved in toluene (0.5 M) and the solution cooled to 0 ^oC. Triethylamine (1.2 eq.) was then added, followed by the dropwise addition of 2-

bromoisobutyryl bromide (1.1 eq.). The reaction was then allowed to warm to room temperature and stirred for 24 h. The reaction was then quenched by the addition of water and the phases separated. The organic phase was then washed with 2 M HCl, dried over MgSO4 and filtered before being concentrated *in vacuo* to give the product. No further purification was required.

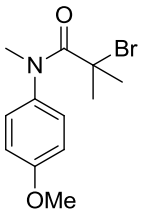
2-Bromo-*N*-isopropyl-2-methyl-*N*-phenylpropanamide[223] (397b)



397b

The general procedure for the synthesis of anilides (6.5.1) was applied using *N*-isopropylaniline (370 mg, 2.74 mmol), triethylamine (0.456 mL, 3.28 mmol), 2-bromoisobutyryl bromide (0.372 mL, 3.01 mmol) and toluene (5.50 mL). The product was obtained as a pale yellow crystalline solid (490 mg, 67%). R_f 0.39 (pet ether/EtOAC, 6:1); m.p. 58-60 ^{o}C; υ_{max} 2976 (C-H), 1629 (C=O), 708 (C-Br); δ_H (400 MHz, $CDCl_3$) 7.42 – 7.36 (3H, m, Ar<u>H</u>), 7.32 – 7.24 (2H, br m, Ar<u>H</u>), 4.98 (1H, septuplet, *J* = 6.5 MHz, C<u>H</u>$(CH_3)_2$), 1.69 (6H, br s, C($C\underline{H}_3)_2$Br), 1.06 (6H, d, *J* = 6.5 Hz, CH($C\underline{H}_3)_2$); δ_C (400 MHz, $CDCl_3$) 169.5 (<u>C</u>=O), 137.8 (<u>Ar</u>N), 131.9 (Ar), 128.5 (<u>Ar</u>), 128.3 (<u>Ar</u>), 59.3 (<u>C</u>$(CH_3)_2$Br), 49.3 (<u>C</u>H$(CH_3)_2$), 33.5 (C($\underline{C}H_3)_2$Br), 20.6 (CH($\underline{C}H_3)_2$); *m/z* (ES^+) $C_{13}H_{19}BrNO$ requires 284.0645, found: 284.0646 $[M+H]^+$.

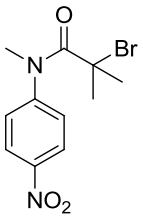
2-Bromo-*N*-(4-methoxyphenyl)-*N*,2-dimethylpropanamide[223] (397e)



397e

The general procedure for the synthesis of anilides (6.5.1) was applied using 4-methoxy-*N*-methylaniline (1.00 g, 7.29 mmol), triethylamine (1.21 mL, 8.75 mmol), 2-bromoisobutyryl bromide (0.991 mL, 8.02 mmol) and toluene (14.5 mL). The product was obtained as a yellow crystalline solid (1.95 g, 93%). R_f 0.19 (pet ether/EtOAC, 6:1); υ_{max} 2973 (C-H), 1737 (C=O), 662 (C-Br); δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* = 9.0 Hz, 2 x Ar<u>H</u>), 6.91 (2H, d, *J* = 9.0 Hz, 2 x Ar<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$), 3.30 (3H, s, NC<u>H</u>$_3$), 1.75 (6H, s, C(C<u>H</u>$_3$)$_2$Br); δ_C (400 MHz, $CDCl_3$) 170.5 (<u>C</u>=O), 159.0 (<u>Ar</u>OCH$_3$), 137.0 (<u>Ar</u>N), 129.7 (2 x <u>Ar</u>), 114.2 (2 x <u>Ar</u>), 58.0 (<u>C</u>(CH$_3$)$_2$Br), 55.5 (O<u>C</u>H$_3$), 42.0 (N<u>C</u>H$_3$), 33.4 (C(<u>C</u>H$_3$)$_2$Br); *m/z* (ES^+) $C_{12}H_{17}BrNO_2$ requires 286.0437, found: 286.0440 $[M+H]^+$.

2-Bromo-*N*,2-dimethyl-*N*-(4-nitrophenyl)propanamide (397f)



397f

The general procedure for the synthesis of anilides (6.5.1) was applied using *N*-methyl-4-nitroaniline (1.00 g, 6.57 mmol), triethylamine (1.09 mL, 7.89 mmol), 2-

bromoisobutyryl bromide (0.894 mL, 7.23 mmol) and toluene (13.0 mL). The product was obtained as a bright yellow solid (1.87 g, 94%). R_f 0.11 (pet ether/EtOAC, 6:1); m.p. 70-71 ^oC; υ_{max} 2971 (C-H), 1637 (C=O), 837 (C-Br); δ_H (400 MHz, $CDCl_3$) 8.28 (2H, d, *J* = 9.0 Hz, Ar<u>H</u>), 7.54 (2H, d, *J* = 9.0 Hz, Ar<u>H</u>), 3.51 (3H, s, NC<u>H</u>$_3$), 1.91 (6H, s, C(C<u>H</u>$_3$)$_2$Br); δ_C (100 MHz, $CDCl_3$) 170.4 (<u>C</u>=O), 150.4 (<u>Ar</u>NO_2), 146.5 (<u>Ar</u>N), 128.8, 126.4, 124.7 (<u>Ar</u>), 57.0 (<u>C</u>$(CH_3)_2$Br), 41.4 (N<u>C</u>H_3), 32.9 (C(<u>C</u>H_3)$_2$Br); *m/z* (ES^+) $C_{11}H_{14}BrN_2O_3$ requires 301.0182, found: 301.0183 $[M+H]^+$.

6.5.2 General Procedure for Cu(TPA)Br and KBH_4 Mediated Synthesis of Oxindoles

Anilide (1 eq.), $CuSO_4.5H_2O$ (0.2 eq.) and TPA (0.2 eq.) were dissolved in methanol (0.12 M) and stirred for 5 mins. KBH_4 (2 eq.) was then added portionwise and the reaction mixture heated to 50 ^oC for 24 h. The reaction mixture was then cooled and filtered through a silica plug with DCM (25 mL). The filtrate was then washed with water (30 mL), dried over MgSO4, filtered and concentrated *in vacuo* to give the crude product.

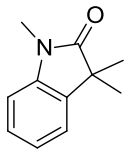
6.5.3 General Procedure for Cu(TPA)Br Mediated Synthesis of Oxindoles in Methanol

Anilide (1 eq.), CuBr (1 eq.) and TPA (1 eq.) were dissolved in methanol (0.1 M) under nitrogen and the reaction mixture heated to 50 ^oC for 24 h. The reaction mixture was then cooled and filtered through a silica plug with EtOAC (50 mL) and the filtrate was concentrated *in vacuo* to give the crude product.

6.5.4 General Procedure for Cu(TPA)Br Mediated Synthesis of Oxindoles in Toluene

Anilide (1 eq.), CuBr (1 eq.) and TPA (1 eq.) were dissolved in toluene (0.1 M) under nitrogen and the reaction mixture heated to 110 ^{o}C for 24 h. The reaction mixture was then cooled and filtered through a silica plug with EtOAC (50 mL) and the filtrate was concentrated *in vacuo* to give the crude product.

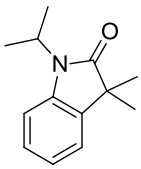
1,3,3-Trimethylindolin-2-one[223] (399a)



399a

R_f 0.28 (6:1, pet ether/EtOAc); mpt ; υ_{max} 2968 (C-H), 1703 (C=O); δ_H (400 MHz, $CDCl_3$) 7.26 (1H, t, *J* = 7.5 Hz, Ar<u>H</u>), 7.20 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 7.06 (1H, t, *J* = 7.5 Hz, Ar<u>H</u>), 6.84 (1H, d, *J* = 7.5 Hz, Ar<u>H</u>), 3.21 (3H, s, NC<u>H</u>$_3$), 1.37 (6H, s, C(C<u>H</u>$_3$)$_2$); δ_C (400 MHz) 181.4 (<u>C</u>=O), 142.6 (<u>Ar</u>-N), 135.8 (<u>Ar</u>), 127.7 (<u>Ar</u>H), 122.5 (<u>Ar</u>H), 122.3 (<u>Ar</u>H), 108.0 (<u>Ar</u>H), 44.2 (<u>C</u>(CH$_3$)$_2$), 26.2 (N<u>C</u>H$_3$), 24.4 (C(<u>C</u>H$_3$)$_2$); *m/z* (ES$^+$) 176.1 $[M+H]^+$.

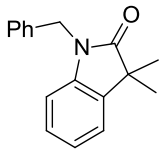
1-Isopropyl-3,3-dimethylindolin-2-one[223] (399b)



399b

R_f 0.35 (6:1, pet ether/EtOAc); υ_{max} 3053, 2970 (CH), 1692 (C=O); δ_H (400MHz, $CDCl_3$) 7.22 (1H, t, *J* = 8.0 Hz, ArH), 7.21 (1H, d, *J* = 8.0 Hz, ArH), 7.04 (1H, d, *J* = 8.0 Hz, ArH), 7.02 (1H, d, *J* = 8.0 Hz, ArH), 4.65 (1H, septuplet, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.48 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.31 (6H, s, $C(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 181.0 (C=O), 141.2 (ArCN), 136.4 (ArC), 127.3, 122.5, 121.9, 109.9 (ArCH), 43.8 ($C(CH_3)_2$), 43.4 ($CH(CH_3)_2$), 24.5 ($C(CH_3)_2$), 19.4 ($CH(CH_3)_2$); *m/z* (ES^+) 204.1 $[M+H]^+$.

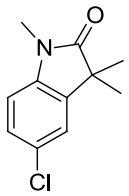
1-Benzyl-3,3-dimethylindolin-2-one[250] (399c)



399c

R_f 0.29 (6:1, pet ether/EtOAc); υ_{max} 2970 (C-H), 1708 (C=O); δ_H (400MHz, $CDCl_3$) 7.24 – 7.28 (5H, m, ArH), 7.20 (1H, d, *J* = 7.5 Hz, ArH), 7.12 (1H, td, *J* = 7.5, 1.0 Hz, ArH), 7.01 (1H, t, *J* =7.5 Hz, ArH), 6.72 (1H, d, *J* = 7.5 Hz, ArH), 4.91 (2H, s, NCH_2), 1.43 (6H, s, $(C(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 181.0 (C=O), 141.7 (ArCN), 136.1 (ArC), 135.8 (ArC), 128.8, 127.6, 127.5, 127.2, 122.5, 122.4, 109.1 (ArCH), 44.2 ($C(CH_3)_2$), 43.6 (NCH_2), 24.8 ($C(CH_3)_2$); *m/z* (ES^+) 252.1 $[M+H]^+$.

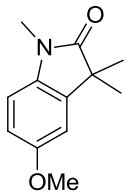
5-Chloro-1,3,3-trimethylindolin-2-one[251] (399d)



399d

R_f 0.18 (6:1, pet ether/EtOAc); υ_{max} 2977 (C-H), 1706 (C=O), 813 (CCl); δ_H (400MHz, $CDCl_3$) 7.16 (1H, dd, J = 8.0, 2.0 Hz, ArH), 7.10 (1H, d, J = 2.0 Hz, ArH), 6.69 (1H, d, J = 8.0 Hz, ArH), 3.13 (3H, s, NCH_3),1.30 (6H, s, $C(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 180.8 (C=O), 141.2 (ArCN), 137.5 (ArC), 127.9 (ArCCl), 127.6, 122.9 , 108.9 (ArCH), 44.5 ($C(CH_3)_2$), 26.3 (NCH_3), 24.3 ($C(CH_3)_2$); *m/z* (ES^+) 232 $[M+Na]^+$.

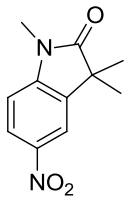
5-Methoxy-1,3,3-trimethylindolin-2-one[250] (399e)



399e

R_f 0.10 (6:1, pet ether/EtOAc); υ_{max} 2968 (CH), 1699 (C=O); δ_H (400MHz, $CDCl_3$) 6.81 (1H, d, J = 2.5 Hz, ArH), 6.77 (1H, dd, J = 8.5, 2.5 Hz, ArH), 6.72 (1H, d, J = 8.5 Hz, ArH), 3.78 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 1.34 (6H, s, $(C(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 181.1 (C=O, quaternary), 156.1 (ArC-OCH_3), 137.3 (ArCN), 136.2 (ArC), 111.6, 110.1, 108.2 (ArCH), 55.3 (OCH_3), 44.6 ($C(CH_3)_2$), 26.3 (NCH_3), 24.4 ($C(CH_3)_2$); *m/z* (ES^+) 206.1 $[M+H]^+$.

1,3,3-Trimethyl-5-nitroindolin-2-one[252] (399f)



399f

R_f 0.08 (6:1, pet ether/EtOAc); υ_{max} 2976 (CH), 1721 (C=O); δ_H (400MHz, $CDCl_3$) 8.26 (1H, dd, *J* = 8.5, 2.5 Hz, ArH), 8.10 (1H, d, *J* = 2.5 Hz, ArH), 6.94 (1H, d, *J* = 8.5 Hz, ArH), 3.30 (3H, s, NCH_3), 1.40 (6H, s, $C(CH_3)_2$); δ_C (100MHz, $CDCl_3$) 181.3 (C=O), 148.4 (ArC-N), 145.0 ($ArCNO_2$), 136.5 (ArC), 125.2, 118.3, 107.6 (ArCH), 44.2 ($C(CH_3)_2$), 26.6 (NCH_3), 24.2 ($C(CH_3)_2$); *m/z* (ES^+) 221.1 $[M+H]^+$.

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