WARWICK
THE UNIVERSITY OF WARWICK

A Thesis Submitted for the Degree of PhD at the University of Warwick

Permanent WRAP URL:

http://wrap.warwick.ac.uk/101538/

Copyright and reuse:
This thesis is made available online and is protected by original copyright.
Please scroll down to view the document itself.
Please refer to the repository record for this item for information to help you to cite it.
Our policy information is available from the repository home page.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk

warwick.ac.uk/lib-publications

Axially Chiral Enamides: Rotation Barriers, Substituent Effects, and Cyclisation Reactions

By

Jessica M. Phillips

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Chemistry

University of Warwick, Department of Chemistry

September 2017

Contents

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Andrew Clark, for both the opportunity to work on this project and all his help along the way. Within the department, additional thanks go to Professor Tim Bugg and Dr Andrew Marsh, for their interest and assistance as my advisory panel and to Dr Ivan Prokes and Mr Robert Perry for their excellent NMR service which I have abused for four years. I would also like to thank past and present members of the Clark, Rourke and Chan groups, for the excellent Cake Fridays, the dubious humour and occasional chemistry assistance.

A massive thank you to The Squad (Danielle, Ben and Josie) for keeping me going through the last four years (eight, in Ben's case). To Danielle, because you're as much of a nerd as I am and I'm so glad we adopted you. To Josie, because fancy-tea-and-cocktail-drinking companions are very important. And to Ben, because I actually cannot imagine what Warwick would be like without you, nor do I want to (sorry about stalking you to Sheffield). Thank you also to Caro, Camille and Anaïs, who have been providing support from afar all these years (not so far in Anaïs' case but the trains are so bad it may as well be Canada). To Amy, for the occasional much-needed encouraging prod and dose of realism. And most of all to Sophie, despite the fact that there aren't words to describe how much you mean to me. You're the most amazing person I've ever been lucky enough to be friends with and I love you so much.

Lastly, to my family, because they're actually kind of awesome: I love you all, and thank you for being there for me. Jonny and Christian, thank you for laughing at me when necessary. And finally Mum and Dad: thank you so much for supporting me through this and everything else I've ever done. Your love and support mean the world to me, and I hope you're proud of me.

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 completed in the Department of Chemistry at the University of Warwick between October 2013 and September 2017 and has not been submitted for a degree at any other institution.

Jessica Phillips

Abstract

The work presented in this thesis focuses on the synthesis, analysis and cyclisations of a series of *N*-halobenzylcycloalkenamides. Chapter 1 provides an introduction to atropisomerism, radical cyclisation and Heck cyclisation, including developments in the reaction conditions for radical and Heck cyclisations. The use of atropisomers in synthesis, and particularly in cyclisation reactions, is also discussed.

Chapter 2 reports investigations into the effects of aryl, acyl and alkene substitution on the barrier to rotation about the *N*-alkenyl bond in a series of enamides. A range of enamides were synthesised and their barriers to rotation were investigated by ^{1}H VT NMR, and where desirable, by racemisation of an enriched atropisomer. The highest barriers to rotation were obtained with tetrasubstituted enamides, although additional bulk adjacent to the double bond (such as in tetralone-based compounds) was found to increase the barrier to rotation to a lesser degree. A precursor analogue to the natural product norchelidonine was also synthesised and was found to have a barrier to rotation between 20 and 24 kcal/mol.

Chapter 3 describes the results of Bu_3SnH-mediated radical cyclisation of the enamides synthesised in Chapter 2. A range of cyclised products was obtained in most cases, resulting from either the 5-*exo* pathway or the 6-*endo* pathway, although the 6-*endo* pathway was found to predominate in almost all cases. Cyclisations of enamides with higher barriers to rotation proved more difficult, and indeed it was not possible to cyclise some of them, such as the precursor to the natural product norchelidonine. Chiral transfer should be possible with at least one α,α',α'-substituted enamide, under the conditions used in this chapter.

Chapter 4 describes attempts to find a viable alternative method for the cyclisation of the enamides synthesised in Chapter 2, to combat the many disadvantages of the tin method. Samarium diiodide radical cyclisation and palladium Heck cyclisation of the simplest substrate were both successful. Samarium cyclisation generated the same products as tin cyclisation, in a slightly different ratio due to the difference in reaction conditions. Palladium Heck cyclisation gave only 5-*exo* cyclisation products: the direct product and the isomerised product, in varying ratios depending on the conditions used. The palladium Heck reaction conditions were then optimised for these compounds, and the optimised conditions were used to cyclise a selection of the compounds from Chapter 2.

Schemes and Figures

Abbreviations

Ac	Acetyl
ABCN	1,1’-Azobis(cyclohexanecarbonitrile)
AGET	Activators generated by electron transfer
AIBN	Azabisisobutyronitrile
Ar	Aryl
ATRC	Atom-transfer radical cyclisation
App t	Apparent triplet
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bipy	Bipyridine
Bn	Benzyl
br	Broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
BuLi	Butyl lithium
Bu_3SnH	Tributyltin hydride
cy	Cycloalkyl
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DMF	Dimethylformamide
dt	Doublet of triplets
ee	Enantiomeric excess

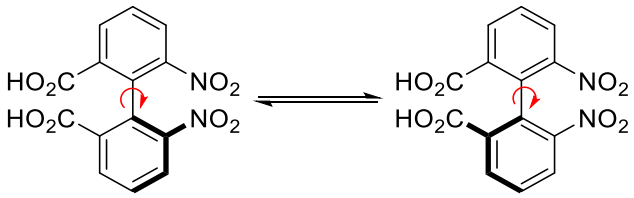
EI	Electron ionisation
eq	Equivalents
er	Enantiomeric ratio
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
$\Delta G^{\ddagger}$	Gibbs free energy (of rotation)
h	Hours
h	Planck's constant
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Hz	Hertz
k_b	Boltzmann constant
k_c	Rate of cyclisation
k_{rot}	Rate of rotation
m	Multiplet
maj	Major
Me	Methyl
Me_6-Tren	*N, N, N', N', N'', N''*-Hexamethyltriethylenetetramine
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
min	Minute
mins	Minutes

NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Pet ether	Petroleum ether 40-60^{o}C
Ph	Phenyl
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
TZVP	Triple zeta valence plus polarisation
VT NMR	Variable temperature nuclear magnetic resonance

Chapter 1: Introduction

1.1 Atropisomerism

Atropisomerism is a phenomenon where chirality is exhibited due to restricted rotation around a chemical bond. Atropisomers need not contain a stereogenic centre: the spatial arrangement of the two groups on either end of the chemical bond in question provides the two necessary enantiomers. These are designated by P and M descriptors rather than R and S.



1.1 (P) **1.1 (M)**

Figure 1.1: First isolated atropisomers.

By definition, atropisomers must be fully resolvable at room temperature for 1000 seconds, which corresponds to an energy barrier of 23.3 kcal.mol^{-1}.[1] This differentiates them from rotamers, which have no such requirement. Several factors can influence the configurational stability of a compound about a specific axis: the size of substituents in proximity to the axis, the presence, length and rigidity of bridging elements, and the involvement of other chemically- or photochemically-induced processes.

Although the term was not coined until 1933, the first stable atropisomers **1.1** were identified in 1922 by Christie and Kenner.[2] The chirality exhibited around the aryl-aryl bond resulted in two separate and separable atropisomers, as shown in Fig. 1.1,. The atropisomers could be separated by co-crystallisation with the chiral amino alkaloid brucine. Following this discovery, little attention was paid to the possibilities represented by atropisomerism, until it was realised that many natural products contain

a chiral biaryl unit,[3,4] and that 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP),[5–7] QUINAP[8–10] and other biaryl ligands were extremely useful for asymmetric synthesis. Biaryl systems therefore provided the majority of the inspiration for the first wave of investigations into atropisomerism.

1.1.1 Atropisomerism in biaryl systems

Atropisomerism in biaryl systems can, by virtue of their asymmetry, have interesting effects in asymmetric synthesis, and can be a decisive factor in determining the pharmacological properties of a compound. Many natural products exhibit this type of chirality, for example vancomycin **1.2**[11], viriditoxin **1.3**[12,13] and (-)-N-acetylallocolchinol **1.4**[14], a structural analogue of colchicine.

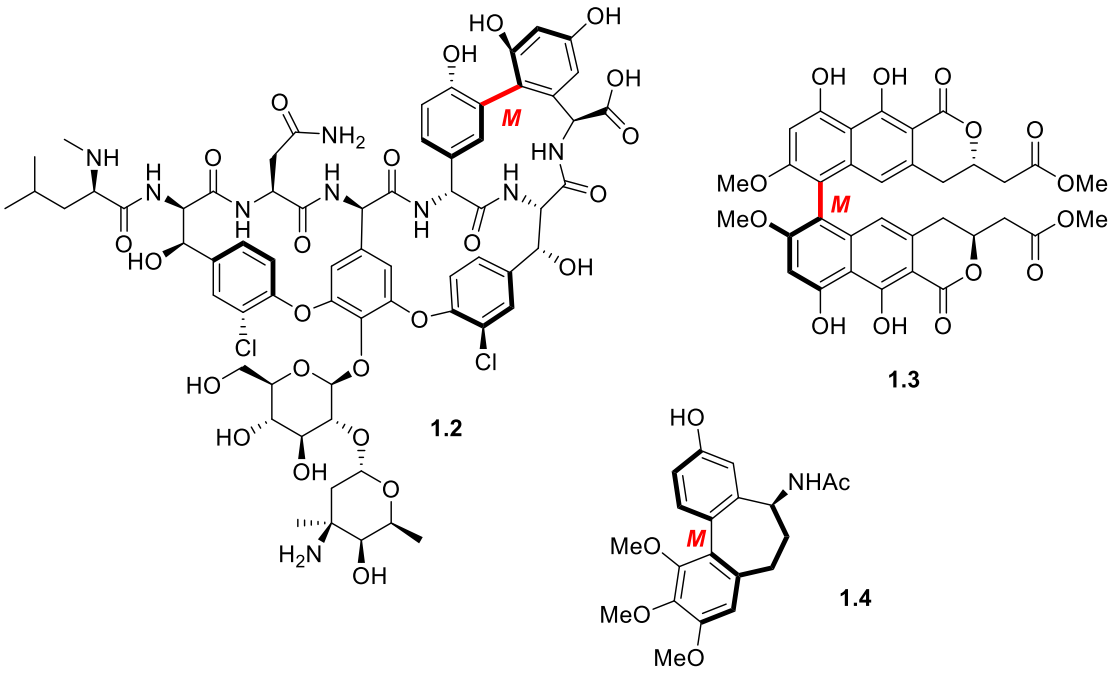


Figure 1.2: Natural products exhibiting atropisomerism

Vancomycin **1.2**, one of the "last defence" antibiotics[11,15,16], contains many points of chirality and two atropisomeric chiral planes formed from the bisaryl ethers with a chiral axis about the aryl-aryl bond, as shown. This is an example of an atropisomeric axis which works in conjunction with other points of chirality to ensure the correct

functioning of a molecule. The key biaryl linkage in vancomycin was first synthesised by Evans, using VOF_3[17], and subsequently by Nicolaou, using a Suzuki coupling.[18] The latter went on to report the total synthesis of vancomycin,[19] which has yet to be improved upon. Viriditoxin **1.3** was first extracted from *Aspergillus veridinutans* in 1971,[20] but was subsequently found to be present in many fungal extracts, including one derived from jellyfish.[12] It has been shown to cause apoptosis and autophagy in human prostate cancer cells.[13] The key 6,6'-binaphthopyranone atropisomeric linkage has been prepared by a vanadium-catalysed cross-coupling.[13] Interestingly, good remote diastereocontrol was induced by the lactone chiral centre. The use of chiral catalysts could enhance or reverse this selectivity. (-)-*N*-Acetylallocolchinol **1.4**, under the form of the pro-drug *N*-acetylallocolchinol-*O*-phosphate, has been seen to cause damage to tumour vasculature without damaging normal tissue,[14] provoking a resurgence of interest in colchicine derivatives as cancer chemotherapy drug possibilities. A range of analogues have been prepared with the asymmetric linkage synthesised *via* a double elimination at the oxa bridge on the 7-membered ring,[21] previously synthesised by oxidative rearrangement using *m*CPBA.[22]

Atropisomerism around an aryl-aryl bond, as exhibited by these natural products, has been extensively studied and synthetically exploited. The rate of racemisation in biaryl systems, according to a review by Adams[23] and a study of steric interference values by Bott and Sternhell,[24] depends on the size of the four *ortho*-substituents around the biaryl bond (see Fig. 1.3). If three of the four *ortho* substituents are larger than hydrogen, the molecule is usually separable as two atropisomers at room temperature.

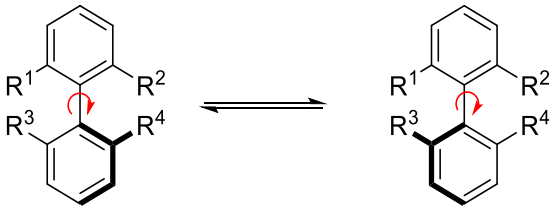
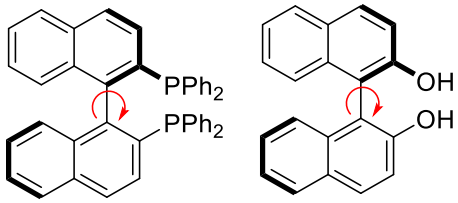


Figure 1.3: Rotation in biaryl systems.

A wide range of biaryl systems have been shown to exhibit atropisomeric behaviour, and their synthesis and uses are detailed in the following sections.

1.1.1.1 Simple isocyclic biaryls

This category contains those biaryls that contain a single atropisomeric axis between two carbon atoms in identical aryl systems. Commonly seen examples of biaryl systems of this variety exhibiting atropisomerism are 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)[25] and its diol analogue 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) (Fig. 1.4).[26]

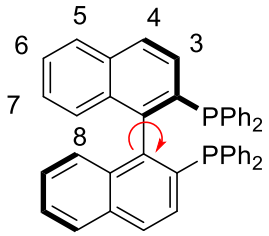


1.5 **1.6**

Figure 1.4: Isocyclic biaryl ligands BINAP and BINOL.

BINAP is an organophosphorous compound which is commonly used in asymmetric synthesis, when complexed to a metal such as rhodium, ruthenium and palladium. BINAP was first synthesised and resolved in 1980 by Noyori, using an optically active amine-Pd(II) complex.[5] However, a more convenient synthesis was reported in 1986, also by Noyori, using camphorsulfonic acid or 2,3-*O*-dibenzoyltartaric acid to resolve the racemic diphosphine dioxide, which was then reduced with trichorosilane.[27] This

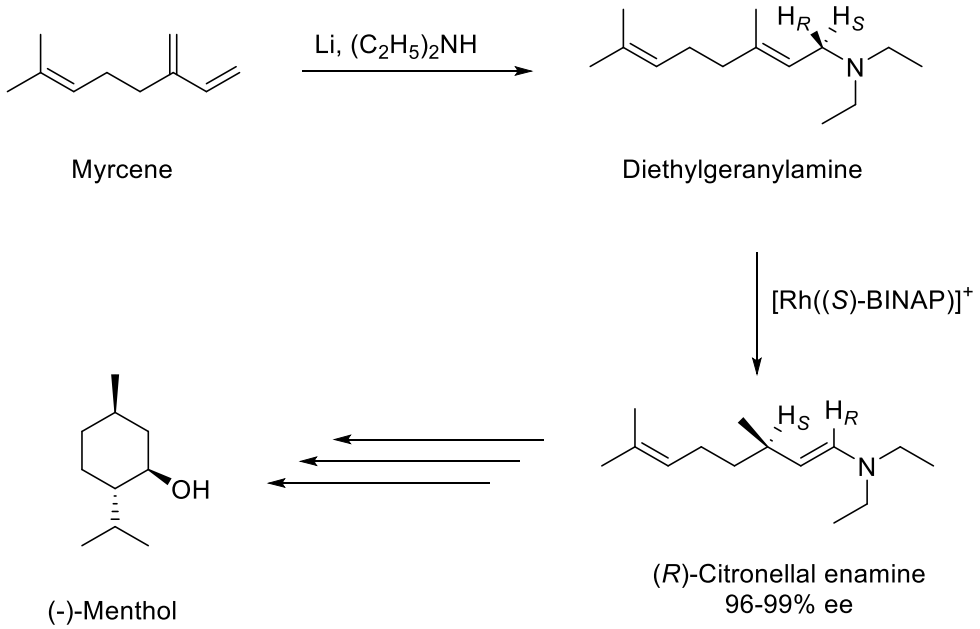
practical synthesis allowed for the scale-up and variation of the reaction, resulting in the synthesis of analogues of BINAP.[28] These analogues included variations and substitutions at both the phenyl and naphthyl sites, the former to increase specificity and activity of the catalyst, the latter to facilitate removal and recycling of the catalysts.[28] The 3-, 4-, 5-, and 6-positions on BINAP have been the subject of most research thus far: substitution in the 3,3'positions has the most effect on the chiral outcome of many processes, by forming a "chiral pocket" through restriction of the rotation of the phosphine groups.[28]



1.5

Figure 1.5: Substitution positions on BINAP.

This ligand has been immensely useful ever since its discovery: in the paper which detailed the first synthesis of the molecule, Noyori also used BINAP complexed to rhodium to asymmetrically hydrogenate α-(acylamino)acrylic acids.[5] The metal to which BINAP is complexed has a strong effect on the utility of the resultant catalyst. When complexed to rhodium, the catalyst has a narrow range of use, and is mainly employed to asymmetrically isomerise allylic amines, while the BINAP-Ru catalyst has a broader chemical utility.[29] Importantly, Rh-BINAP is used on an industrial scale in order to synthesise (-)-menthol from myrcene, thus confirming the utility of atropisomeric ligands in chiral catalysts.[30]



Scheme 1.1: Takasago menthol synthesis

BINOL (Fig. 1.4, pg 4) is a precursor to BINAP which can itself be complexed to various metals to form catalysts, most notably the lanthanide Shibasaki catalysts (Fig 1.6). These can be used as asymmetric catalysts in nitroaldol, Michael, Diels-Alder and hydrophosphonylation reactions.[26]

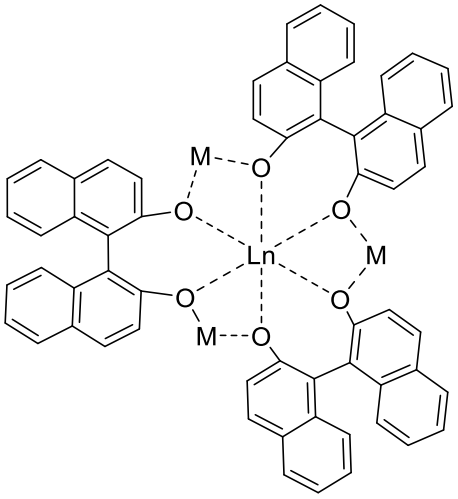
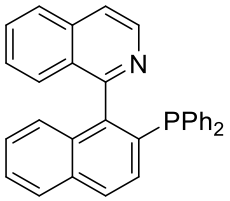


Figure 1.6: General structure of a Shibasaki catalyst (Ln=lanthanide, M=metal).

A similar ligand, (*R*,*S*)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline or QUINAP, was synthesised in 1993.[31] Rhodium and palladium complexes of this ligand were subsequently used to perform asymmetric catalytic hydroborations of olefins[32] and

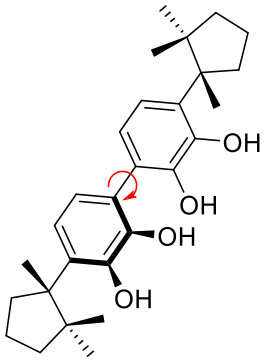
catalytic allylic alkylation[33] respectively. A series of APN (*atropos* P,N) compounds based on QUINAP have since been synthesised and used in asymmetric catalysis, notably for the hydroboration and diboration of alkenes, 1,3-dipolar cycloadditions, alkynylation of iminium salts, and conjugate additions of copper acetylides.[8]



1.6

Figure 1.7: QUINAP

Isocyclic biaryl atropisomerism can also be found in natural products: for example, mastigophorene A has been isolated alongside mastigophorene B from the liverwort *Mastigophora diclados*, and shown to stimulate nerve growth.[34] The first atroposelective synthesis of mastigophorenes A and B was reported by Degnan and Meyers in 1999,[35] where the key biaryl bond was formed *via* an asymmetric Ullman coupling.

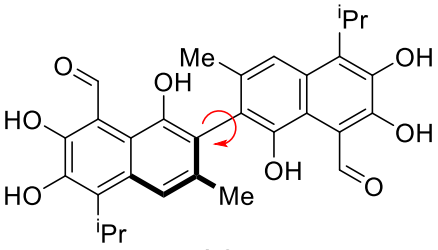


1.7

Figure 1.8: Mastigophorene A

This is a representative of a relatively small set of naturally occurring biphenyls: due to the small size of the phenyl ring, most biphenyl systems in naturally occurring molecules do not have a sufficiently high barrier to rotation to be considered

atropisomers. Most examples of atropisomerism in synthetically or medically significant natural products are provided by compounds containing dinaphthyls, as these are inherently more restricted in rotation, such as (-)-gossypol (**1.8**), which has anti-cancer and anti-spermatogenic properties, and selectively inhibits HIV-1 replication. Gossypol was first isolated as a racemic mixture from the seeds of the cotton plant *Gossypium hirsutum* by Lonmore in 1886, but the first atroposelective synthesis was not reported until 1997,[36] where the biaryl bond was formed by the same Ullman coupling that was used for the synthesis of mastigophorene A.

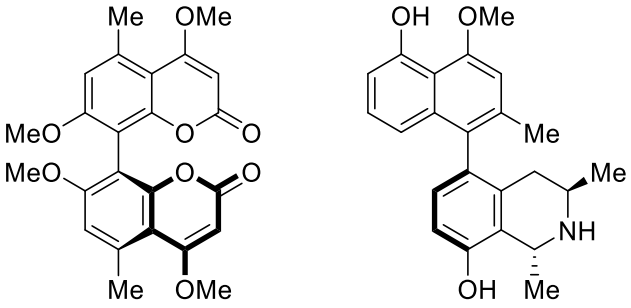


1.8

Figure 1.9: (-)-Gossypol

1.1.1.2 Biaryls containing fused heterocycles and heterobiaryls

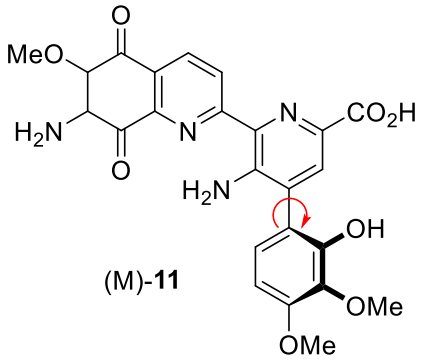
Biaryl systems containing fused heterocycles have also been shown to exhibit atropisomeric behaviour in certain natural products, such as viriditoxin (**1.3**, Fig. 1.2, pg 2), but also (+)-kotanin (**1.9**)[37] and dioncophylline C (**1.10**).[38] Kotanin is a naturally occurring bicoumarin, isolated from *Aspergillus glaucus* cultures. A racemic mixture was synthesised by metalation with BuLi, followed by oxidation with $CuCl_2$ to form the key aryl-aryl bond. Dioncophylline C, an antimalarial lead compound, was synthesised by ring-formation and subsequent $LiAlH_4$-mediated ring-opening.



1.9 **1.10**

Figure 1.10: Naturally occurring (+)-kotanin and dioncophylline C

Streptonigrin is a highly functionalised aminoquinone heterobiaryl that exhibits broad-spectrum anti-cancer activity and as such was the subject of investigations by both synthetic organic chemists and biochemists. Unfortunately, after reaching phase II clinical trials in the 1970s, medical trials were abandoned due to the side effects caused by the high level of toxicity. The total synthesis of this compound was reported by Donohoe, Jones and Barbosa in 2011[39] and involved the ring-closing metathesis of the pentasubstituted pyridine, as well as cross-coupling reactions to form the biaryl bonds.



(M)-**11**

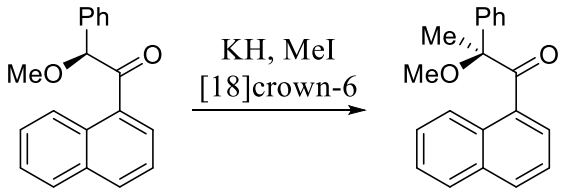
Figure 1.11: Streptonigrin

Heterobiaryls and biaryls containing fused heterocycles have attracted increasing attention, due to their potential both as chiral catalysts and as chiral substrates.[40,41] Natural products containing *N*-heterocycles are an attractive scaffold for use in medicinal and pharmaceutical chemistry, as the wide range of pharmacological properties displayed by such compounds is highly favourable to their investigation.[42]

1.1.2 Atropisomerism in non-biaryl systems

1.1.2.1 Arylamides and anilides

Biaryl systems may have provided the first wave of inspiration for investigations into atropisomerism, but an increased interest in non-biaryl systems was sparked by Clayden[43–50] and Curran[46,51–55], both of whom published studies of non-biaryl atropisomers in the 1990s and 2000s. This work sprang from the discovery by Fuji in 1991 that chiral ketone **1.11** could be stereospecifically alkylated using potassium hydride and methyl iodide, despite the intermediacy of a supposedly achiral enolate.[56]



1.11 **1.12** 66% ee

Scheme 1.2: Selective alkylation reported by Fuji

Clayden later proved that the "chiral memory" shown in this reaction resulted from restricted rotation in the enolate intermediate.[55] The term "atroposelective" was coined by Curran in order to describe reactions with stereocontrolling atropisomers. Non-biaryl atropisomerism is less common in natural products, and has traditionally been less exploited by synthetic chemists. However, over the course of the subsequent two decades, investigations into non-biaryl atropisomers, their synthesis and their uses has become more prevalent.[40,50,57,58] While former work had focussed on the isolation, structure and rotation barriers of such compounds[40,45,47,50,51,57–62], the emphasis in recent years has shifted towards what can be accomplished with such molecules.[40,50,63–69] Asymmetric reactions of amides and imides have proven to be of particular interest, given that *N*-Ar bond rotation can be slowed when the aryl group is appropriately substituted. Radical reactions can thus be accomplished much faster than the rotation

of the *N*-Ar bond, and chiral transfer can often ensue. Atropisomerism has been observed in many such systems, including arylamides[45,62] **1.13**, anilides[62,70] **1.14** and enamides **1.15**.[69,71,72]

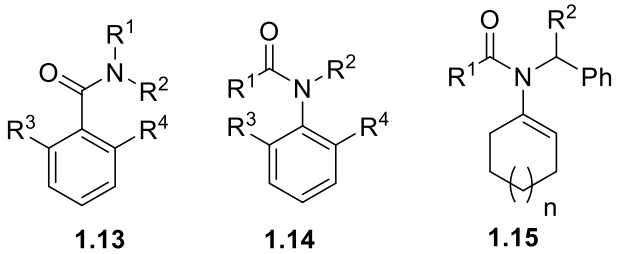


Figure 1.12: Atropisomerism in amide systems.

In the mid-1990s, Clayden published work on non-biaryl atropisomerism, focussed in the first instance on arylamides such as **1.16** and **1.17**.[44]

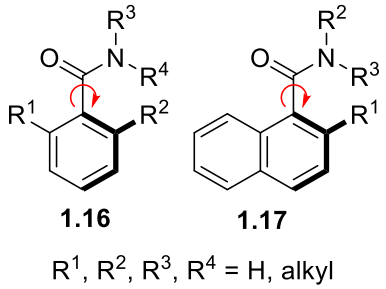
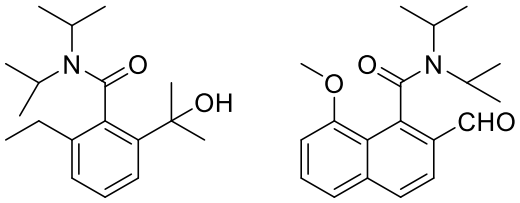


Figure 1.13: Arylamides originally studied by Clayden

Atropisomerism in arylamides **1.16** had been proven to be contingent on the amide group being flanked by *ortho*-substituents on either side of the phenyl ring.[73] Mannschreck[73] and Pirkle[74] both isolated enantiomers of **1.16a** (R^1=R^2=R^3=Me) by chiral HPLC. Compounds **1.16** proved useful even when non-atropisomeric (if R^1=H and R^2=R^3=alkyl, the half-life for racemisation at room temperature ranges from 0.01-2 seconds) due to their ready functionalisation by lithiation in the 2-position, which produced a series of atropisomers[43,44,49,55] **1.16** and **1.17** where R^2 and R^3 are alkyl groups and R^1 can be any group larger than hydrogen. Clayden subsequently synthesised and investigated many such systems, their rates of racemisation and the stereoselectivity of their reactions.[67] Complete stereochemical stability could only be

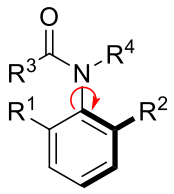
attained with the most hindered of naphthamides (2,8-disubstitution of a naphthamide yields a half-life measurable in years) and benzamides (any fully-substituted carbon at one *ortho* position and any non-hydrogen substituent at the other yields a similar half-life) (Figure 1.14). Both **1.16b** and **1.17a** have estimated half-lives of 100 years at 25ºC, and ΔG values of approximately 31 kcal.mol^{-1}. Clayden also established that such atropisomers could exert conformational control over reactions occurring near to the bond about which rotation was restricted, and even, under certain circumstances, remotely.[46]



1.16b **1.17a**

Figure 1.14: Atropisomers isolated by Clayden.

Curran[75]also published work on atropisomeric non-biaryls in the 1990s, although his focus was on the atropisomeric properties of anilides **1.18**.

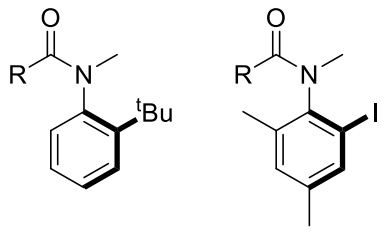


1.18

Figure 1.15: Non-biaryl atropisomeric anilides discussed by Curran

Curran observed that if R^1 and R^2 in compound **1.18** were hydrogens, the barrier to rotation around the C-N bond was low and the torsion angle between the amide and the phenyl moiety was around 30°. While encouraging, as the molecule was not planar and therefore the aryl group did not rotate freely through the plane of the amide, the small size of the *ortho*-substituents meant that the barrier to rotation was insufficient

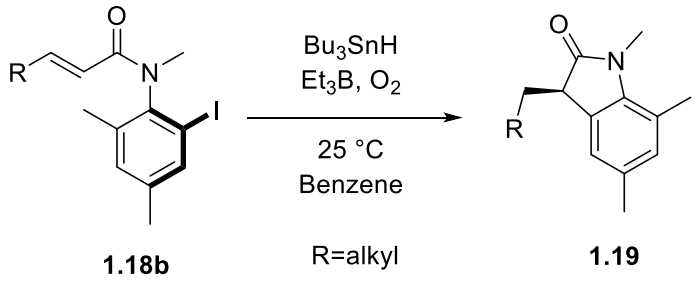
to envisage atropisomeric possibilities. However, if both *ortho*-substituents were replaced with medium-sized alkyl or heteroatom groups, the *N*-Ar torsion angle and the barrier to rotation around the *N*-Ar bond were substantially increased. Curran hypothesised[75] and subsequently showed[76] that if one *ortho*-substituent was a large group such as a tertiary alkyl, and the other a hydrogen, then the system would be "stable to racemisation" (non-freely-rotating) at room temperature and also would possess a shape conducive to applications in stereoselective synthesis. In proof of this, he synthesised compound **1.18a-b**: these compounds and analogues thereof were found to have barriers to rotation of 28-30 kcal.mol^{-1}.[75] This barrier to rotation is sufficiently high to envisage the possibility of stereoselective cyclisation reactions at room temperature and below.



1.18a **1.18b**

Figure 1.16: Atropisomeric compounds synthesised by Curran

As depicted in Scheme 1.3, enantioenriched *N*-allyl-*o*-iodoanilides of type **1.18b** can undergo radical cyclisation to oxindole **1.19** with faithful chirality transfer (enantiomeric ratio > 90:10), thus proving the feasibility and utility of atropisomeric molecules as pro-chiral compounds.[53]



Scheme 1.3: Radical cyclisation of anilide 1.18b.

Soon after Curran's initial report, other groups began investigating anilide derivatives for atropisomeric activity: Simpkins[77] and Taguchi[78] both synthesised derivatives of compound **1.18** where the R^2 and R^3 groups (i.e. those not on the phenyl ring) were altered. Simpkins found that good stereocontrol was obtained with alkylation and aldol reactions of anilides **1.18c** (R^1=^{t}Bu, R^2=Et, R^3=Me/MEM), providing further proof of the utility of atropisomeric anilides, while Taguchi used anilide **1.18d** (R^1=^{t}Bu, R^2=$CHCH_2$, R^3=CH_2CHCH_2) in a Diels-Alder reaction with cyclopentadiene, which proceeded with high diastereoselectivity. Koide[62]also developed an asymmetric synthesis of atropisomeric benzanilides such as **1.20** using planar chiral (arene)chromium complexes.

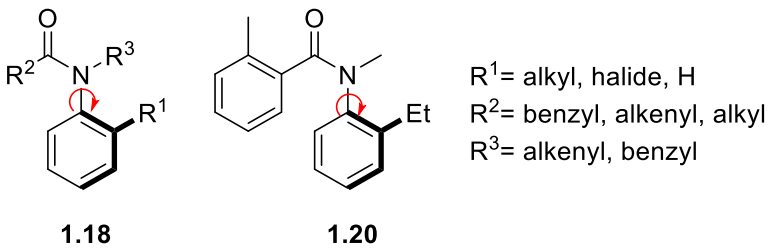


Figure 1.17: Atropisomeric anilides 1.18 and benzamides 1.20.

1.1.2.2 Enamides

Similar to anilides are enamides **1.21**, which are remarkably versatile building blocks in organic synthesis, if the enamide is secondary (R^2=H).[79,80] The chemistry of tertiary enamides has only recently started to receive attention.[81] The reason for this is that

tertiary enamides have complicated rotation dynamics due to rotation around both the amide *N*-CO bond and the *N*-alkenyl bond (Figure 1.18).

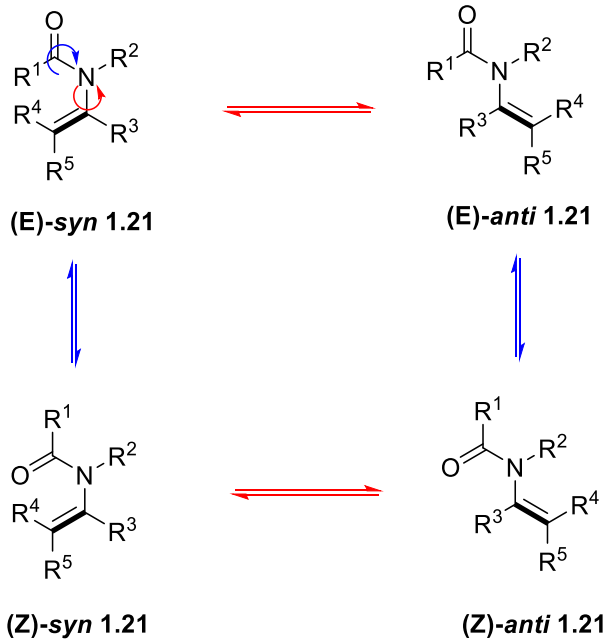


Figure 1.18: General enamide configurational possibilities.

The amide bond rotation barrier in enamides **1.21a** (R^1=R^2=Me, R^3=R^4=R^5=H) was calculated to be 14.0 kcal.mol^{-1}, lower than the general value for amides (15-20kcal.mol^{-1}).[82,83] Clark reported in 2009 on the bond rotation dynamics of a series of enamides **1.22**, with a view to determining which substitution patterns would yield resolvable atropisomers.[71] Cycloalkenyl-*N*-alkylacetamides of this variety exhibit a clear preference for the *E*-rotamer of the amide, as shown (Figure 1.19), and exhibit axial chirality on an NMR timescale,[71] which can be exploited in NMR studies to calculate the barrier to rotation around the *N*-cycloalkenyl bond.

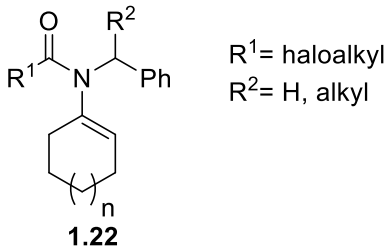
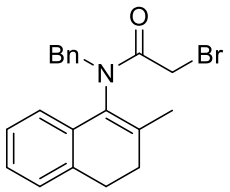


Figure 1.19: Enamides investigated by Clark

Substitution at the alkene was found to increase the barrier to rotation about the *N*-cycloalkenyl bond, when a dihydronaphthyl moiety replaced the simple cycloalkenyl. The tetrasubstituted enamide **1.23** exhibits rotation so slow that individual enantiomeric atropisomers can be separated by preparative chiral HPLC.[69,84]



1.23

Figure 1.20: Atropisomeric tetrasubstituted enamide 1.23.

The rotation barrier associated with the *N*-cycloalkenyl bond in compound **1.23** has been estimated to be approximately 29.3kcal.mol^{-1}, corresponding to a half-life of 5.6 years at 298K. It is possible that analogues of this structure would allow the tailoring of molecules which exhibit correct rotation dynamic requirements necessary for stereoselective cyclisation reactions.

1.1.3 Measurement of the barrier to rotation in atropisomers

Atropisomers have a half-life which can be measured using the barrier to rotation around the atropisomeric bond. The investigation into this barrier to rotation in benzamides and naphthamides **1.24** and **1.25** has been done by Clayden using three different analytical methods: variable temperature NMR spectroscopy, resolution by HPLC on chiral stationary phase, followed by analysis of subsequent racemisation, and chromatographic separation on silica, followed by analysis of subsequent epimerisation.[45] Clayden found that VT NMR analysis was of most use when considering singly *ortho*-substituted benzamides (R^2=H), as chromatography methods could not achieve separation of atropisomers when the barrier to rotation was lower.

However, when dealing with disubstituted benzamides **1.24** or with naphthamides **1.25**, chromatographic methods could achieve separation of the atropisomers and thus these were preferred.

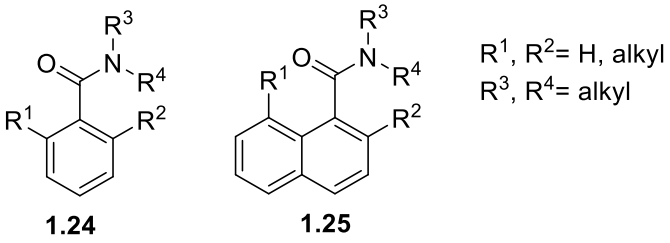


Figure 1.21: Benzamides and naphthamides studied by Clayden.

The VT NMR method was also used by Clark[69,71] to calculate the barriers to rotation in a series of *N*-benzylated enamides (for example **1.26**, Figure 1.22).

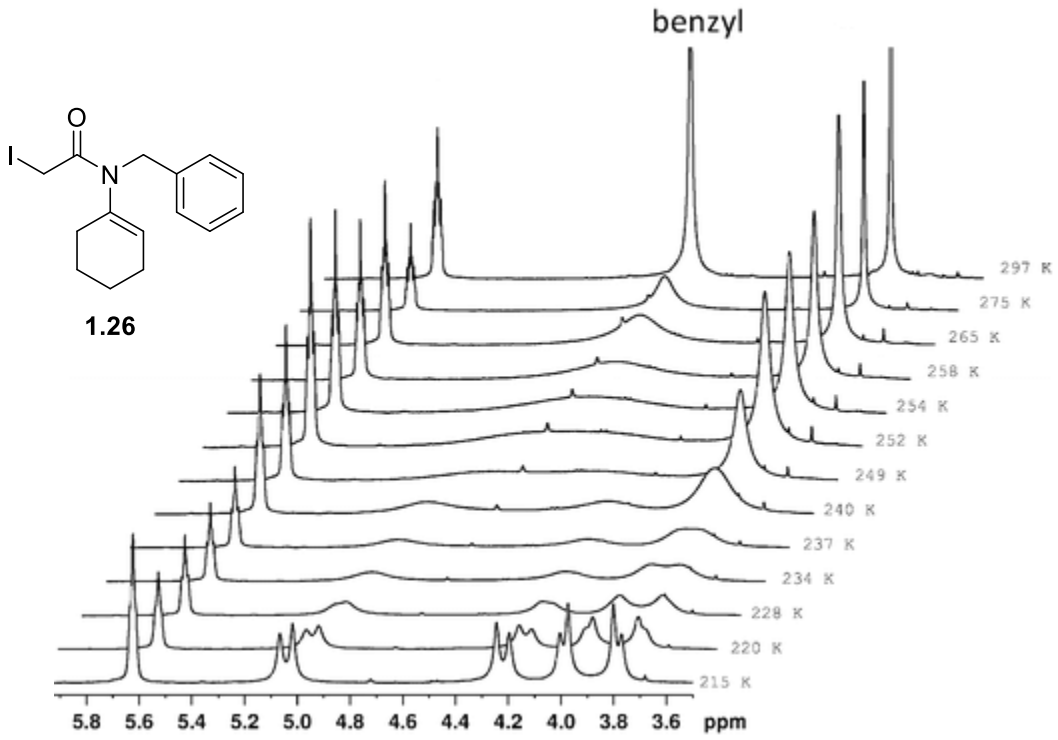


Figure 1.22: Expansion of the ^{1}H NMR spectra of 1.26 at 215−297 K.[71]

Low temperature NMR analysis of **1.26** showed the benzyl protons to be diastereotopic under these conditions, appearing as mutually coupled doublets due to slow rotation about the *N*-alkenyl bond. When heated to room temperature these doublets coalesce

into a singlet, as the rate of rotation increases. The rotational rate constant, k_{rot}, was calculated for each temperature using line-fitting software, and an Eyring plot of these values allowed rate of rotation at 298 K, k_{298}, to be calculated. This was then factored into the Arrhenius equation to give the barrier to rotation about the *N*-alkenyl bond. Compounds which had *N*-alkenyl barriers to rotation too high to be calculated by this method, such as **1.23**, were analysed using chiral HPLC (Figure 1.23).[69]

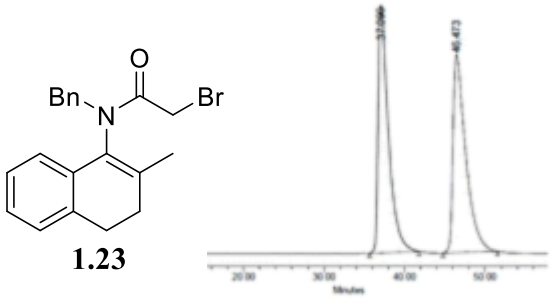
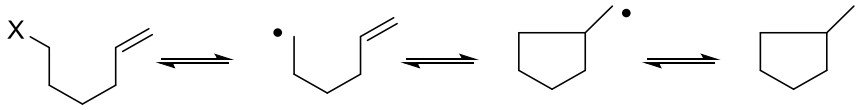


Figure 1.23: Chiral HPLC trace for compound 1.23.[69]

1.2 Radical Cyclisations

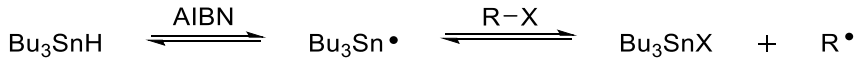
1.2.1 Traditional radical cyclisations

Radical cyclisation reactions are perhaps the simplest way of forming a carbocycle or heterocycle. As shown in Scheme 1.4, the generally accepted mechanism consists of generation of the radical by abstraction of a leaving group, commonly a halide[85–87], followed by cyclisation of the radical onto an available multiple bond, and finally termination of the radical, which can be done in a variety of ways depending on the reaction conditions.



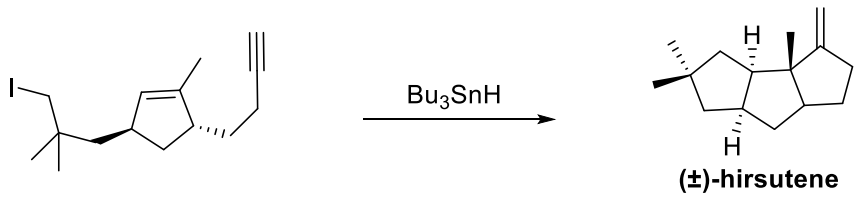
Scheme 1.4: Overall mechanism of a radical cyclisation

Radical termination can occur by being trapped by a radical scavenger, undergoing a fragmentation reaction, or being converted in an electron transfer reaction to a cation or anion. Traditional radical cyclisations used organostannane or organosilane reagents, such as Bu_3SnH[85,86] or $(SiMe_3)_3SiH$[88], to mediate the reactions, accompanied by a radical initiator such as AIBN or ABCN (Scheme 1.5).



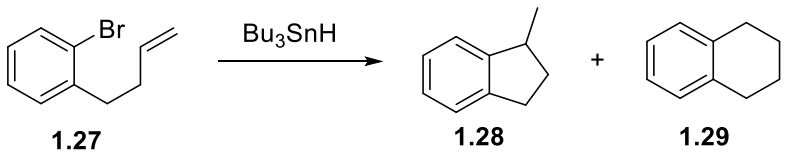
Scheme 1.5: Radical generation using Bu_3SnH and AIBN.

These conditions have broad utility and were thus widely used for many years. They have been used to synthesise heterocycles containing nitrogen, oxygen, sulfur, and silicon, amongst others,[89] as well as carbocycles. A review by Curran in 1993 detailed some uses for these conditions in the synthesis of natural products, including a tandem radical cyclisation as a key step in the synthesis of cyclopentanoid (±)-hirsutene (Scheme 1.6).[90,91]



Scheme 1.6: Key step in the synthesis of hirsutene.

These conditions were also useful for mediating aryl radical cyclisation reactions (Scheme 1.7), and are now widely used for the synthesis of fused aromatic compounds. Work by Beckwith[92] showed that aryl radicals will cyclise primarily in a 5-*exo* fashion in compounds such as **1.27**. The 6-*endo* product does not arise in this case by direct cyclisation, but *via* a neophyl rearrangement from the 5-*exo* product.

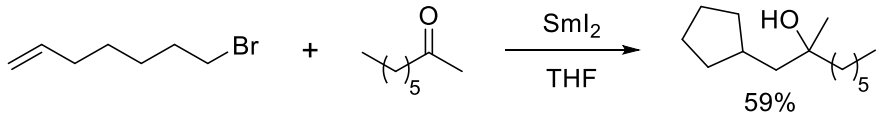


Scheme 1.7: Aryl radical cyclisation.

These conditions, while exceptionally useful in the arena of carbon-carbon bond formation, have several non-trivial drawbacks: for organostannanes the reagents are extremely toxic, the residues of the reagents are difficult to remove from the product, rendering purification more complicated, and the reductive nature of the reaction is also an issue.[89] The termination of the reaction by hydrogen abstraction means that there is a loss of two functional groups during the transformation. The purification issue is of particular concern when considering pharmaceutical applications: acceptable impurity levels are very low, and as such tributyltin hydride reactions in particular are undesirable. Equally, the need for comparatively large amounts of mediating species (stoichiometric quantities of organostannane reagent are required) and the cost of the reagents contribute to the undesirability of these conditions. Despite all this, tributyltin hydride and AIBN are used to this day in radical cyclisation reactions, as they have an unparalleled range of utility and are often used to investigate the scope of cyclisation of a starting material.

1.2.2 Modern radical cyclisation alternatives

Attempts were therefore made to find alternative radical cyclisation conditions to remove some of the disadvantages of the organostannane and organosilane methods. In 1981, Kagan reported the use of samarium diiodide in water to mediate the reductive cyclisation of 6-bromo-1-hexene, where the cyclised intermediate was coupled with 2-octanone (Scheme 1.8).[93]

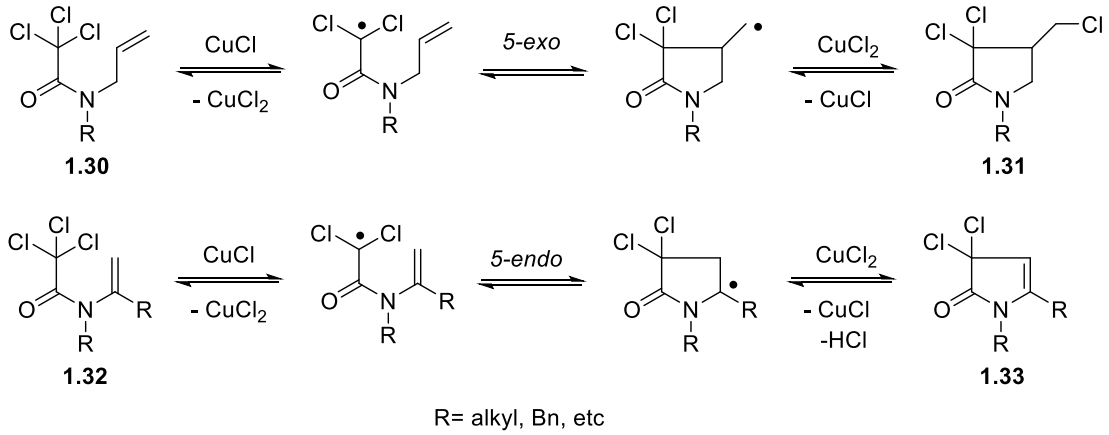


Scheme 1.8: SmI_2/H_2O-mediated cyclisation of 6-bromo-1-hexene.

The radical is generated by radical abstraction from the R-X species by Sm^{2+}, generating Sm^{3+} and the radical anion, which then loses X^- to generate the $R^{\cdot}$ radical. Termination occurs by proton abstraction from the solvent. This work was later expanded on by Molander, who introduced HMPA as an additive and co-solvent to facilitate cyclisation,[94] given the insolubility of many starting materials in water. These conditions maintain many of the disadvantages of the organostannane cyclisations, but the residues are easier to remove from reaction mixtures, simplifying product purification, and the reaction conditions are also milder, as a common reaction temperature is 25°C instead of 80°C for the tin methods.[94] Ease of purification was also the rationale behind solid-supported tributyltin hydride cyclisation: when a series of bromoethylacetals were attached to a polymer resin and reacted under standard tributyltin hydride radical cyclisation conditions, the corresponding set of γ-butyrolactones were generated in good yield and released from the resin by Jones oxidation, once all organostannane residues had been removed.[95] The purification issue can therefore be avoided by judicious substitution of the organostannane conditions for alternative radical generation options, or by solid-supported starting materials, but that does not change the reductive nature of the reaction, nor is it rendered cost-effective or non-toxic. Alternative radical cyclisation methods were therefore required to combat these issues.

1.2.3 Atom Transfer Radical Cyclisation

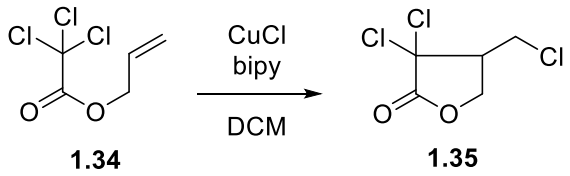
The atom transfer radical cyclisation process, derived from the similar atom transfer radical polymerisation reaction, was reported by several groups in the mid-to-late nineties as an efficient radical cyclisation process of haloacetates and haloacetamides onto alkenes[95–100] and alkynes.[101] This method has a number of advantages over traditional radical cyclisation methods: it is cost-effective, easy to work up and required catalytic amounts of copper, rather than the stoichiometric amounts used in tin cyclisations.[86]



Scheme 1.9: CuCl-catalysed ATRC of haloacetamides 1.30 and 1.32.

The reaction proceeds *via* a catalytic redox mechanism. For **1.30** the radical is generated by abstraction of a chlorine radical by CuCl. This radical then cyclises onto the double bond in a 5-*exo* fashion, and the primary radical thus created removes a chlorine radical from $CuCl_2$, regenerating the CuCl catalyst. In both cases shown in scheme 1.9, the ATRC reactions are selective for the product shown,[86,100] for **1.32** and despite the usual preference of 5-*exo* radical cyclisation the e*ndo* pathway predominates. For compounds **1.32** this selectivity was at first not fully understood and the observed regioselectivity was rationalised by the steric disfavouring of the 4-membered ring systems due to ring strain. However, it became clear that structures **1.32** are not planar around the enamide functionality and as a consequence exhibit

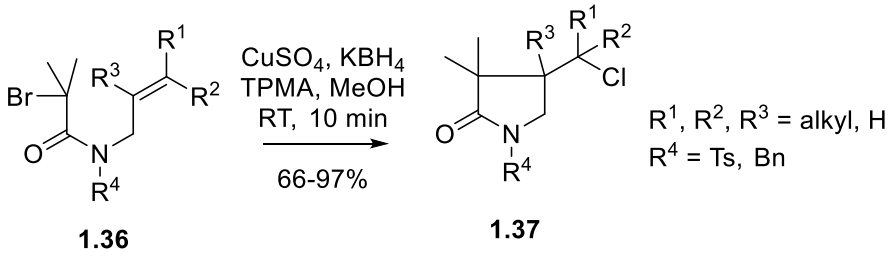
atropisomerism around the *N*-alkenyl bond (see section 1.1.2.2). This places the carbon at the 5-position with the correct orbital overlap for efficient cyclisation. Various attempts were made to improve the process by altering the solvent, temperature and adding a ligand for the copper. A comprehensive review by Clark[86] covered all the work done in the area up until early 2002 and more recently in 2016 this has been updated.[102] In particular, certain copper ligands have been proven to accelerate the reaction rate, allowing the cyclisation of less reactive substrates. The addition of 2,2'-bipyridine (bipy) in a 1:1 ratio with CuCl to the reaction of haloacetetate **1.34** was found to accelerate the rate of reaction fourfold.[86]



1.34 **1.35**

Scheme 1.10: ATRC reaction of haloacetate 1.34.

N,N,N',N'-Tetramethylethylenediamine (TMEDA) also proved useful in the optimisation of the ATRC reaction, and made the catalyst system ($Cu(TMEDA)_2Cl$) more reactive than the bipy ligands, improving yields as well as allowing for lower catalyst loadings.[86] Further work introduced additives such as AIBN to accelerate the reaction further[103] and reported the success of the ATRC-AGET (Activators Generated by Electron Transfer) method, which altered the copper source to the cheap and oxidatively stable $CuSO_4$, in extremely low loading (0.05%) and used it in conjunction with borohydride salts to cyclise haloacetamides **1.36** in good to excellent yield within ten minutes (Scheme 1.11).

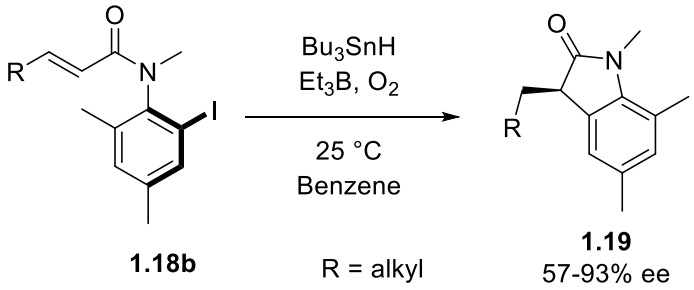


1.36 **1.37**

Scheme 1.11: ATRC-AGET reaction of haloacetamide 1.36.

1.2.4 Radical cyclisation of atropisomers

Control of absolute stereochemistry in radical cyclisation reactions has long been a synthetic challenge. Several strategies were attempted to achieve this, of which one of the most successful was chiral transfer from an atropisomeric anilide. Curran used the axial chirality occurring in iodoanilides such as **1.18** to show that efficient chiral transfer could be achieved. Enantiomerically enriched samples of **1.18b** were cyclised to give chirality transfer in the oxindole product of 72-96%, as discussed in section 1.1.2.1 (pg 14).[53]

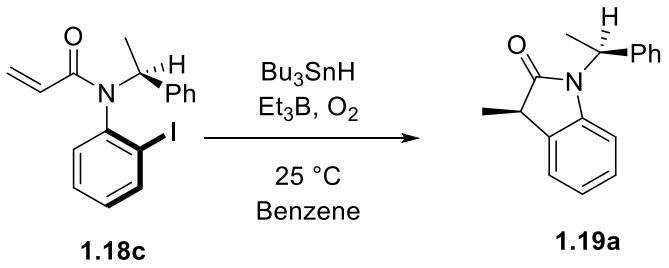


1.18b R = alkyl **1.19** 57-93% ee

Scheme 1.12: Cyclisation of 1.18b.

It is unsurprising that radical cyclisation was deemed an exciting possibility for application to atropisomers. The rapidity of cyclisation of aryl radicals (rate of radical cyclisation on the order of 1 x 10^{-8} s^{-1} for 5-*exo* cyclisation)[104] compared to the rate of rotation around atropisomeric bonds implied the possibility of chiral transfer from a single atropisomer of the starting material to the product, which was seen to be the case for the above example of radical cyclisation under traditional conditions with no

chirality-inducing additive in the reaction. An excellent review by Sibi and Sivaguru details the work done on reactions using atropisomers (literature to 2015).[40]

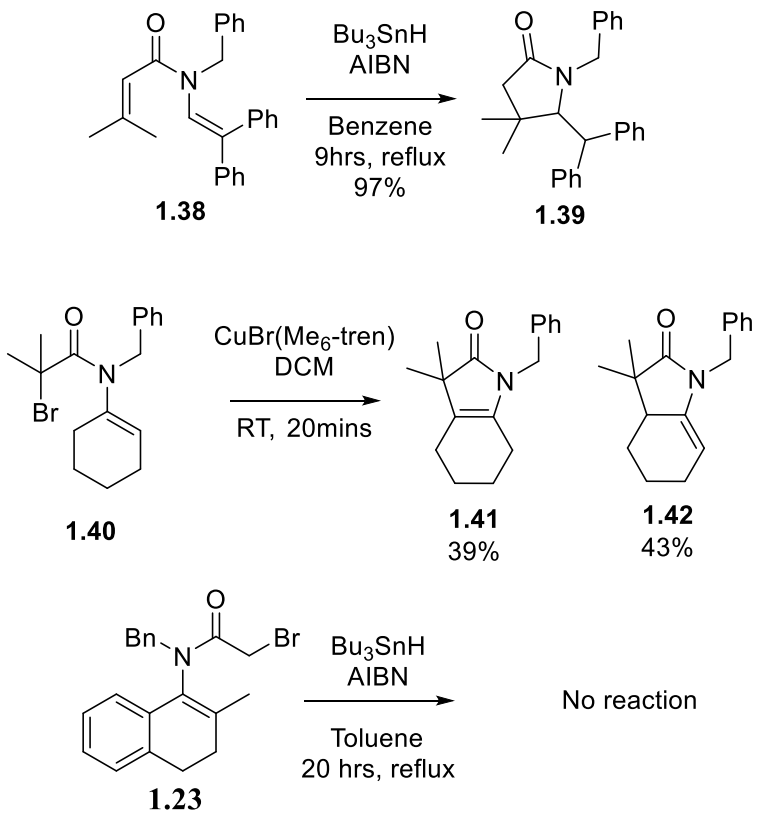


1.18c **1.19a**

Scheme 1.13: Radical cyclisation of 1.18c.

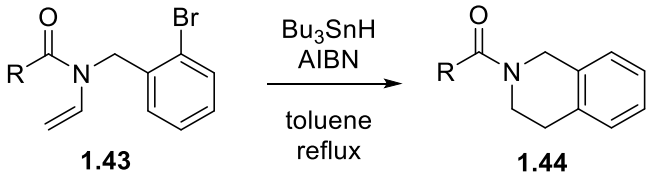
Clayden proposed that compounds such as **1.18c** possess a "chiral memory" when being cyclised, as the abstraction of the iodine to form the aryl radical must necessarily diminish the barrier to rotation, and therefore lead to an overall lack of chiral transfer.[46,48] That this did not occur (84% chiral transfer was observed when the resolved starting material was used) argued that the compound retained some memory of its previous chiral nature. This extra chiral element, however, proved unnecessary to obtain chirality transfer, as seen with cyclisation of **1.18b**, which contains no chiral point and merely exhibits axial chirality. Axially chiral molecules can thus be cyclised in such a way as to achieve chiral transfer.

Radical cyclisation of enamides has also been reported using conditions detailed in sections 1.2.1-1.2.3. Ishibashi used tributyltin hydride to cyclise enamide **1.38**,[105] while Clark used both Bu_3SnH and ATRC methods to cyclise **1.40** (generating in both cases the 5-*endo* product),[100] providing examples of both *exo*- and *endo*-cyclisation pathways in enamides. Selectivity for each pathway is largely dependent on the sterics of the substrate being cyclised: 5-membered rings exhibit minimal ring strain compared to 4-membered rings, and in general the 5-position is closest to the reacting radical. Unfortunately, cyclisation of atropisomeric enamide **1.23** proved unsuccessful, yielding only reduction products.



Scheme 1.14: Radical cyclisations reported by Ishibashi and Clark.

Radical generation and cyclisation on the acyl side of the enamide has therefore been reported,[71,106] but aryl radical enamide cyclisations have been less investigated. Ishibashi[107] has reported cyclisations of *N*-bromobenzylenamides such as **1.43**, which were found to cyclise in a 6-*endo*-*trig* manner in relatively low yield (20-40%).



Scheme 1.15: *N*-bromobenzylenamide radical cyclisation.

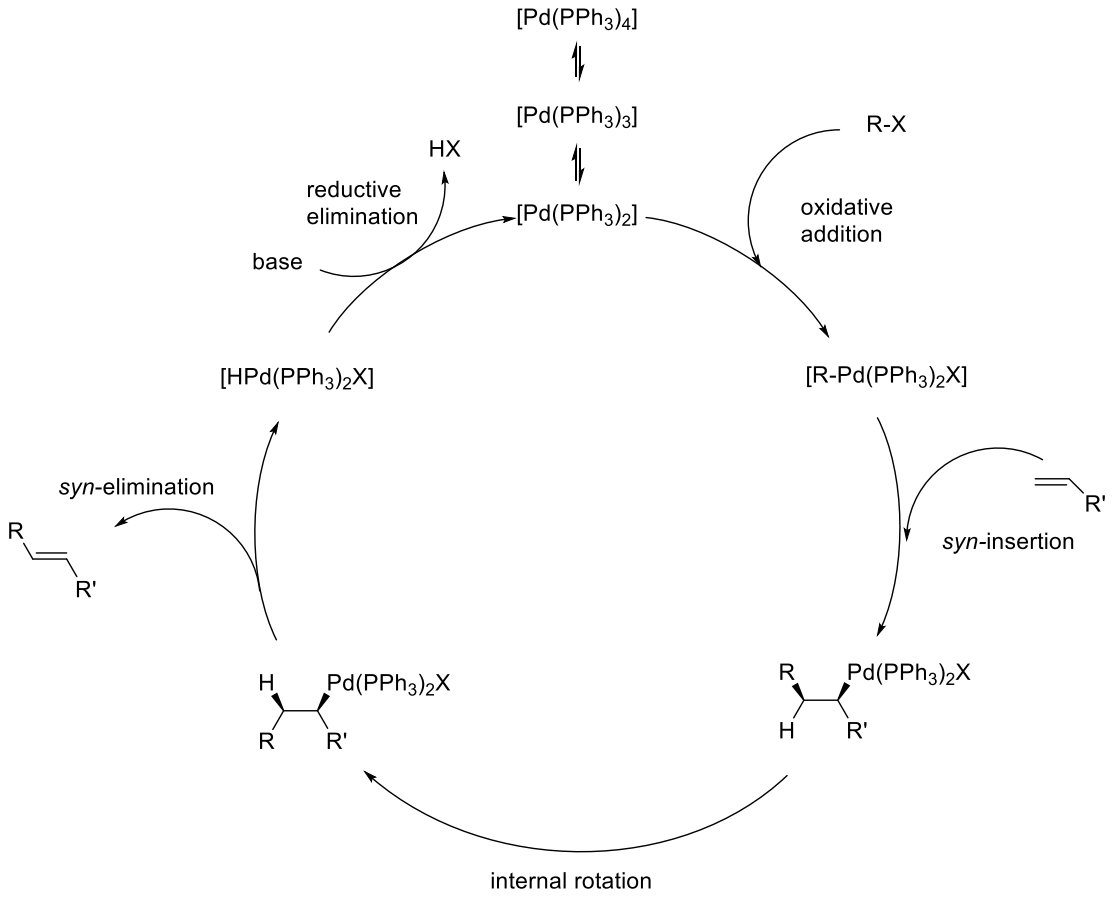
The use of radical cyclisation methods to cyclise atropisomers is therefore sufficiently well-established in anilides, although there has been less research into the behaviour of *N*-halobenzylenamides under common radical cyclisation conditions.

1.3 The Heck reaction

The Heck reaction is another powerful tool for carbon-carbon bond formation. First reported in 1968 by Heck[108], it started gaining traction as a useful tool in organic synthesis in the late eighties. Several excellent reviews have covered the area: by De Meijere[109] up until 1994,[109] by Shibasaki[110] until 2004, and by Muzart[111] until 2011.

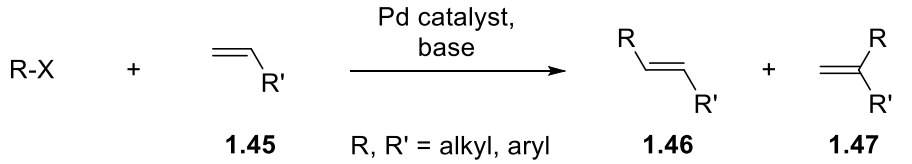
1.3.1 Mechanism and conditions of the Heck reaction

The Heck reaction proceeds *via* a catalytic cycle, as shown in Scheme 1.16. The catalytically active compound is the coordinatively unsaturated 14-electron [$Pd(PPh_3)_2$] complex, commonly generated *in situ* from [$Pd(PPh_3)_4$], to which R-X (R= aryl or alkenyl, X= halide or triflate) oxidatively adds, followed by *syn*-insertion of the alkene into the R-palladium bond. This is followed by β-hydride elimination of the alkene product and reductive elimination of HX from the palladium complex using base, regenerating the initial active catalyst [$Pd(PPh_3)_2$].[109–111]



Scheme 1.16: General mechanism of a Heck reaction using $Pd(PPh_3)_4$.

The reason for the initial lack of interest in the Heck reaction as a tool for organic synthesis can perhaps be supplied by the lack of regioselectivity observed when asymmetric alkenes were used, as well as isomerisation occurring after the fact. Thus, reaction of **1.45** with R-X will generate two regioisomers of the alkene product, **1.46** and **1.47**, depending on how the alkene inserted onto the palladium. This will in turn largely depend on the steric hindrance surrounding the alkene.[109–111]



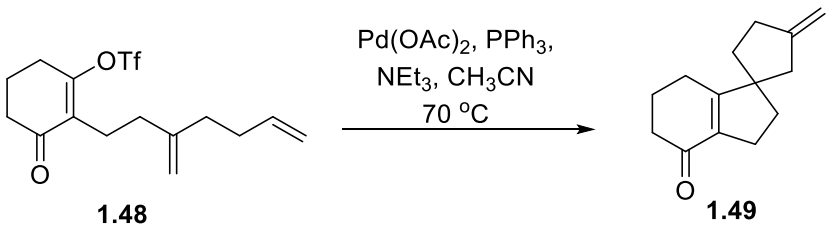
Scheme 1.17: Two possible regioisomeric products of the Heck reaction.

Generally speaking, there are six variables to be considered in a Heck reaction protocol: the pre-catalyst, the ligand, the base, the solvent, the temperature and the

additive, although this last one is not always necessary.[112] Common pre-catalysts include both Pd(II) and Pd(0) species, of which the most frequently used are $Pd(OAc)_2$ and $Pd_2(dba)_3$,[112] although palladacycles can also be used.[113,114] Ligands must be weak electron donors such as tertiary phosphines (PPh_3, P^tBu_3, etc)[109], and in the case of asymmetric reactions chiral ligands such as BINAP[112] can be used. The choice of base in the reaction is of lesser importance, as most inorganic bases (K_2CO_3, $CaCO_3$ etc) can be used, or alternatively tertiary amine bases such as triethylamine.[109,112] Polar aprotic solvents such as THF, acetonitrile and DMF are usually preferred for asymmetric Heck reactions, although benzene, toluene and DCE can also be used.[109,112] Beletskaya reported in 1989 the successful Heck reaction of iodobenzoic acids and acrylic acid in aqueous media[115], which introduced the possibility of running these reactions in water. The reaction temperature can range from room temperature to over 100^{o}C, depending on the reactivity of the starting materials, and in particular of the organohalide, as the oxidative addition of this compound to the palladium complex is generally considered to be the rate-determining step of the Heck reaction.[112] In certain cases additives can be used to accelerate the rate of reaction: silver salts are particularly popular due to their ability to act as halide scavengers, removing the halide or triflate from the palladium complex after oxidative addition of the R-X compound and thereby vacating a coordination site on the palladium so insertion into the alkene is easier.[112]

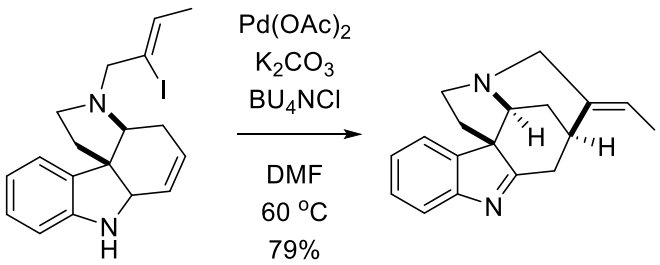
1.3.2 The intramolecular Heck reaction

The first case of an intramolecular Heck reaction was reported by Overman and co-workers in 1989[116], using palladium acetate to intramolecularly cyclise a set of trienyl triflates **1.48**.



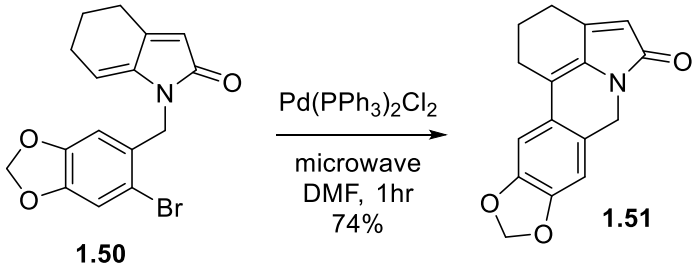
Scheme 1.18: Trienyl triflate cyclisation under Heck conditions

The use of intramolecular Heck cyclisations in organic synthesis accordingly became widespread[109,112] and gained a foothold in natural product synthesis: in 1993 Rawal synthesised (±)-dehydrotubifoline[117] (Scheme 1.19), a member of the *Strychnos* alkaloid family, which combines an intricate structure with powerful physiological activity.



Scheme 1.19: Synthesis of (±)-dehydrotubifoline

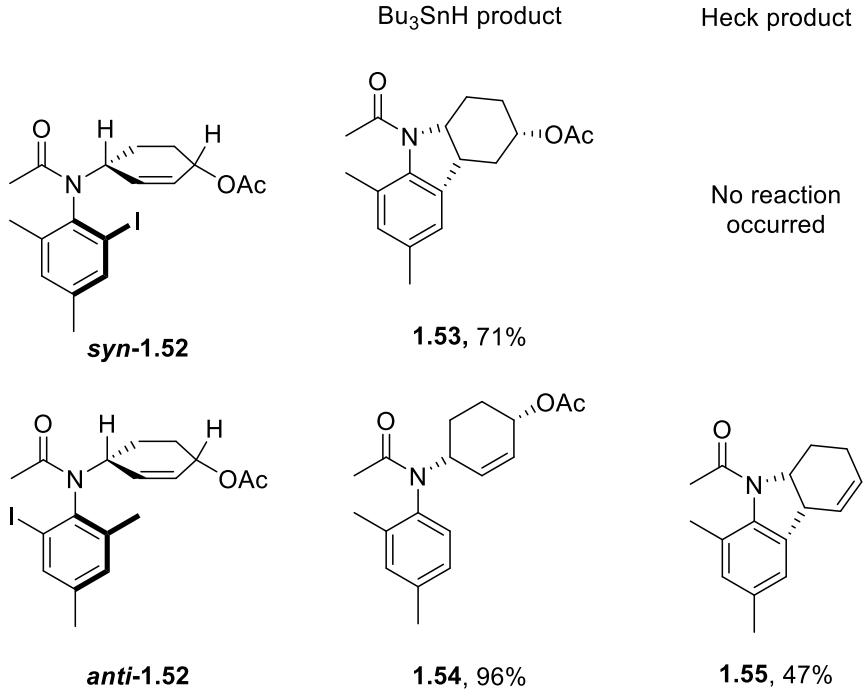
The use of Heck reactions in natural product synthesis has not flagged over the past twenty years: earlier this year Hilton used a microwave-assisted intramolecular Heck reaction to form the key pentacyclic core of lycorane **1.51** from **1.50**.[118]



Scheme 1.20: Key step in the synthesis of lycorane.

1.3.3 Intramolecular Heck cyclisations of atropisomers

The use of chiral ligands in Heck cyclisation to obtain chiral transfer to the product has been well documented,[40,109,112,119,120] but the use of atropisomerism alone to ensure chiral transfer in such reactions has been less investigated. In 2011, Curran and co-workers published a paper comparing the radical and Heck cyclisations of a series of diastereomeric *ortho*-haloanilide atropisomers, and found that the results of radical and Heck cyclisations of iodoanilides **1.52** depend on the configurations of the chiral axis and the stereocenter.[66] If the precursor was in the *syn*-position, tin cyclisation resulted in a good yield of cyclised product **1.53**, while Heck cyclisation did not take place. If the precursor was in the *anti*-position, radical cyclisation did not occur, and instead the reduced product **1.54** was obtained, but Heck cyclisation proceeded with acceptable yield to give **1.55**.



Scheme 1.21: Comparing tin and Heck cyclisations.

In the case of the organostannane cyclisation, *anti*-geometry resulted in the reduced product 1.54 due to the relative rates of rotation and reduction: the reduction pathway was in this case much faster than the cyclisation pathway (this would involve both a rotation of the aryl ring to bring it closer to the double bond, and the cyclisation itself); whereas in the *syn*-geometry, the generated radical is sufficiently close to the double bond to make the rate of cyclisation greater than the rate of reduction, as the molecule is already in the correct configuration for cyclisation. For the Heck reaction, Curran postulated that once oxidative addition of the palladium had occurred, concomitant rotation around the *N*-aryl and *N*-cyclohexenyl bonds from the *anti*-geometry would bring the reacting sites closer together and thus enable cyclisation to occur, whereas *syn*-geometry would sterically hinder the iodine to such an extent that oxidative addition did not take place. Axial chirality can therefore have a dramatic effect on the outcome of a reaction.

1.4 Summary

Atropisomerism is exhibited by a wide range of natural products, as well as a growing range of synthetic molecules, including ligands for chiral catalysts and precursors for asymmetric reactions. Clark reported the atropisomeric behaviour of a series of *N*-benzylenamides, which could be separated at room temperature in order to allow reaction on isolated rotational isomers. Radical and Heck cyclisation methods are excellent tools for carbon-carbon bond formation, and can be used to cyclise atropisomeric compounds, in order to exploit the axial chirality exhibited to achieve chiral transfer to the product. Traditional Bu_3SnH radical cyclisation methods have been found to result in the widest range of products, but display different reactivity

towards atropisomers than Heck conditions. Axial chirality can therefore dictate the reactivity of a molecule. Herein investigations into the barrier to rotation exhibited by enamides related to those previously studied by Clark are reported, and the results of their cyclisations using different methods studied.

Chapter 2: Axially Chiral *N*-*o*-Halobenzyl-*N*-acetylenamides: Substituent Effects, Rotation Barriers, Conformation Effects and Implications for their Cyclisation Reactions.

2.1 Introduction

As discussed in Chapter 1, 2,6-disubstituted anilides **2.1a** (R^3 and $R^4 \neq H$) exhibit axial chirality due to slow rotation around the *N*-aryl bond.[51] Individual atropisomers of such anilides have been separated and shown to undergo a range of reactions,[121–123] including radical cyclisations with transfer of chirality.[53] Tertiary enamides **2.1b** also exhibit atropisomerism with barriers of rotation between 8-31 kcal mol^{-1} and half-lives for rotation up to 99 years at 298 K.[69]

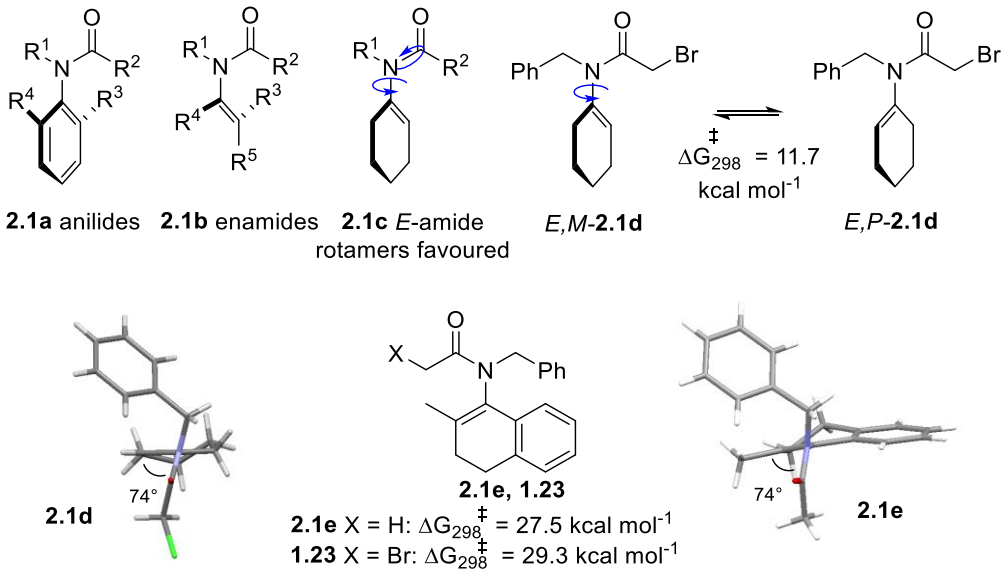
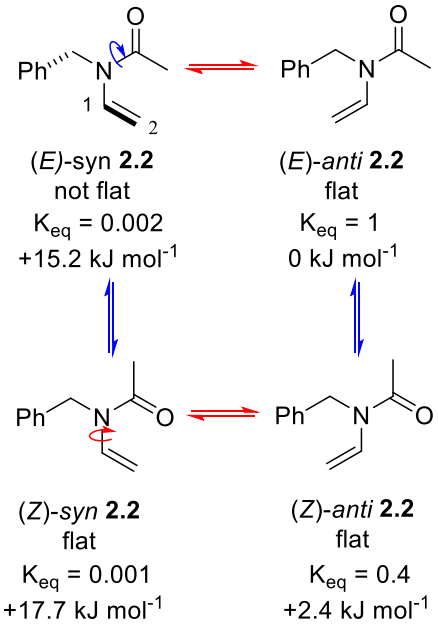


Figure 2.1: Structures of atropisomeric anilides and enamides.

Two forms of restricted rotation complicate the rotation dynamics of tertiary enamides **2.1c**: around the amide N-CO bond and around the *N*-alkenyl bond. The N-CO bond in **2.1b** ($R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$) has a measured barrier to rotation of 14.0 kcal mol^{-1}, lower[82] than the general amide value of 15-20 kcal mol^{-1}.[83] *N*-Cycloalkenyl-*N*-alkyl-acetamides such as **2.1c** prefer the amide N-CO *E*-rotamer[124] and exhibit

transient axial chirality on the NMR timescale. The rotational dynamics around the *N*-alkenyl bond are therefore easy to study by VT ^{1}H NMR.[124] Trisubstituted alkene derivatives **2.1d** have comparatively low barriers to rotation, unlike tetrasubstituted derivatives **2.1e-f**, which have barriers high enough that individual atropisomers can be separated at room temperature.[69] The X-ray structures of **2.1d-e** have both been solved[69] and confirm the N-CO *E*-rotamer geometry in the solid state. Structures **2.1d-e** both have torsional angles of the key *N*-alkenyl bond C=C-NC(O) of 74°, similar to related anilides.[125] The sum of the angles around the nitrogen atom in **2.1e** is 359.9°, confirming the planarity of the nitrogen. For relatively unsubstituted enamide **2.2**, computational analysis using the TZVP basis set[126] and the B3LYP-D3(BJ) functional[127] has proven the (*E*)-*anti* geometry to be the major contributor. Related anilides[125] show a similar effect at equilibrium, with a minor contribution from the (*Z*)-*anti* isomer (2:1) which is corroborated by ^{1}H NMR studies.[69]



Scheme 2.1: Calculated relative energies and equilibrium contributions of conformers

Interestingly, two diastereomeric versions of the non-polar (*E*)-*syn* **2.2** exists, where the vinyl group is orientated either in front or behind the plane of the amide, suggesting that the nature of the aryl group may have some influence upon rotation.

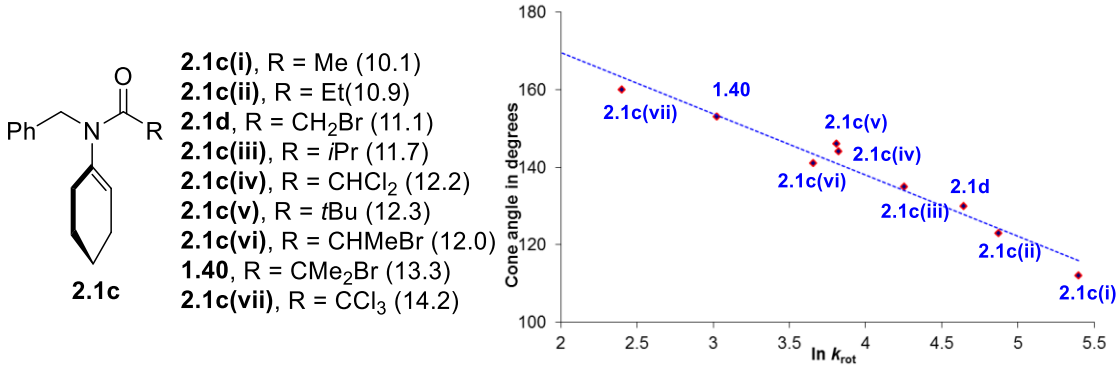
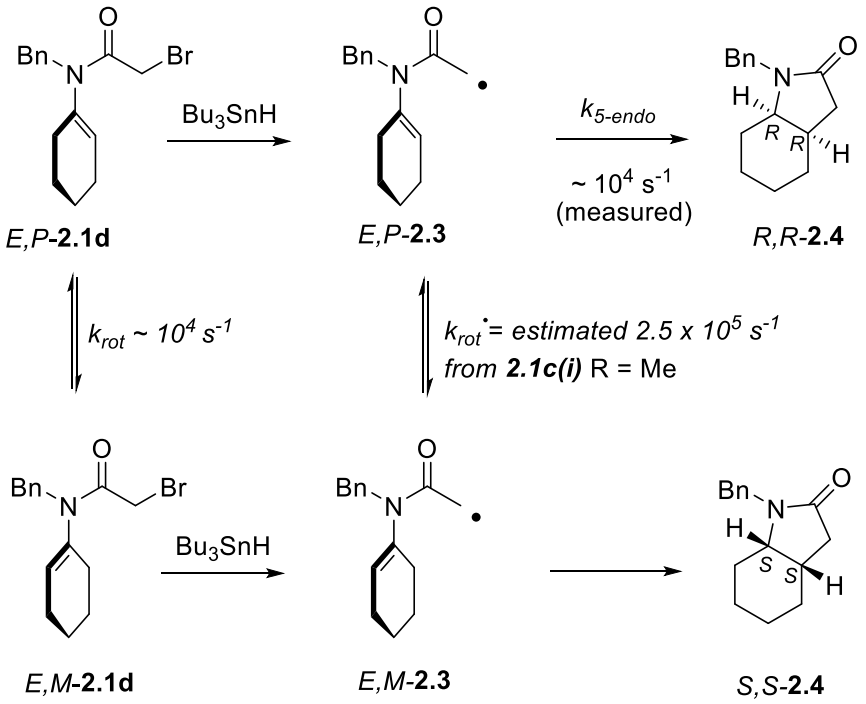


Figure 2.2: Correlation between R group cone angle (θ_R) and ln k_{rot} (ΔG (kcal/mol) in parentheses for each compound)

The acyl group in tertiary enamides exerts a solely steric effect on the *N*-alkenyl rotation barrier, according to a study of enamides[128] containing electron-poor and electron-rich substituents which demonstrated the negligible effect of the electronic nature of the group, and the effect of the size of the acyl group R in **2.1c** has been shown to be moderate.[71,72] An increase in barrier to rotation of 4.1 kcal mol^{-1} was observed when replacing an acetyl group (**2.1c(i)** $\Delta G^{\ddagger}_{298\ rot}$ = 10.1 kcal mol^{-1}) with a much larger trichloroacetyl group (**2.1c(vii)** $\Delta G^{\ddagger}_{298\ rot}$ = 14.2 kcal mol^{-1}). In the case of small acyl groups (**2.1c(i)**), rotation around the *N*-alkenyl bond is likely to be faster than around the amide N-CO bond (the amide barrier to rotation is approximately 14.0 kcal mol^{-1}, as discussed earlier); however, if the acyl group is larger (**2.1c(vii)**), the barriers to rotation are likely to be similar.[82]

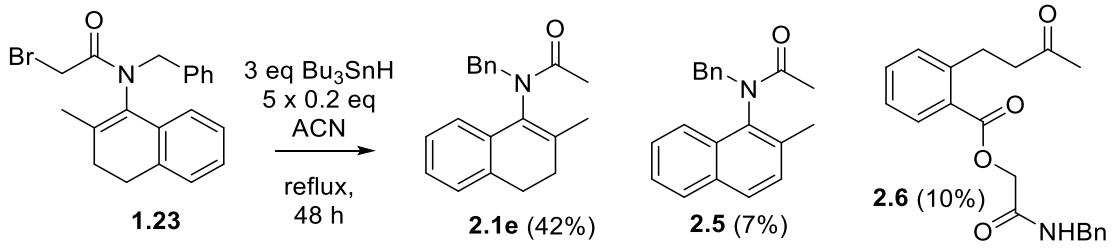
Enantiomerisation (*E,M* → *E,P*) is therefore possible *via* a number of potential mechanisms, ranging from simple enamide rotation to a geared process such as a cooperative coupled rotation of the amide and enamide (*E,M*→ *Z,M*→ *E,P*).[43] A plot of ln(k_{rot}) values for **2.1c** against the cone angle θ_R of the acyl substituent produced a

linear correlation[129] (R^2 = 0.958), suggesting that the rotation mechanism is likely to be the same for all compounds in the series and that the cone angle of the acyl substituent could be used to predict rotation barriers for a given series of enamides.



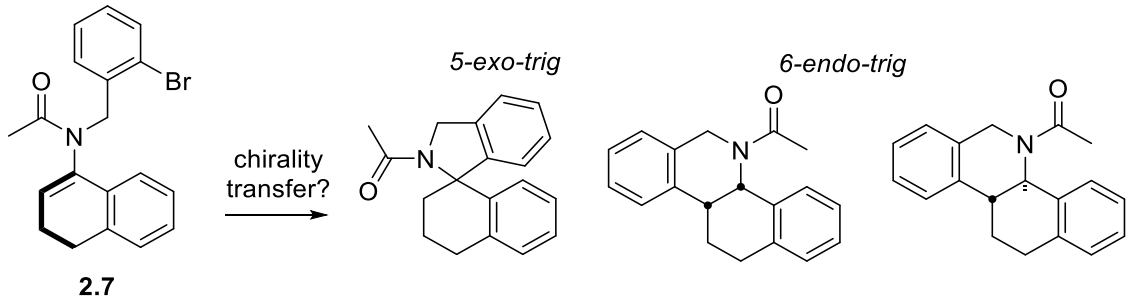
Scheme 2.2: Rotamers of radical 2.3 and Bu_3SnH mediated cyclisation to give 2.4

The bromide substrate **2.1d** is known to undergo reductive Bu_3SnH-mediated 5-*endo*-*trig* radical cyclisation to give heterocycle **2.4**.[130–132] Unfortunately, the rates of rotation around the *N*-cycloalkenyl bond of **2.1d** and intermediate radical **2.3** have been estimated to be comparable or faster than the rate of 5-*endo* cyclisation (**2.3** → **2.4**), precluding the possibility of chirality transfer during the cyclisation. Reaction of **1.23** could potentially lead to chirality transfer during cyclisation, as the rate of enantiomerisation of the intermediate radical was estimated to be 5.6 years at 298 K. However, attempts to cyclise **1.23** under high dilution conditions or at elevated temperatures failed and a number of non-cyclised materials were isolated.[69]



Scheme 2.3: Attempted cyclisation of 1.23 with Bu_3SnH

It is known that the rate of 5-*exo-trig* cyclisation of aryl radicals is about 5 x 10^8 M^{-1} s^{-1} at 50 °C, (5 x 10^4 times faster than the 5-*endo* cyclisation of **2.1c**).[104,133] Due to the inherently greater reactivity of aryl radicals compared to α-carbonyl radicals, it was desirable to investigate whether chirality transfer could occur during a 5-*exo-trig* or 6-*endo-trig* cyclisation of enamide-derived substrates such as **2.7**. These substrates are closely related to compounds **2.1d** but interestingly, their cyclisation reactions have not been reported in the literature.



Scheme 2.4: Is chirality transfer possible from *N*-*o*-halobenzyl-*N*-acetyl-enamides 2.7?

2.2 Aims of Chapter

- To gain a better understanding of the rotation dynamics (and hence potential chirality transfer) of substituted halobenzyl-derived enamides **2.8**.
- To prepare a range of substrates **2.8**, where the effect of halogen (X, Y), acyl (R^4) and alkene (R^1- R^3) substitution on the barriers to rotation around the *N*-C=C bond is assessed.
- Compare substituent effects, rotation barriers and conformation effects in **2.8** with those of anilides **2.1a** and enamides **2.1b** where R^1 is a simple benzyl group.

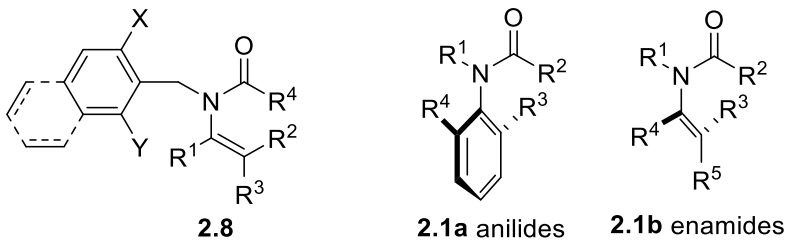
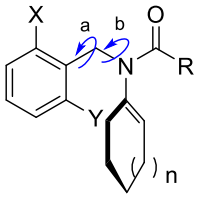


Figure 2.3: Substrates 2.8 used in this study and substrates 2.1a and 2.1b used for comparison.

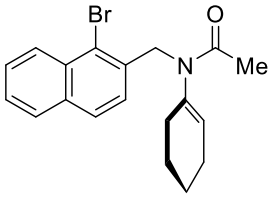
2.3 Initial choice of targets.

Despite the remoteness of any *ortho* aryl substituents to the enamide bond in substrates **2.8**, there is evidence from modelling and X-ray structures (already highlighted) that the benzyl substituent has the potential to influence rotation around the *N*-alkenyl bond. *N*-Cycloalkenyl-*N*-benzylacetamide derivatives **2.8a-u** were prepared because they should be amenable to analysis using variable temperature (VT) NMR. However, if X ≠ Y and the substituents are both large, then a further complication of a second element of restricted rotation around bonds 'a' or 'b' may arise in **2.8**.[70] This would make any variable temperature ^{1}H NMR spectra more difficult to analyse. In order to

remove the possibility of diastereomers arising from differently substituted 2,6-disubstituted aryl groups, those where X = Y, (e.g. **2.8f-h**) were focussed on initially. For monosubstituted analogues (e.g. **2.8b-e**, X =H, Y = halogen) it was expected that free rotation around bonds 'a' and 'b' would not be hindered significantly due to one of the *ortho* substituents being a hydrogen atom. A range of molecules with different ring (n = 1-3) and acyl group (R) sizes were prepared as these are known to effect barriers to rotation.[69]



2.8



2.9

n = 1

2.8a X= H, Y = H, R = Me
2.8b X= H, Y = F, R = Me
2.8c X= H, Y = Cl, R = Me
2.8d X= H, Y = Br, R = Me
2.8e X= H, Y = I, R = Me
2.8f X= F, Y = F, R = Me
2.8g X= Cl, Y = Cl, R = Me
2.8h X= Br, Y = Br, R = Me
2.8i X= H, Y = H, R = Et
2.8j X= H, Y = Br, R = Et
2.8k X= Br, Y = Br, R = Et
2.8l X= H, Y = H, R = *i*Pr
2.8m X= H, Y = Br, R = *i*Pr
2.8n X= Br, Y = Br, R = *i*Pr

n = 2

2.8o X= H, Y = Br, R = Me
2.8p X= Br, Y = Br, R = Me
2.8q X= H, Y = Br, R = Et
2.8r X= H, Y = Br, R = *i*Pr
2.8s X= Br, Y = Br, R = *i*Pr

n = 3

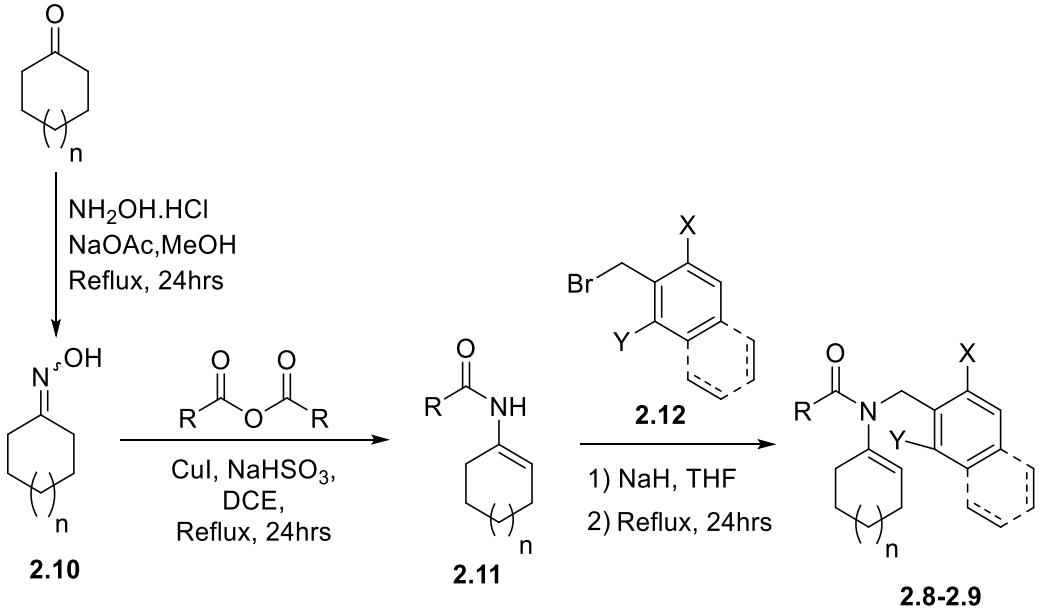
2.8t X= H, Y = Br, R = Me
2.8u X= Br, Y = Br, R = Me

Figure 2.4: Substrates 2.8a-u and 2.9 used in this study

2.4 Synthesis of targets.

Compounds **2.8a-u** and **2.9** were prepared in a two-step procedure from the corresponding oximes **2.10** by an initial copper iodide mediated reaction to give the secondary enamides **2.11**. Deprotonation of the enamide **2.11** with NaH in dry THF

followed by addition of the appropriate benzyl bromide **2.12** furnished the desired precursors **2.8-2.9**.



Scheme 2.5: Synthesis of substrates 2.8-2.9

Where the oxime **2.10** was not available commercially, it was prepared from the cyclic ketone by reaction with hydroxylamine hydrochloride and NaOAc in MeOH at reflux for 24 hrs.

2.5 Method for measuring barriers to rotation (^{1}H VT NMR).

The barriers to rotation around C-N bonds in anilides,[45] benzamides,[45,62] and enamides[69,71,72] have been measured using ^{1}H VT NMR analysis. The *N*-benzyl enamides **2.8-2.9** are particularly well suited for analysis using this approach as they are expected to have barriers within the range accessible by this technique (8-20 kcal mol^{-1}).[69] This is illustrated below using data for **2.8g**.

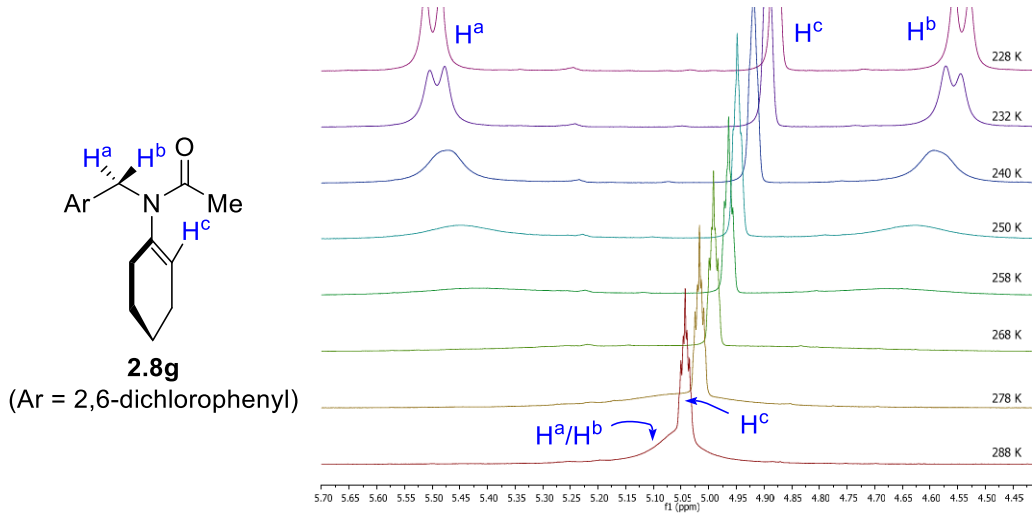


Figure 2.5: 500 MHz ^{1}H VT NMR of 2.8g between 228-288 K in d_8-toluene

The two benzyl methylene protons H^a and H^b appear as a singlet in the ^{1}H NMR when the *N*-alkenyl bond is rotating freely (**2.8g**, br s, 5.15-4.95 ppm at 288 K), and as two mutually coupled doublets (5.50 and 4.55 ppm at 228 K) when the rotation about the N-C=C bond is slow: the protons become diastereotopic due to the orthogonal nature of the amide and alkene functional groups. Note that the peak 5.05 ppm at 288 K which moves to 4.90 ppm at 228 K is assigned to the alkenyl proton H^c. Line shape analysis of the VT NMR spectra using the WINDNMR or TOPSPIN software allowed values for k_{rot} to be determined at each temperature, which, when factored into the Arrhenius equation (Eq 2.1), allowed determination of $\Delta G^{‡}$ at each temperature. Eyring plots of 1/T against ln(k/T) were then produced, providing values for $k_{rot\ 298}$, $\Delta G_{298}^{‡}$, $\Delta S^{‡}$, and $\Delta H^{‡}$ for the bond rotation, using equations 2.2 - 2.4.

$$\Delta G = RT\ln\left(\frac{kh}{k_B T}\right) \quad \text{.....Equation 2.1}$$

$$k_{rot\,298} = 298K \cdot e^{\frac{slope}{298K}+intercept} \quad \text{.....Equation 2.2}$$

$$\Delta H = -R \cdot slope \quad \text{.....Equation 2.3}$$

$$\Delta S = R \cdot \left(intercept - ln\frac{k_B}{h}\right)$$ .....Equation 2.4

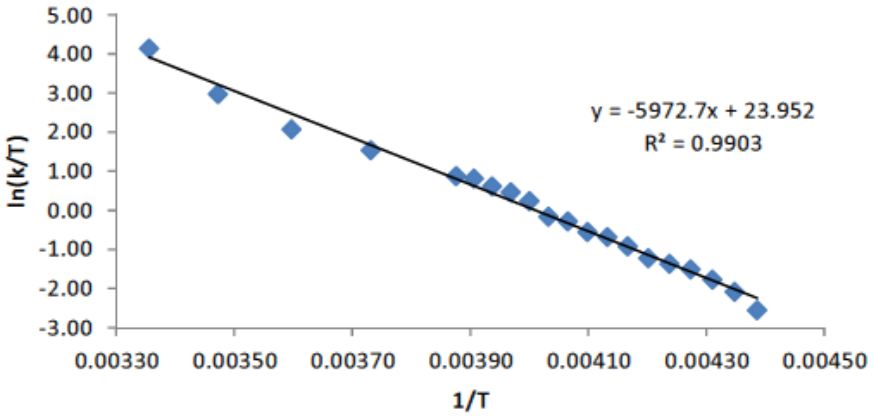
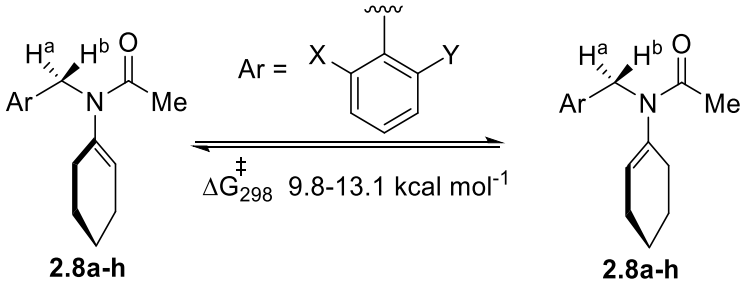


Figure 2.6: Eyring plot for 2.8g in d_8-toluene

2.6 Substitution effects

2.6.1. Effect of the halogen group.



2.8a-h **2.8a-h**

Comp.	X	Y	$\Delta G^{\ddagger a}$ (kcal mol^{-1})	$k_{rot\ 298K}{}^{a}$ (s^{-1})	$\Delta S^{\ddagger a}$ (cal mol^{-1} K^{-1})	$\Delta H^{\ddagger a}$ (kcal mol^{-1})
2.8a[b]	H	H	10.1	2.51 x 10^5	-2.9	9.2
2.9	2-bromonaphthyl		10.8	7.40 x 10^4	-11.7	14.4
2.8b	H	F	9.9	3.57 x 10^5	-7.1	7.7
2.8c	H	Cl	9.8	4.15 x 10^5	-11.4	6.4
2.8d	H	Br	10.5	1.12 x 10^5	-9.3	7.8
2.8e	H	I	10.0	3.04 x 10^5	-1.7	9.5
2.8f	F	F	10.9	6.30 x 10^4	-6.7	8.9
2.8g	Cl	Cl	11.7	1.49 x 10^4	-0.4	11.9
2.8h	Br	Br	13.1	1.63 x 10^3	-7.3	10.9

[a] Estimated errors k_{rot} 298 K ± 13%, $\Delta H^{\ddagger}_{298}$ = ± 0.3 kcal mol^{-1}, $\Delta S^{\ddagger}_{298}$ = ± 1.0 cal mol^{-1}, $\Delta G^{\ddagger}_{298}$ = ± 0.2 kcal mol^{-1}, these are in line with related work. [b] See reference.[72]

Table 2.1: Rotation data for 2.8a-h

For the series **2.8a-e** containing one halogen *ortho* substituent, the values of $\Delta G^{\ddagger}_{298}$ and k_{rot} 298 K are similar within the error for the analysis. It can therefore be concluded that variation of the type of halogen on the benzyl ring has very little bearing on the rotation barrier of the *N*-cycloalkenyl bond, suggesting that the halogen itself is positioned away from the rotating bond. Evidence for this is provided by (a) the X-ray structure of the related compound **2.21** (*vide infra*) which clearly shows the bromine atom positioned away from the rotating bond of interest and (b) the fact that the structure **2.8a** (X = Y = H) has similar rotation rates and activation parameters. The 2-naphthyl derivative **2.9** has similar measurements to **2.8d** indicating the extra ring is positioned away from the rotating bond.

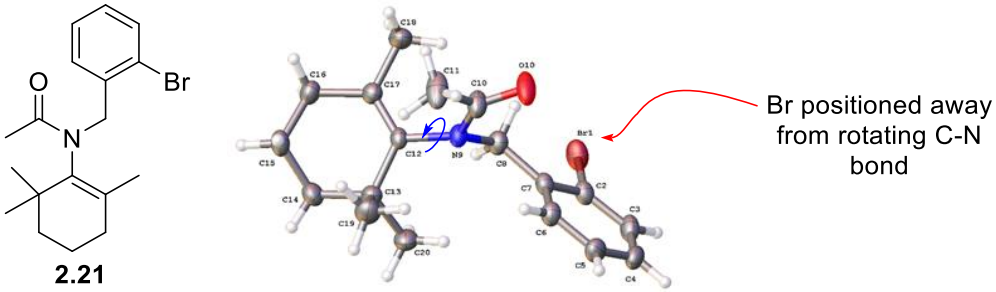


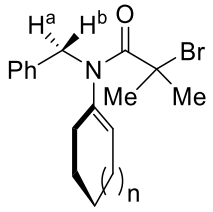
Figure 2.7: X-ray structure of compound 2.21 showing position of bromine substituent

On the other hand, benzyl groups containing two *ortho* aryl substituents increase the barrier to rotation in line with their size (**2.8f** F = +1.0 kcal mol^{-1}, **2.8g** Cl = +1.9 kcal mol^{-1}, **2.8h** Br = +2.6 kcal mol^{-1}), despite their distance from the key *N*-alkenyl bond rotation. While it was not possible to solve the X-ray structure of any of the 2,6-disubstituted substrates to provide information about the conformation of these molecules, examination of the $\Delta S^{\ddagger}_{298}$ parameters provided some tentative insight. The vast majority of entropy values for rotation around the *N*-alkenyl bond of tertiary enamides are relatively small and negative.[71,72] This suggests an ordering in the

transition state for rotation relative to the ground state. This can be readily explained, when one considers that in the transition state it is likely that a degree of co-operative gearing of rotation around key bonds (N-(CO), *N*-alkenyl, acyl substituent) is required in order for the molecule to achieve some level of planarity. In the ground state the general molecular motions of these bonds will be more randomised. The $\Delta S^{\ddagger}_{298}$ values for di-substituted aryl substituents are slightly lower than for their mono-substituted analogues. This may indicate that while there is little movement required of the benzyl substituent during *N*-alkenyl bond rotation in mono-substituted molecules (as the ground state already has the large atom pointing away from the area of interest) but that there is more movement required (more disorder) for di-substituted ones. While the differences in $\Delta S^{\ddagger}_{298}$ are small (and for **2.8b** and **2.8f**, within experimental error), they are more likely to be greater in molecules with higher barriers to rotation (e.g. when the acyl substituent is larger than methyl or when the cycloalkenyl ring is larger, or both). This is indeed observed (*vide infra*) and in some cases leads to a positive $\Delta S^{\ddagger}_{298}$ value (**2.8k**, **2.8n** and **2.8s**).

2.6.2. Effect of the acyl group and ring size.

Previous work has shown that varying the size of the cycloalkenyl group has a moderate effect on the barrier to rotation,[69] with barriers lowering as the ring was pinned back by its decreasing size. The exception was the cyclooctene derivative **2.13d**, where the puckered conformation effectively decreased its cone angle, (Table 2.2).



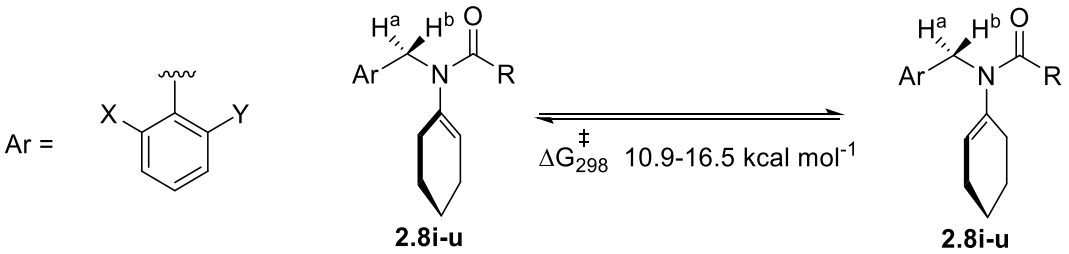
2.13a-d

Comp.	n	$\Delta G^{\ddagger a}$ (kcal mol^{-1})	$k_{rot\ 298K}{}^{a}$ (s^{-1})	$\Delta S^{\ddagger a}$ (cal mol^{-1}K^{-1})	$\Delta H^{\ddagger a}$ (kcal mol^{-1})
2.13a[b]	0	10.0	3.11 x 10^5	-6.6	8.0
2.13b[b]	1	13.3	1.06 x 10^3	-6.6	11.3
2.13c[b]	2	13.5	735	-5.7	11.8
2.13d[b]	3	12.7	3.09 x 10^3	-4.3	11.4

[a] Estimated errors k_{rot} 298 K ± 13%, $\Delta H^{\ddagger}_{298}$ = ± 0.3 kcal mol^{-1},$\Delta S^{\ddagger}_{298}$ = ± 1.0 cal mol^{-1}, $\Delta G^{\ddagger}_{298}$ = ± 0.2 kcal mol^{-1}, these are in line with related work. [b] See reference.[71]

Table 2.2: Rotation data for 2.13a-d

A similar trend was observed in this work. For the two acetamide series (R = Me) where (a) X = H, Y = Br, (*series 1*: **2.8d** → **2.8o** → **2.8t**) and (b) X = Y = Br (*series 2*: **2.8h** → **2.8p** → **2.8s**) the cycloheptenyl derivatives **2.8o** and **2.8p** have the highest barriers, (series 1: $\Delta G^{\ddagger}_{298}$ = 10.5 → *12.0* → 11.3 kcal mol^{-1}, series 2: $\Delta G^{\ddagger}_{298}$ = 13.1 → *14.8* → 12.4 kcal mol^{-1}) (Table 2.3).



Comp	R	n	X	Y	$\Delta G^{\ddagger a}$ (kcal mol^{-1})	$k_{rot\ 298K}$[a] (s^{-1})	$\Delta S^{\ddagger a}$ (cal mol^{-1}K^{-1})	$\Delta H^{\ddagger a}$ (kcal mol^{-1})
2.8a[b]	Me	1	H	H	10.1	2.51 x 10^5	-2.9	9.2
2.8d	Me	1	H	Br	10.5	1.12 x 10^5	-9.3	7.8
2.8h	Me	1	Br	Br	13.1	1.63 x 10^3	-7.3	10.9
2.8i[b]	Et	1	H	H	10.9	7.46 x 10^4	-14.7	6.4
2.8j	Et	1	H	Br	11.3	3.04 x 10^4	-13.1	7.4
2.8k	Et	1	Br	Br	13.4	9.46 x 10^2	17.1	18.5
2.8l[b]	^{i}Pr	1	H	H	11.7	1.80 x 10^4	-10.6	8.5
2.8m	^{i}Pr	1	H	Br	12.2	6.83 x 10^3	-11.4	8.8
2.8n	^{i}Pr	1	Br	Br	14.4	158	2.14	15.1
2.8o	Me	2	H	Br	12.0	1.04 x 10^4	-4.9	10.5
2.8p	Me	2	Br	Br	14.8	83.0	-11.2	11.5
2.8q	Et	2	H	Br	12.7	3.16 x 10^3	-3.3	11.7
2.8r	^{i}Pr	2	H	Br	13.9	4.11 x 10^2	-9.02	11.2
2.8s	^{i}Pr	2	Br	Br	16.5	5.24	3.6	17.5
2.8t	Me	3	H	Br	11.3	3.07 x 10^4	-14.3	7.1
2.8u	Me	3	Br	Br	12.4	5.03 x 10^3	1.4	12.8

[a] Estimated errors k_{rot} 298 K ± 13%, $\Delta H^{\ddagger}_{298}$ = ± 0.3 kcal mol^{-1}, $\Delta S^{\ddagger}_{298}$ = ± 1.0 cal mol^{-1} $\Delta G^{\ddagger}_{298}$ = ± 0.2 kcal mol^{-1}, these are in line with related work. [b] See reference.[72]

Table 2.3: Rotation data for 2.8i-u and 2.13a-d

Increasing the size of the acyl substituent R from Me → Et → *i*Pr generally increases the barrier to rotation by approximately 0.7-1.0 kcal mol^{-1} per carbon. This is corroborated by the benzyl derivatives, *series a*, n = 1, X = Y = H, (Me → Et: **2.8a** → **2.8i** $\delta\Delta G^{\ddagger}_{298}$ = +0.8 kcal mol^{-1}, Et → *i*Pr: **2.8i** → **2.8l** $\delta\Delta G^{\ddagger}_{298}$ = +0.8 kcal mol^{-1}), for the 2-bromobenzyl derivatives, *series b*, n=1, X=H, Y=Br, (Me → Et: **2.8d** → **2.8j** $\delta\Delta G^{\ddagger}_{298}$ = +0.8 kcal mol^{-1}, Et → *i*Pr: **2.8j** → **2.8m** $\delta\Delta G^{\ddagger}_{298}$ = +0.9 kcal mol^{-1}), and for the 2,6-dibromobenzyl derivatives, *series c*, n = 1, X = Y = Br, (Me → Et: **2.8h** → **2.8k** $\delta\Delta G^{\ddagger}_{298}$ = +0.3 kcal mol^{-1}, Et → *i*Pr: **2.8k** → **2.8n** $\delta\Delta G^{\ddagger}_{298}$ = +1.0 kcal mol^{-1}). Similarly for the cycloheptenyl derivatives, n = 2, the increase for Me → *i*Pr, *series d*,

is $\delta\Delta G^{\ddagger}_{298}$ = 1.9 kcal mol^{-1} (X = H, Y = Br, **2.8o** → **2.8r**) and 1.7 kcal mol^{-1} (X = Br, Y = Br, **2.8p** → **2.8s**, *series d*).

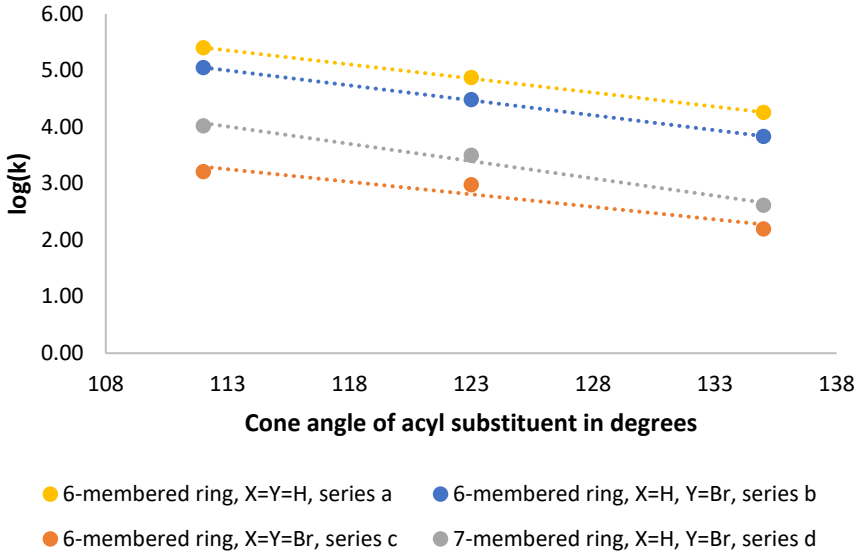


Figure 2.8: Graph of logk_{rot} verses cone angle of acyl substituent

Comparing plots of logk_{rot} against the cone angle of acyl substituents for *series a-d*, Figure 2.8, shows a similar linear trend to that previously reported (gradient -0.05), suggesting similar mechanisms for rotation (series: a = -0.05, b = -0.05, c = -0.06 and d = -0.04). The $\Delta S^{\ddagger}_{298}$ values for the X = Y = Br derivatives **2.8k**, **2.8n** and **2.8s** are positive, indicating a more disordered TS with respect to the ground state for these molecules, presumably for the reasons suggested in section 2.6.1. Increasing the size of the acyl group, in combination with other sterically bulky groups **2.8s**, could only drive the barrier to rotation up to 16.5 kcal mol^{-1} (various attempts to synthesise *t*-butylacetamides were unsuccessful). This is insufficiently high to envisage chiral transfer possibilities, and thus other methods of increasing the barrier to rotation must be investigated.

2.7 Increasing the barrier to rotation further

Recent work has suggested that in order to isolate individual atropisomers the alkene must be tetra-substituted.[69] However, for substrates containing relatively large acyl substituents, such as **2.14**, the barrier for N-(CO) amide bond rotation was found to be lower than that of *N*-alkenyl bond rotation. Figure 2.9b. Analysis of the 400MHz ^{1}H NMR of **2.14** at 298K showed a doubling of all peaks, indicative of both (*E*)- and (*Z*)-amide rotamers at room temperature. Heating at 373K led to coalescence of the four sets of doublets to two broad singlets, indicative of a rapid interconversion on the NMR timescale between the (*E*)- and (*Z*)-amide rotamers with a slower rotation around the enamide N-C bond, Figure 2.9a. In addition, the X-ray crystal structure of **2.14** clearly shows the (*Z*)-amide rotamer in the solid state, Figure 2.9c. On the other hand, molecules with a smaller acyl group (R = Me), **2.15**, only showed one amide rotamer in solution. Consequently, initial investigations compared the *N*-benzyl **2.16a**, 2-bromo **2.16b** and 2,6-dibromobenzyl **2.16c** derivatives.

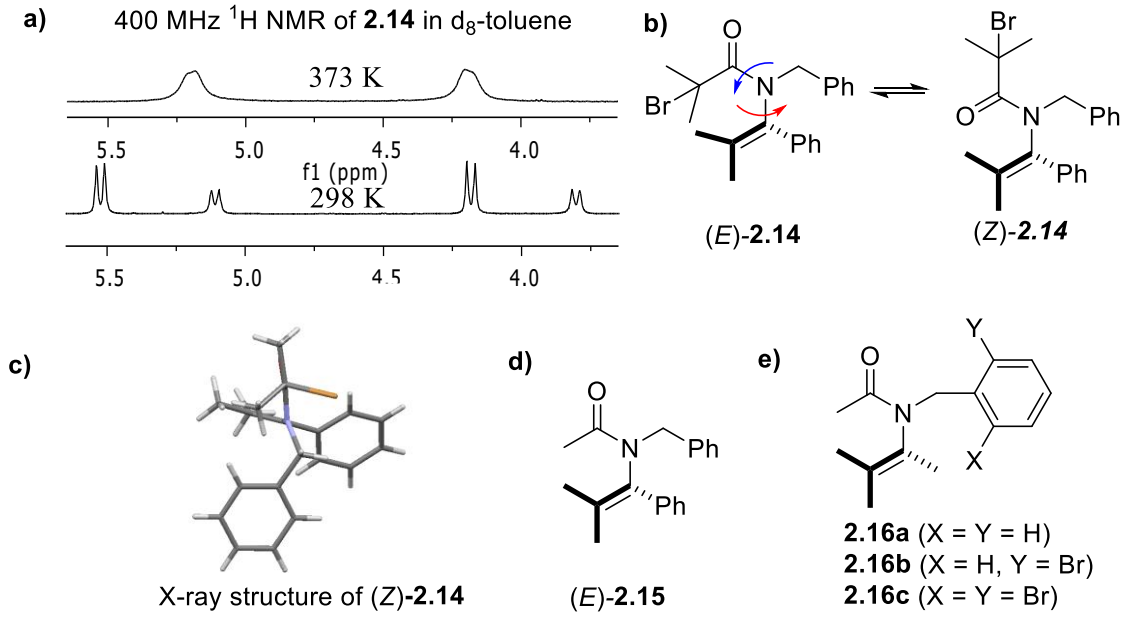
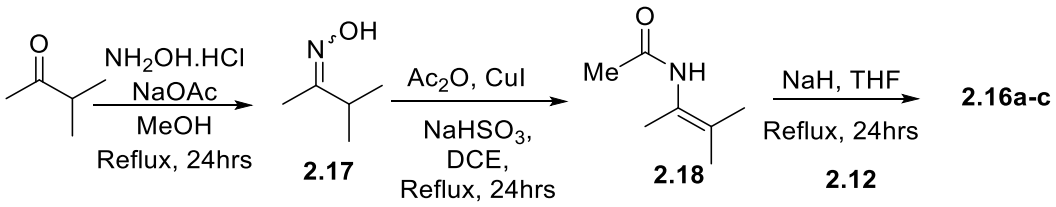


Figure 2.9 a) 400 MHz ^{1}H NMR spectra of 2.14 in d_8 toluene at 298K and 373K, b) Co-operative rotation during *N*-alkenyl bond rotation, c) X-ray crystal structure of 2.14, d) structure of (*E*)-2.15 and e) structures of enamides 2.16a-c.

The targets **2.16a-c** were synthesised using the method reported in section 2.4. Hence, reaction of 3-methylbutan-2-one with hydroxylamine hydrochloride and NaOAc at reflux provided oxime **2.17**, after which copper mediated acetylation and rearrangement furnished the secondary enamide **2.18** in 15% yield as a 4:1 mixture of isomers. Alkylation with the appropriate benzyl bromide **2.12** gave the targets **2.16a-c** in yields of 80%, 28% and 20% respectively. The ^{1}H NMR of the enamides **2.16a-c** showed clearly resolved doublets for the benzyl protons at room temperature. Heating to 373K broadened the peaks but they did not reach the point of total coalescence. This meant the barrier to rotation was too high to be calculated accurately by VT NMR, however **2.16b** was estimated to have a $\Delta G^{\ddagger}_{298}$ = 19.9 kcal mol^{-1} (k_{rot} = 1.66 x 10^{-2} s^{-1}). Instead the substrate **2.16c** was sent to 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.[69]



Scheme 2.6: Synthesis of substrates 2.16a-c

Isolation of the pure enantiomer of compound **2.16c** on the Whelk-O was successful (10% iPrOH/90% hexanes), and remained pure while kept on ice. When left at room temperature, the compound began racemising. Figure 2.10 shows the analytical HPLC chromatogram after 80 mins. By studying the kinetics of racemisation, the barrier to rotation was measured at 23.6 kcal mol^{-1}, with a half-life of 176 mins at 298K. While **2.16c** exhibited a relatively higher barrier to rotation than previous compounds **2.8a - 2.8u,** it was not sufficiently high enough to qualify as an atropisomer.

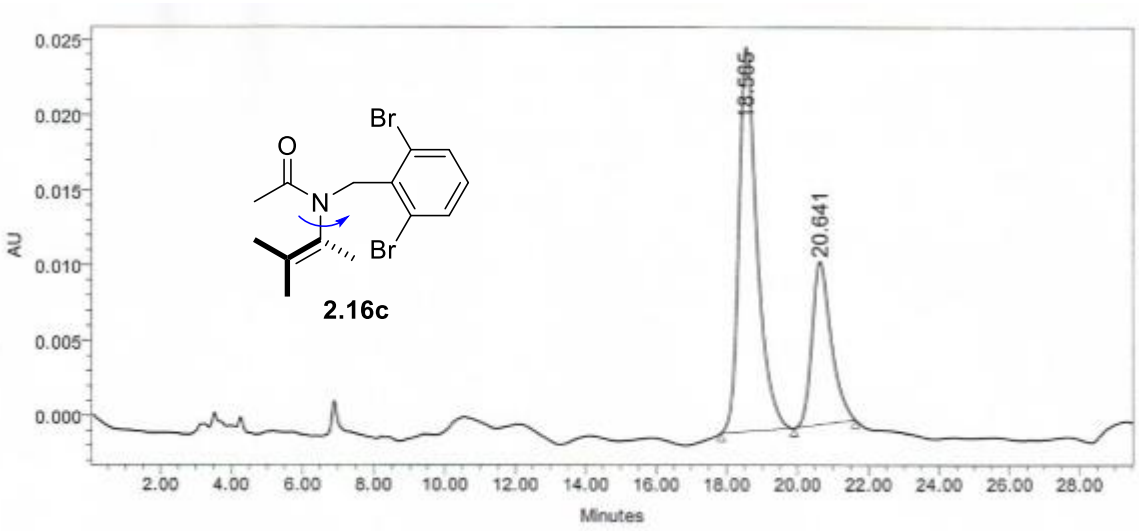
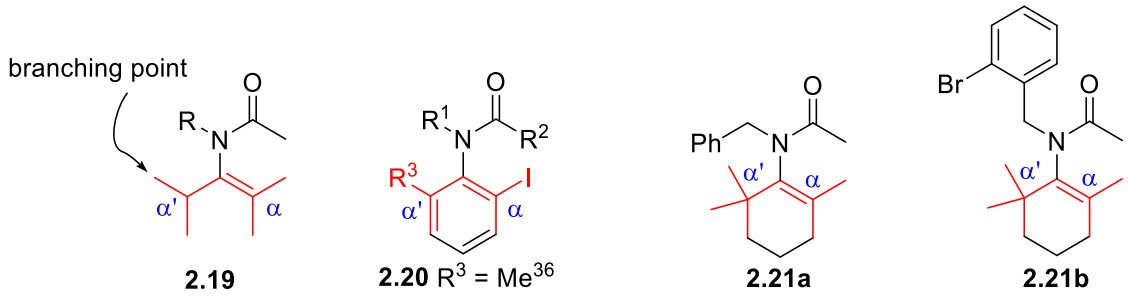


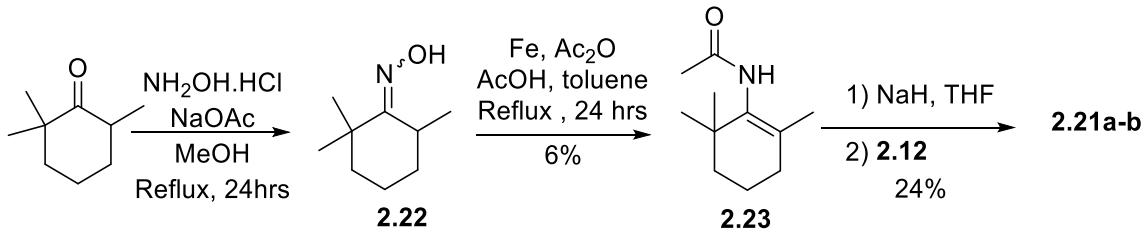
Figure 2.10: HPLC chromatogram of enamide 2.16c after 80 minutes

In order to increase the barrier to rotation further it was deemed necessary to introduce a further branching point at the α'-position such as in **2.19**. In this way, the enamides **2.19** resemble anilides **2.20** with substituents R^3 = Me which have barriers to rotation > 26 kcalmol^{-1}. Recent work in the Clark group has established that compound **2.21a** has a barrier to rotation of 31.0 kcal mol^{-1} and a half-life $t_{½}$ for rotation of 99 years at 298 K. Consequently, the aryl bromide derivative **2.21b** was prepared.



Scheme 2.7: Enamides and anilides with branching at the α' position

Compounds **2.21a-b** could not be synthesised using the copper iodide method described in section 2.4 and instead the oxime **2.22** was reacted with iron powder, acetic anhydride and acetic acid in toluene, to give a 6% yield of **2.23**. Benzylation was then accomplished using NaH at reflux as before.



Scheme 2.8: Synthesis of substrates 2.21a-b

The X-ray structure of **2.21b** (Figure 2.11) was solved. Interestingly, the nitrogen is shown to be slightly pyramidalized: the sum of the three bond angles around the amide

nitrogen N9 is 353.5°. This is unusual, in that the published X-ray structures of **2.1d**, **2.1e**, **2.14** and related molecules have completely planar nitrogen atoms as expected, but it has been observed before in hindered anilides.[61] Presumably pyramidalization occurs to relieve the steric congestion around the *gem*-dimethyl substituent.

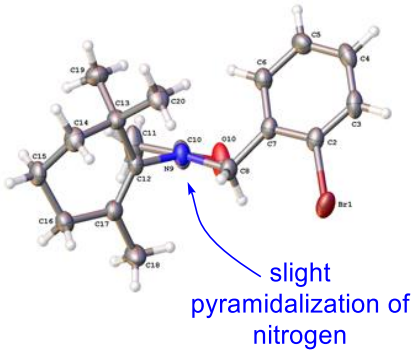


Figure 2.11: X-ray structure of 2.21b showing non-planarity of N9.

Once again, at room temperature the benzyl protons appeared as clearly resolved doublets on the NMR spectrum, and did not fully coalesce when heated either in chloroform or toluene. Therefore, compound **2.21b** was also sent to collaborators in Pittsburgh for attempted separation on a Whelk-O column (enantiomers observed at 12.2 and 16.3 mins, Figure 2.12). Isolation of the pure enantiomer (retention time 12.2 mins) of compound **2.21b** on the Whelk-O column (10% iPrOH/90% hexanes) was successful and found to be configurationally stable at room temperature. When heated to 115°C in *n*-BuOH for 1 hr rotation around the N-C=C bond started to occur, with the other enantiomer (retention time 16.3 mins) appearing in the analytical HPLC chromatogram. The barrier to rotation was measured at 30.6 kcal mol^{-1}, which equates to a half-life of 47.9 years at 298 K. This result was highly satisfactory, as it proved the efficacy of the further branching point in increasing the barrier to rotation in *N*-bromobenzyl enamides, to the point that individual atropisomers could be prepared and stored at room temperature.

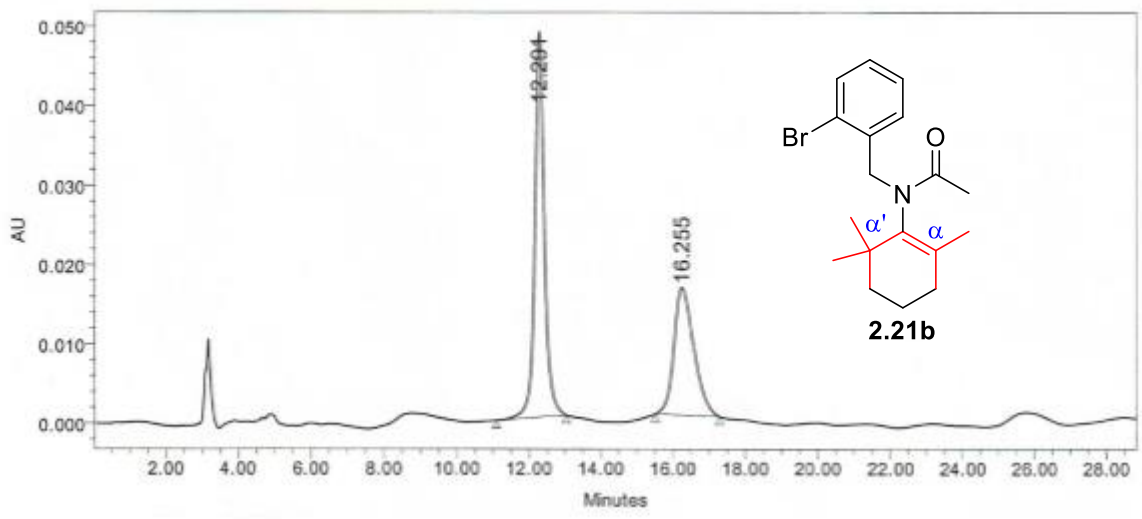


Figure 2.12: HPLC chromatogram of compound 2.21b

2.8 Towards the synthesis of a natural product

Our thoughts turned next to applications of this chemistry. Natural products sanguinarine (**2.24**) and (-)-norchelidonine (**2.25**) were found to possess similar base structures to the supposed products of *6-endo-trig* radical cyclisation of the enamide substrates **2.8**, **2.9**, **2.16** and **2.21** (likely cyclised product frame in red).

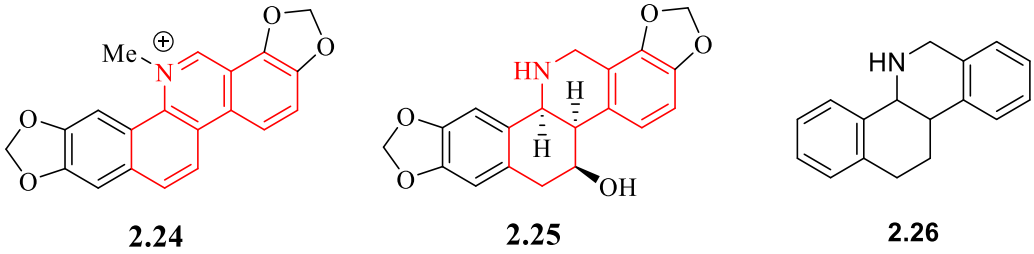
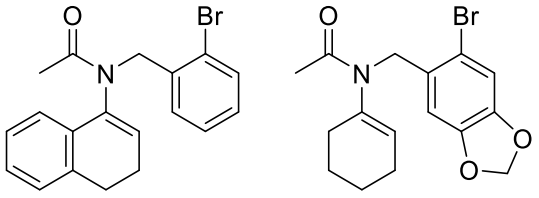


Figure 2.11: Sanguinarine and (-)-norchelidonine

Sanguinarine is a toxic ammonium salt which can be extracted from several plants, including bloodroot, where it was synthesised from dihydrosanguinarine by dihydrobenzophenanthridine oxidase. Low doses have been shown to have apoptotic effects on human cancer cells while leaving healthy cells unharmed by preliminary

preclinical *in vitro* and *in vivo* experiments[134], although higher doses can cause epidemic dropsy if ingested or scabs if applied to the skin (sanguinarine is an escharotic). The apoptotic effect of sanguinarine originates in its action on the sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) transmembrane protein.[135] Norchelidonine is a derivative of chelidonine, a potential anti-cancer drug which can cause mitotic slippage and apoptotic-like cell death.[136] The total synthesis of both (+)-chelidonine and (+)-norchelidonine reported in 2012 by Hsung[137], involving in each case a benzyne-enamide-[2+2] cycloaddition cascade, identified benzophenanthridine **2.26** as a useful intermediate. Hence the dihydronaphthyl substrate **2.27** and the benzodioxole substrate **2.28** were synthesised, as described in scheme 2.5, p41, in order to study the effect of these moieties on the barrier to rotation around the *N*-C=C bond, with a view to the incorporation of these substituents in a larger molecule.



2.27 **2.28**

Figure 2.13: Structures of compounds 2.27 and 2.28

Comp.	$\Delta G^{\ddagger a}$ (kcal mol^{-1})	$k_{rot\ 298K}{}^{a}$ (s^{-1})	$\Delta S^{\ddagger a}$ (cal mol^{-1}K^{-1})	$\Delta H^{\ddagger a}$ (kcal mol^{-1})
2.27	17.9	4.95×10^{-1}	-11.7	14.4
2.28	10.4	1.46×10^{5}	-8.2	7.9

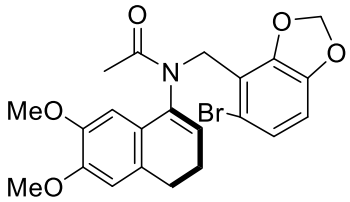
[a] Estimated errors k_{rot} 298 K ± 13%, $\Delta H^{\ddagger}_{298}$ = ± 0.3 kcal mol^{-1},$\Delta S^{\ddagger}_{298}$ = ± 1.0 cal mol^{-1}, $\Delta G^{\ddagger}_{298}$ = ± 0.2 kcal mol^{-1}, these are in line with related work.

Table 2.4: Rotation data for 2.27 and 2.28

Increasing hindrance at one of the alkene groups by incorporating the dihydronaphthyl substituent, as in substrate **2.27**, affords a significant increase in rotational energy (**2.8d**/**2.27** $\delta\Delta G^{\ddagger}$ = +7.4 kcal/mol). In all probability, this is due to the steric clash

present between the acyl hydrogens and the hydrogen at C-8 of the dihydronaphthyl ring during the high energy planar conformation during rotation. This would suggest replacing the C-8 hydrogen substituent with a methyl group should increase the barrier significantly. However removing this in order to synthesise either norchelidonine or sanguinarine would complicate the synthesis, although placing a TMS group here might be useful in chirality control, and could be easily removed afterwards.

It was predicted that due to the incorporation of the steric bulk away from the potential rotation site that the barrier to rotation in **2.28** should be similar to the parent compound **2.8d** and the bromonaphthyl compound **2.9**. This proved to be the case with the $\delta\Delta G^{\ddagger}$ values for **2.8d/2.28** = -0.1 kcal/mol and **2.9/2.28** = -0.4 kcal/mol, almost within the margin of error for the measurements (± 0.2 kcal/mol). It can be concluded that the benzodioxole moiety, like the naphthyl, is rotated out of the way of the cycloalkenyl group and therefore does not affect the barrier to rotation significantly. Given the success of the dihydroaphthalene moiety in driving up the barrier to rotation in **2.27**, a possible precursor **2.29** to an analogue of norchelidonine was synthesised.

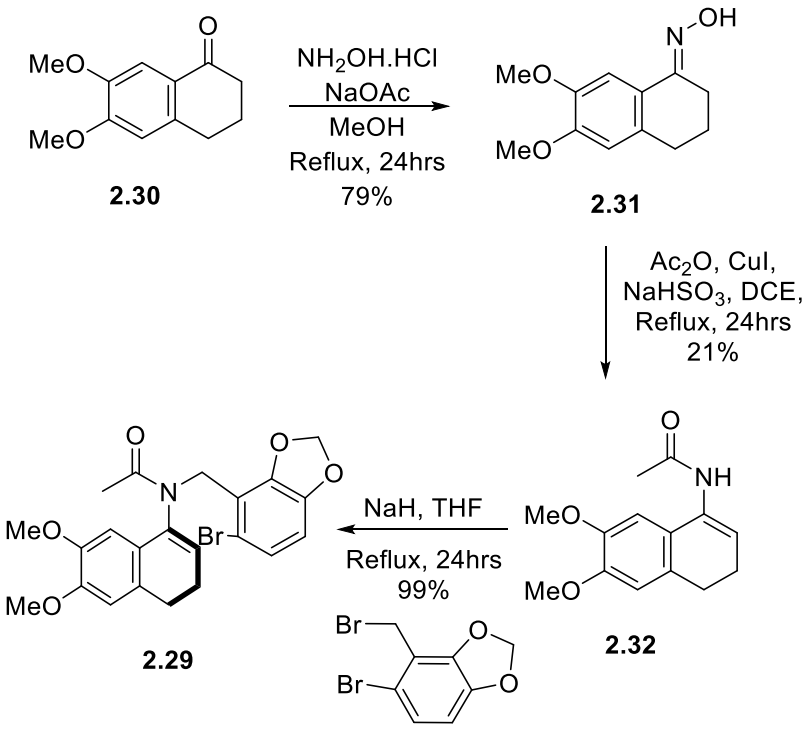


2.29

Figure 2.14: Compound 2.29

A slightly different benzodioxole moiety was used for this compound than in the synthesis of **2.28**, due to both the positioning of the benzodioxole in norchelidonine and to the probable effect on the barrier to rotation of this changed regiochemistry. Rotation of the bromoaryl moiety can no longer remove its influence on the barrier to

rotation around the *N*-cycloalkenyl bond, as both sides of the aryl group are hindered (by the bromine and the methylenedioxy substituent). This, in combination with the steric clash between the dihydronaphthyl and the acyl groups, could therefore be reasonably expected to increase the barrier to rotation in **2.29** to the 25 kcal/mol needed for atropisomerism.



Scheme 2.9: Synthesis of 2.29

As expected, the barrier to rotation for compound **2.29** was too high to be measured by VT-NMR analysis. The compound was therefore sent with the others to collaborators in Pittsburgh in order to attempt separation. This, however, was unsuccessful: the rotamers could not be separated on the Whelk-O column using a variety of solvent systems. The barrier to rotation of **2.29** is therefore higher than the upper limit of what can be measured by VT NMR analysis, and lower than the lower limit of what is possible to separate by chiral HPLC. An impurity was observed at 14.4 minutes, presumably due to decomposition of the compound during transit. Compound

2.29 therefore has a barrier to rotation between 20 and 24 kcal/mol. This is insufficient for atropisomerism, but may prove useful in chiral transfer reactions.

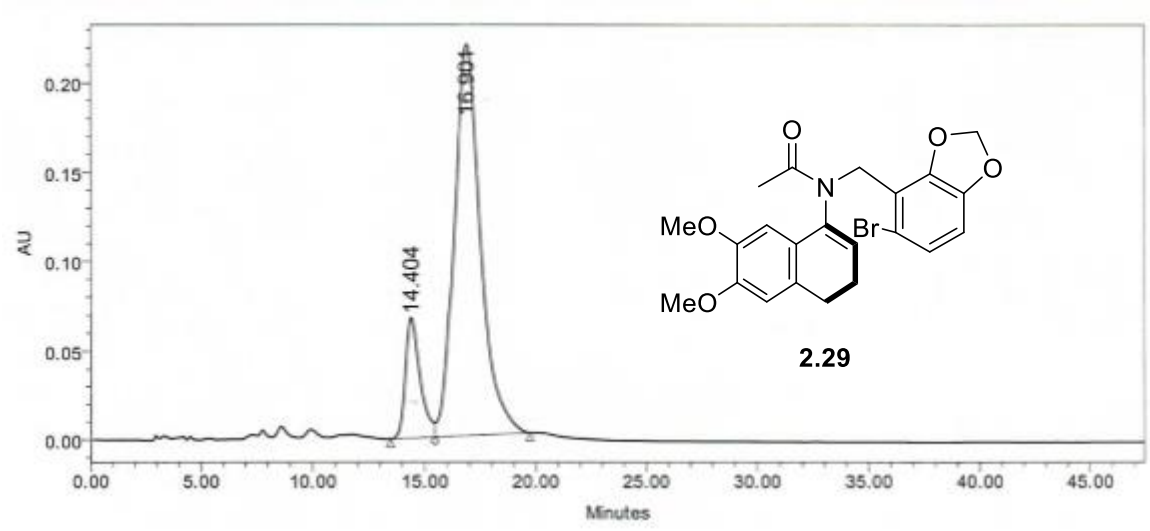


Figure 2.15: HPLC chromatogram of compound 2.29

2.9 Summary

In this chapter, a series of 28 enamides **2.8**, **2.9**, **2.16**, **2.21**, **2.27**-**2.29** has been synthesised and their barriers to rotation have been analysed by VT NMR and chiral HPLC. They all exhibit slow rotation around the *N*-alkenyl bond: their $\Delta G^{\ddagger}$ barriers to rotation range from 9.8-30.6 kcal mol^{-1}. The $\delta\Delta G^{\ddagger}$ barrier to rotation is driven up by: a) the size of the substituent at the acyl group, (~ + 1.6 Kcal mol^{-1}), b) 2,6-disubstitution of the benzyl group (~ + 3 Kcal mol^{-1}), c) the presence of one α'-substituent (~ + 6.2 Kcal mol^{-1}), d) the presence of one α-substituent (~ + 10.2 Kcal mol^{-1}), e) one α- and one α'-substituents (~ + 15.8 Kcal mol^{-1}) and f) one α- and two α'-substituents (~ + 20.1 Kcal mol^{-1}). As a consequence, it is possible to separate atropisomers of tetrasubstituted alkenes such as **2.16c** and **2.21b** by chiral HPLC with **2.21b** having a half-life towards racemisation of 47.9 years at 298 K. However, a

similar, although inferior, effect can be obtained when several effects are combined, (e.g. (b) and (c) above in **2.29**).

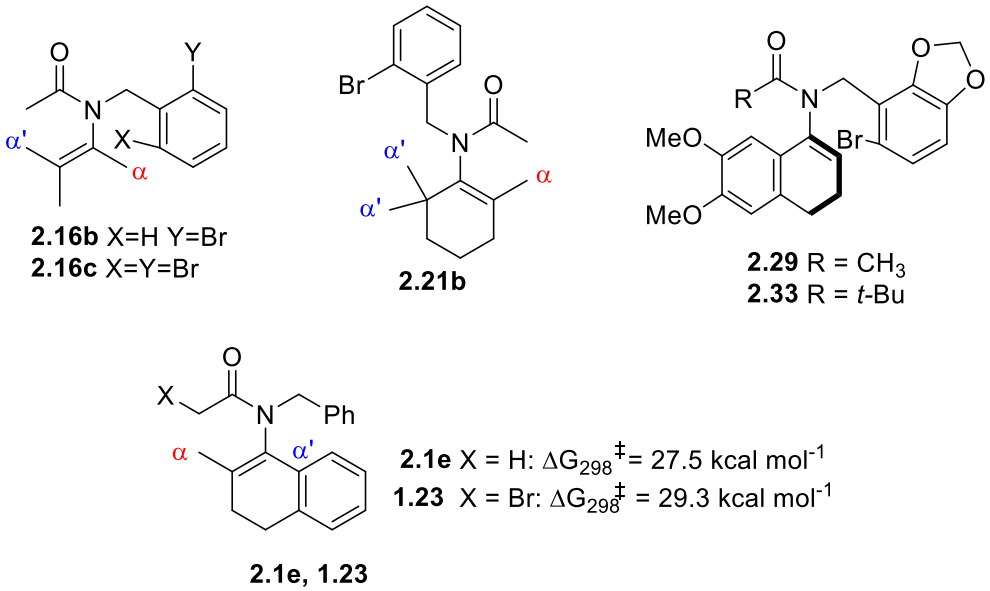


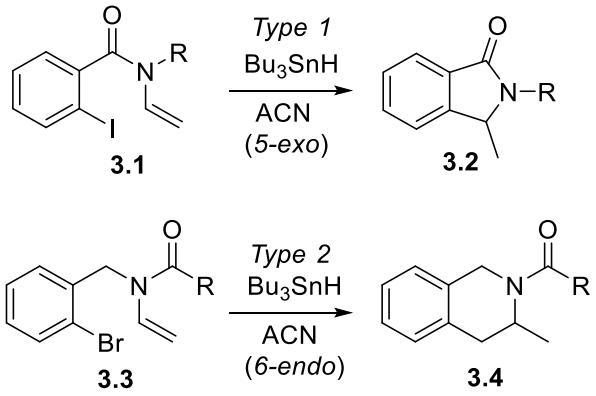
Figure 2.16: Enamides with high barriers to rotation

Although the barrier to rotation in **2.29** was not sufficiently high enough for individual atropisomers to be separated, the results suggest that increasing the acyl group size to a *t*-Bu group (e.g. **2.33)** may provide enough increase for atropisomers to be isolated, although due to time constraints it was not possible to investigate this theory any further.

Chapter 3: Radical Cyclisations of *N*-*o*-Halobenzyl-*N*-acylenamides

3.1 Introduction

Aryl radical cyclisation onto enamides has not been extensively studied. There are two possible cyclisation manifolds, one with reaction taking place *via* the acyl side chain (**3.1** → **3.2**, *type 1*) and one with the amide group exocyclic to the forming ring (**3.3** → **3.4**, *type 2*). The majority of published work has focused on the cyclisations of type 1. Cyclisation of monosubstituted enamides **3.1**, in which the carbonyl group is positioned internal to the forming ring, has been shown to lead primarily to 5-*exo* isoindolone products **3.2**.[138] If the alkene is substituted further, cyclisation can occur in either a 5-*exo* or 6-*endo* mode depending upon the substitution pattern and electronic nature of the alkene.[138]



Scheme 3.1: Modes of aryl radical cyclisation onto enamides

Cyclisation of enamides **3.3**, where the carbonyl group is exocyclic to the forming ring (type 2), has received less attention. Such cyclisations typically lead to tetrahydroisoquinolines **3.4** *via* a 6-*endo*-*trig* mode of cyclisation.[107,139] This *endo* selectivity was postulated to arise due to cyclisation *via* the *syn*-**3.3** conformer (the only conformer detected in solution at room temperature).[139] In this conformer the reacting radical is closer to the β-carbon, leading to the observed *endo* selectivity. The

preponderance of the *syn*-**3.3** conformer over the *anti*-**3.3** conformer was found irrespective of the nature of R^1. Ishibashi concluded that these observations '*strongly suggest that exo and endo selectivities of radical cyclisations onto the alkenic bond of enamides can be controlled by positional change of the carbonyl group'*.[140]

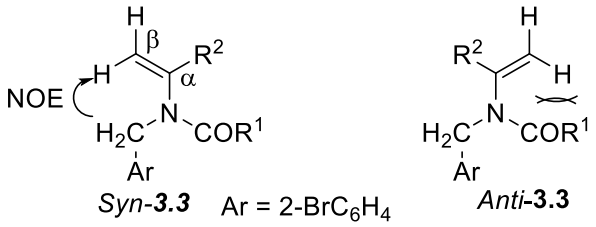
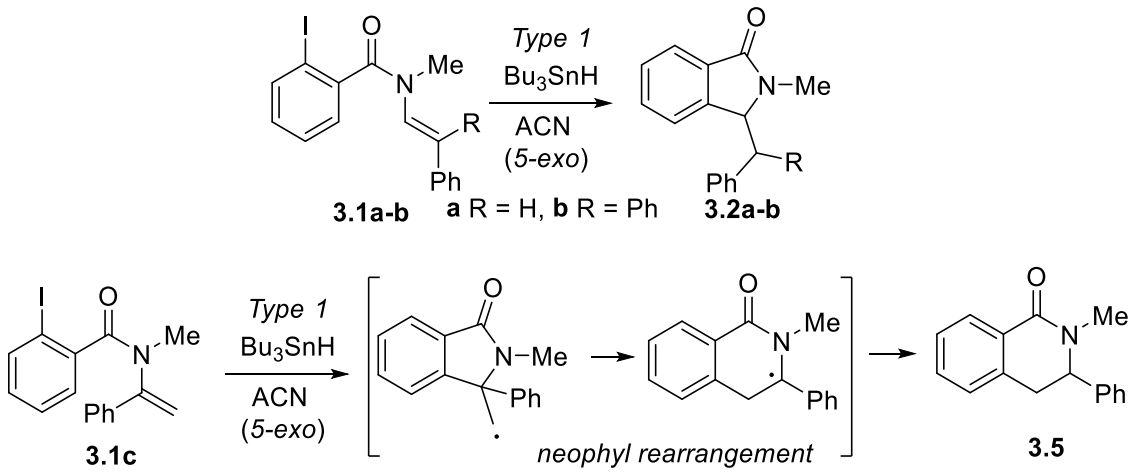


Figure 3.1 Conformations of 3.3.

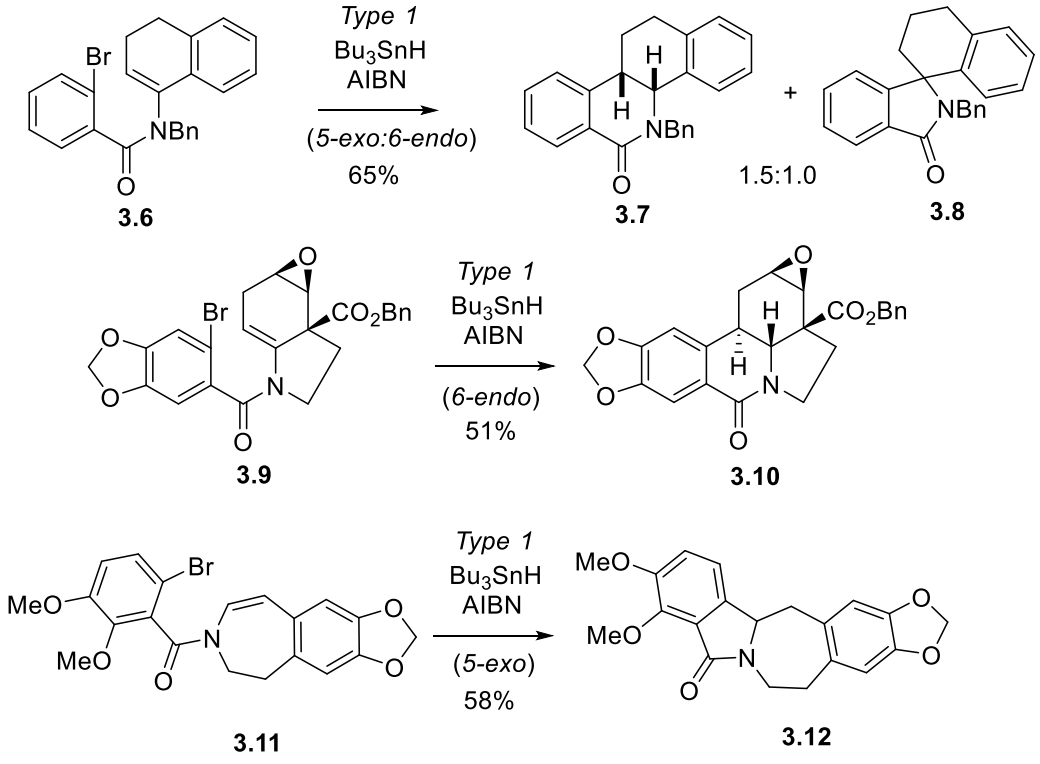
3.1.1 Type 1 Cyclisations

Ishibashi examined the effect of alkene substitution upon the regiochemistry of cyclisation of iodobenzamides **3.1a-c**. Cyclisation of **3.1a-b** gave exclusively 5-*exo* products **3.2a-b** while substitution of a phenyl group at the α-position **3.1c** led to 6-*endo* cyclisation **3.5** predominantly. Experiments utilising different concentrations of Bu_3SnH concluded that the 6-*endo* product **3.5** arose from the kinetically favoured 5-*exo* product radical followed by a neophyl rearrangement.[138,141,142]



Scheme 3.2: Cyclisations of type 1 substrates

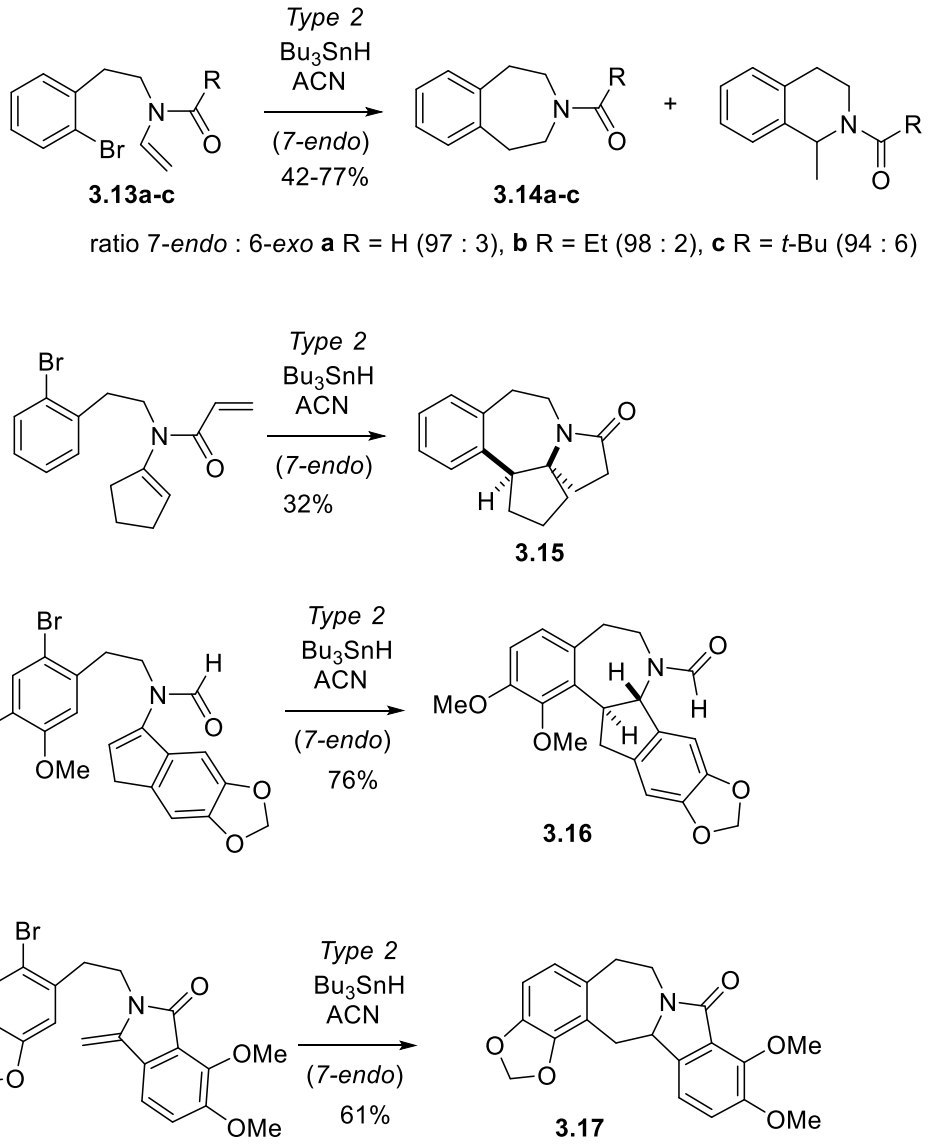
The 6-*endo* mode of cyclisation was also found to predominate when the alkene was constrained within a cyclohexyl ring. Hence, aryl bromide **3.6** gave a 1.5:1.0 mixture of *cis* **3.7** and spiro-isoindolone **3.8,** although it is unclear whether the product **3.7** also arose from a similar neophyl rearrangement.[143] This approach has been applied to the total synthesis of the alkaloids (+)-lycorine (key step **3.9** → **3.10**) and (+)-deoxylycorine in 15 and 13 steps respectively.[144–147] In both cases the nitrogen of the enamide is exocyclic to the alkene-containing ring. If the nitrogen is constrained within the ring then 5-*exo* cyclisation is observed as the major product (**3.11** → **3.12** (±)-lennoxamine)).[148,149] This highlights that the regioselective outcome is likely to be dependent upon a subtle interplay of electronic and conformational effects and is not as straightforward as claimed originally by Ishibashi.[138]



Scheme 3.3: Regiochemistry of type 1 substrate cyclisations

3.1.2 Type 2 Cyclisations

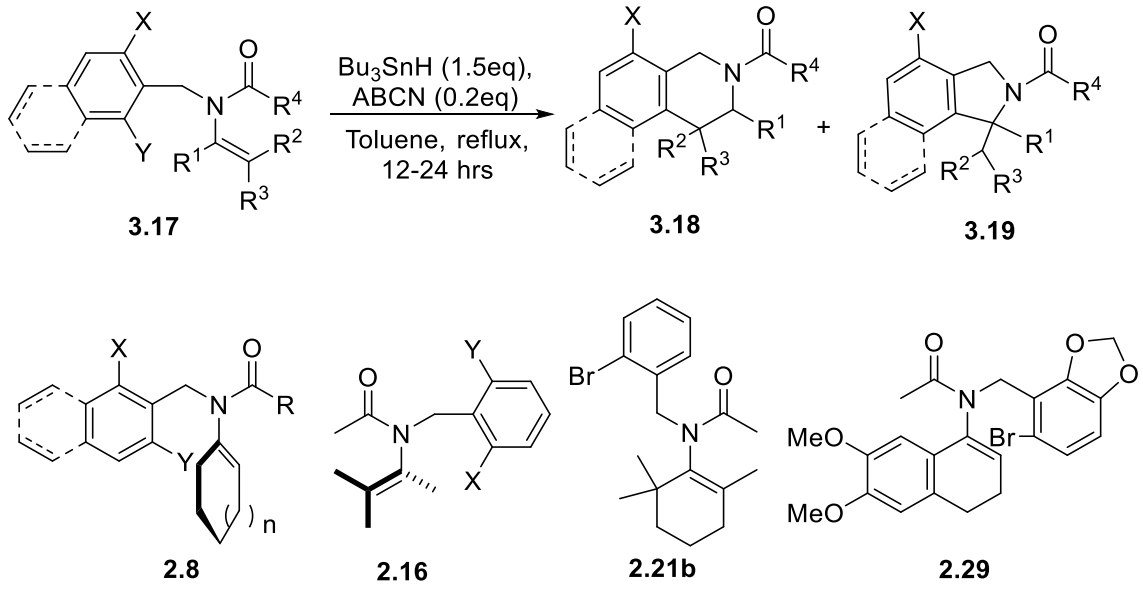
Less information has been reported on the regiochemical outcome of aryl radical cyclisation of *type 2* reactions.[139,140,150] The majority of work has focussed on 6-*exo* verses 7-*endo* cyclisations, with the latter predominating.[151,152] The size of the acyl group (R) in **3.13a-c** was found not to affect the regiochemical outcome of cyclisation with **3.14a-c** predominating. Ring expansion *via* neophyl rearrangement from the corresponding 6-*exo* cyclized radical was not observed.[151] This approach has been applied to the *cis*-ring junction of the cephalotaxine skeleton **3.15**[151] *via* a tandem 7-*endo*: 5-*endo* process as well as to the *trans*-fused benz[d]indeno[1,2-b]azepine skeleton **3.16**[152] and the alkaloid lennoxamine **3.17**.[153]



Scheme 3.4: Regiochemistry of type 2 substrate cyclisations

3.2 Aims of Chapter

A thorough study upon the factors that affect the regio- and stereo-chemistry of type 2 cyclisations of trisubstituted (R^1, $R^3 \neq H$) or tetrasubstituted (R^1, R^2, $R^3 \neq H$) enamide derivatives **3.17** leading to 5-*exo* **3.19** or 6-*endo* **3.18** cyclisation has not been undertaken. This chapter will describe efforts in this area utilizing substrates prepared in chapter 2 (varying R^1, R^2, R^3, R^4, X and Y), more specifically:



Scheme 3.5: Substrates and products of type 2 cyclisations used in this study

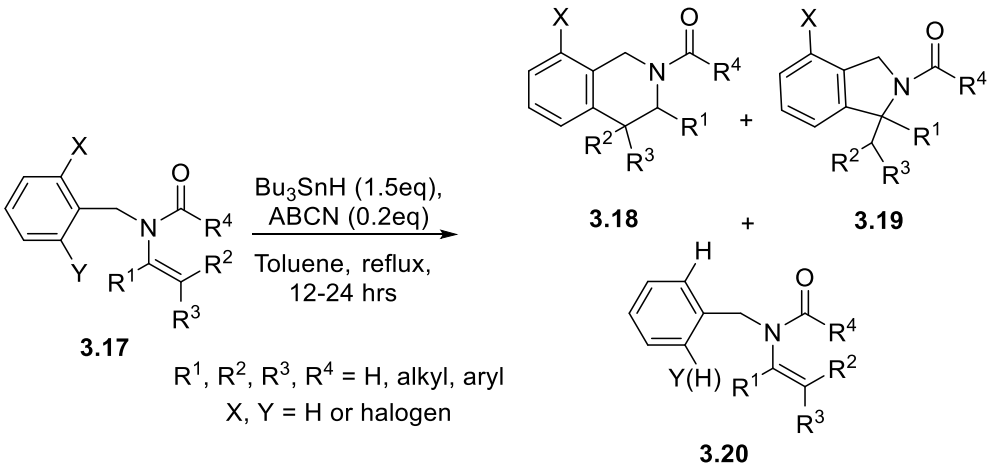
- The effect of ring size (n) in substrates **2.8** upon regio- and stereoselectivity in the cyclisation process.
- The effect of acyl group size R, level of halogenation (X, Y) and other aryl substitution of substrates **2.8** upon regio- and stereoselectivity in the cyclisation process.
- The outcome of cyclisation of substrates with high barriers to rotation around the enamide bond (**2.16** and **2.21b)**, providing information about potential asymmetric atropisomeric cyclisations.
- Application to a natural product skeleton (e.g. cyclisation of **2.29**).

In the case of the enamides with high barriers to rotation (e.g. **2.16c**), it was hypothesised that cyclisation of enantiomerically pure samples of the enamides might lead to chiral transfer if the rate of rotation k_{rot} around the *N*-alkenyl bond of the radical intermediate was slower than the rate of cyclisation k_c. As has been seen in Chapter 2, the halogenation of the aryl ring does not greatly affect the barrier to rotation, and

therefore k_{rot} for the radical intermediate in each cyclisation can be assumed to be similar to k_{rot} of the corresponding halogenated compound.

3.3 Choice of Reaction Conditions

The Bu_3SnH-mediated cyclisation is well known and efficacious, but has problems including high toxicity, lack of stereospecificity and difficulty of removal from the product mixture.[154] However, it is one of the more general methods used, and thus served as a "control" reaction in order to determine the range of products that should be expected from these substrates.

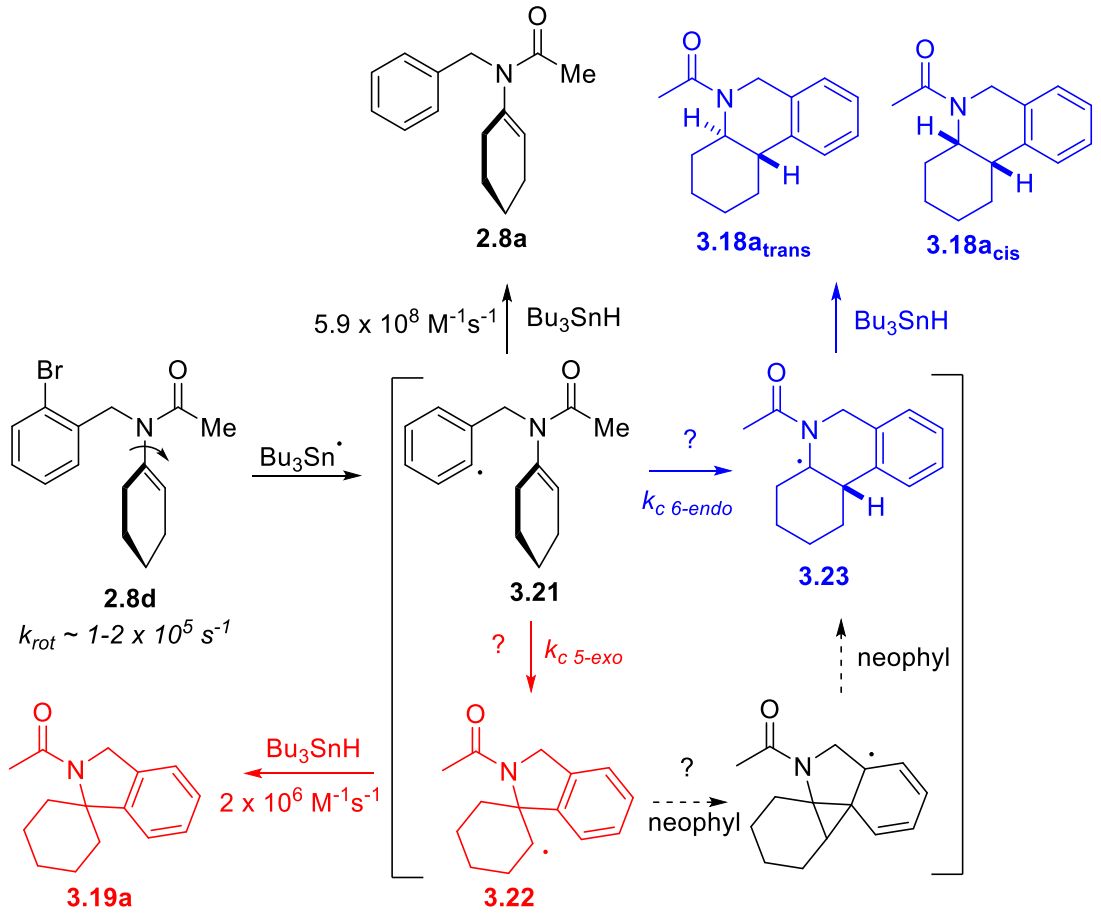


Scheme 3.6: Potential products from cyclisations

The reaction was performed on enamides **2.8** under the conditions detailed in scheme 3.6: the solution of starting material in toluene (0.02M) was allowed to reach reflux before the mixture of Bu_3SnH and ABCN (0.03M and 0.004M respectively) was added dropwise *via* syringe pump, in order to keep the radical concentration low. It was important to determine, not only the ratio of *endo:exo* cyclisation products **3.18**:**3.19** but also the stereochemistry of compounds **3.18** (depending on the configuration of any R groups, the compound can either be *cis* or *trans*). In addition, the amount of

pre-cyclised reduction product **3.20** isolated would also give an indication of the relative rate of cyclisation of these molecules. Products were characterised primarily by ^{1}H NMR, and stereochemistry determined by comparison with previously identified products[84] and analysis of the coupling constants. Ratios of products were determined from ^{1}H NMR of crude mixtures. The range of products obtained from this reaction varied according to the cyclised substrate.

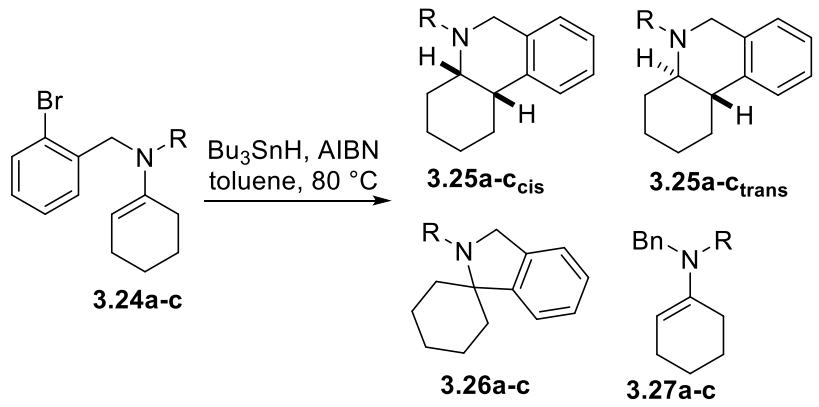
3.4 Cyclisation Reactions



Scheme 3.7: Possible radical cyclisation pathways

There are two possible cyclisation pathways for the compounds cyclised in this chapter (illustrated for the reaction of **2.8d**): the 5-*exo* pathway to give **3.19a** or the *6-endo*

pathway, giving product **3.18a**, (Scheme 3.7). The latter may arise directly (**3.21** → **3.23**) or *via* a neophyl rearrangement of the intermediate radical **3.22** → **3.23**. Interestingly, radical cyclisation of the related enamine system **3.24** has been reported with the *endo:exo* ratio being determined by the size of the nitrogen substituent (Scheme 3.8). In this case, as the alkyl substituent got smaller the relative amount of the 5-*exo* isomer **3.26** increased. In all cases the predominant diastereomer from 6-*endo* cyclisation was determined to be the *cis* isomer **3.25$_{cis}$** and AM1 calculations indicated that Bu_3SnH reduction occurred preferentially from the less sterically demanding face. Kinetic studies revealed the value for $k_{c\ 6\text{-}endo}$ and $k_{c\ 5\text{-}exo}$ to be 4.6 x 10^8 s^{-1} and 1.5 x 10^8 s^{-1} at 80 °C respectively.



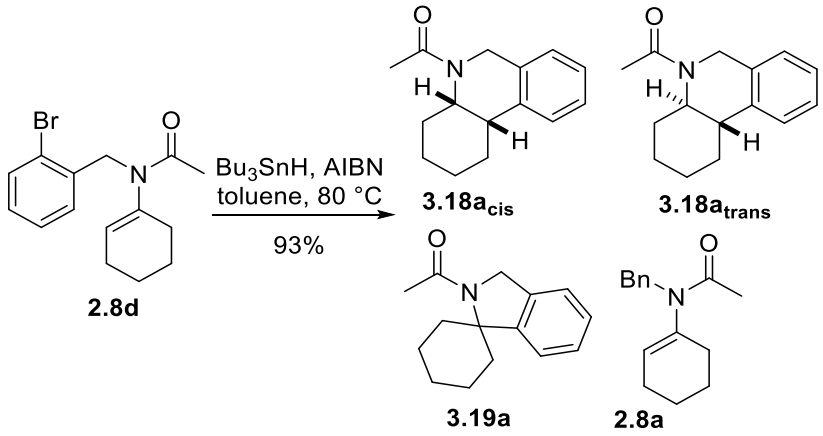
a) R = Me: *endo:exo* = 0.54:1.00, *cis:trans* = > 10:1
b) R = Et: *endo:exo* = 2.90:1.00, *cis:trans* = 3:1
c) R = *n*-Bu:*endo:exo* = 3.10:1.00, *cis:trans* = 2:1

Scheme 3.8: Cyclisation onto related enamines

3.4.1 Cyclisation of control substrate 2.8d

To a solution of **2.8d** in toluene (0.02M) at reflux was added a mixture of Bu_3SnH (0.03M) and ABCN (0.004M) *via* syringe pump over 2.5 hours. The reaction mixture was then refluxed for a further 20 hours, after which it was cooled and the solvent

removed under vacuum. The crude product was obtained as a yellow oil (0.12g), which was taken up in acetonitrile and washed with hexane. The hexane layer was not found to contain any product, and no loss of product was visible in the acetonitrile layer by comparison with the crude NMR. The mixture was then purified by column chromatography (14:1 to 6:1 pet ether/EtOAc). The products obtained were, as depicted in scheme 3.9, the *5-exo* product **3.19a** and the *6-endo* product **3.18a** as a *cis*:*trans* ratio of isomers (1.8:1.0).



endo:exo = 4.2:1.0, *cis:trans* = 1.8:1.0, cyclised:reduced **2.8a** = 14:1

Scheme 3.9: Cyclisation onto enamide 2.8d

The ratios of these products were taken from the crude 400 MHz ^{1}H NMR before purification, as this is the only way to guarantee an accurate depiction of what was obtained. The cyclisation of compound **2.8d** gave the *5-exo* (18%), *6-endo cis* (48%) and *6-endo trans* (27%) products **3.19a**, **3.18a$_{cis}$** and **3.18a$_{trans}$**, as well as some reduced starting material **2.8a** (6%). For the 6-*endo* products **3.18a** the ^{1}H NMR showed mixtures of amide rotamers (**3.18a**$_{cis}$ = 1:0.83, **3.18a**$_{trans}$ = 1:0.54), see Figure 3.2. Only one rotamer is detected for the 5-*exo* product **3.19a**.

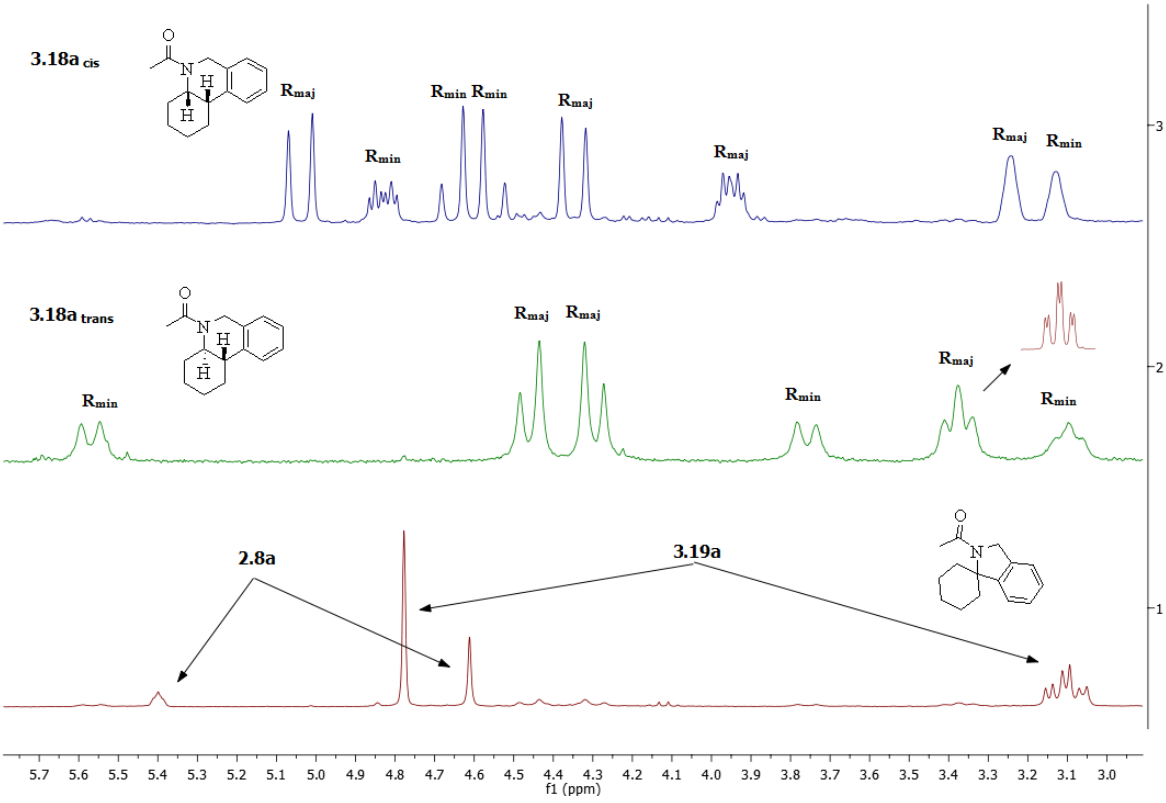


Figure 3.2: ^{1}H NMR spectra (part) of compounds 3.18a$_{cis}$, 3.18a$_{trans}$ (major and minor rotamers indicated) and 3.19a.

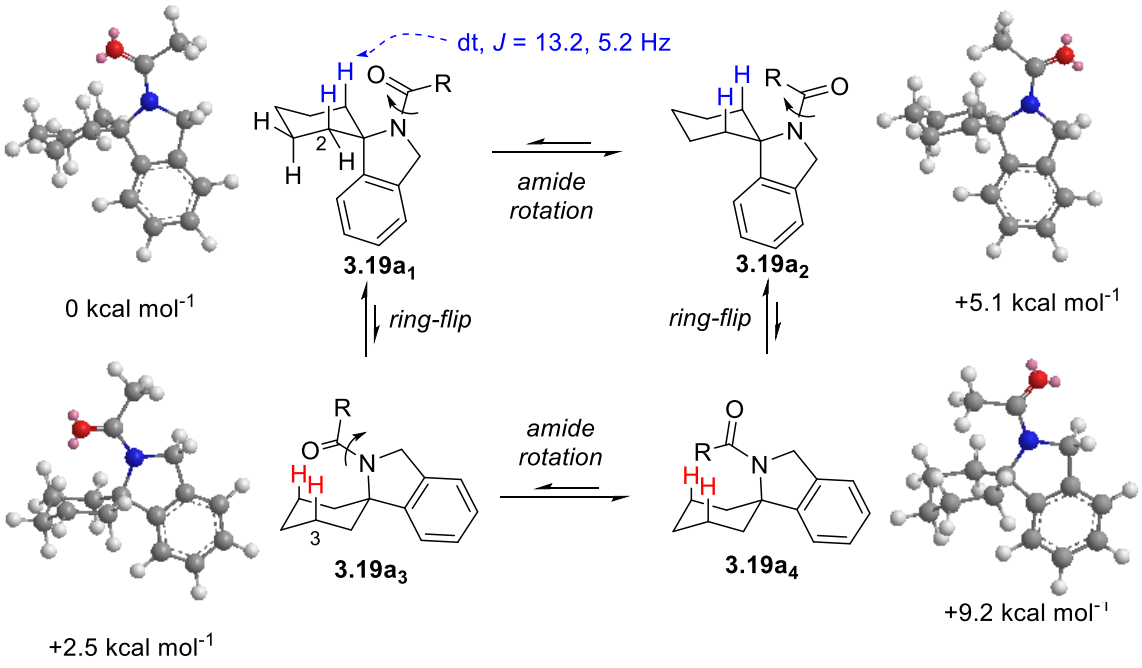


Figure 3.3: Calculated conformations of 3.19a using Chem3D

The ^{1}H NMR clearly indicates that rotamer **3.19a$_1$**, with the aryl group pseudo-axial and the carbonyl pointing towards the cyclohexyl axial protons, is the preferred conformation in $CDCl_3$. The C-2 axial protons (blue, 3.10 ppm, 2H, dt, *J* = 13.2, 5.2 Hz) are substantially downfield of the other cyclohexyl protons due to the anisotropy of the carbonyl group. Chem3D calculations using the MM2 forcefield suggest that the conformations with the oxygen rotated away from the cyclohexyl ring (**3.19a$_2$** and **3.19a$_4$**) are significantly higher in energy than **3.19a$_1$**. Cyclohexyl ring flip to give **3.19a$_3$** where the aryl group is pseudo-equatorial is slightly higher in energy than **3.19a$_1$** and not observed (the axial protons in red at C-3 would be expected to be downfield with a more complex pattern in the ^{1}H NMR). On the other hand, the two rotamers of lowest energy calculated for the 6-*endo cis* conformer **3.18a$_{cis}$** are approximately the same in energy (within the error of the calculation) and this is reflected in their distribution in the ^{1}H NMR. The stereochemical assignment was made based upon nOe data, coupling constants (H_a, 4.82 ppm, dt, J = 12.6, 4.4 Hz) and comparison to known data.[84,155]

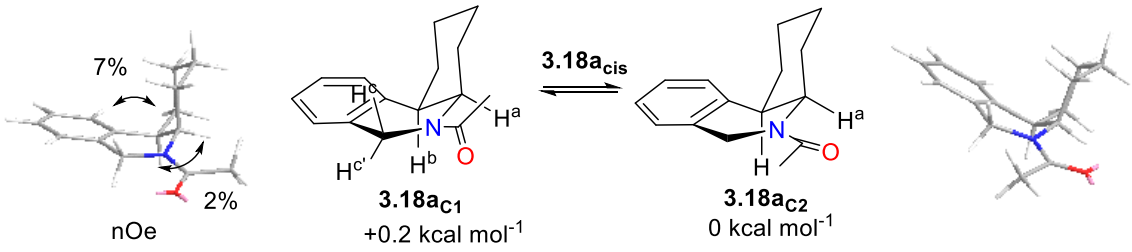


Figure 3.4: Calculated conformations of 3.18a$_{cis}$ using Chem3D

A similar Chem3D analysis for the *trans* isomer **3.18a$_{trans}$** indicates that the lowest energy conformations of the two rotamers **3.18a$_{T1}$** and **3.18a$_{T2}$** are different, of which the conformer with the lowest ground state energy is **3.18$_{T2}$**. In this conformer the carbonyl points towards the ring junction proton H^a, which will appear further

downfield than in **3.18a$_{T1}$**. This is confirmed by the ^{1}H NMR data which shows the major isomer **3.18a$_{T2}$** (H^a = 3.38ppm) and minor isomer **3.18a$_{T1}$** (H^a = 3.11 ppm) respectively. Interestingly, the known compound **3.28** has a relatively low barrier to amide rotation ($\Delta G^{\ddagger}_{rot}$ = 12.4 kcal mol^{-1}) determined by VT ^{1}H NMR (T_c = 263 K).

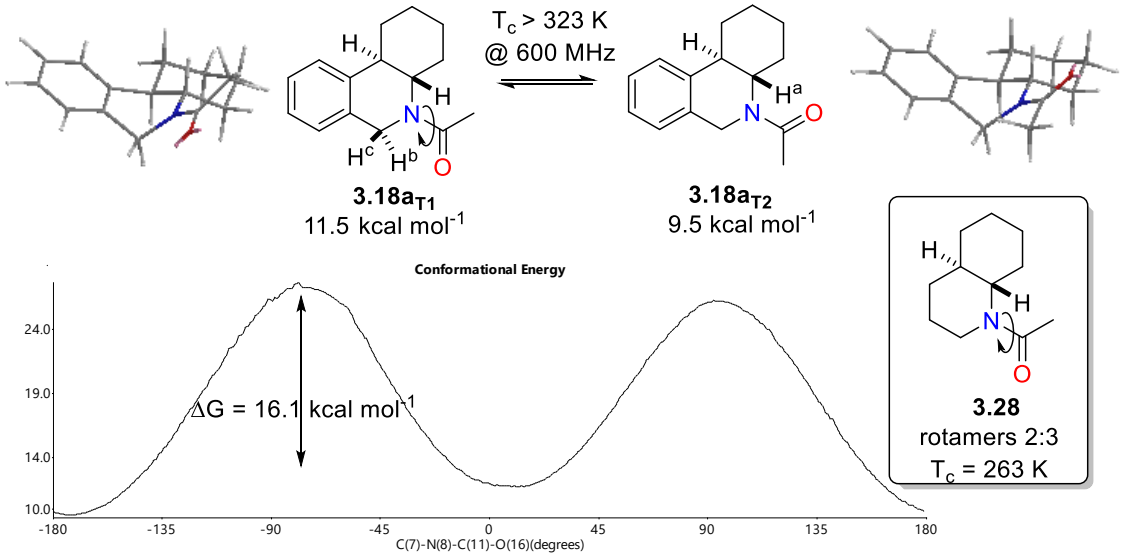
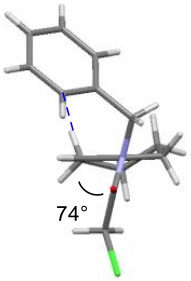
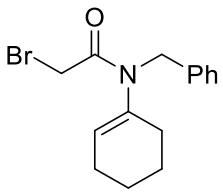


Figure 3.5: Calculated conformations and amide bond rotation of 3.18a$_{trans}$

Work by Milan Fowkes[156] within the Clark research group has shown that although all the ^{1}H NMR rotamer peaks are broadened, they have not coalesced by 323 K (at 600 MHz), indicating a value $\Delta G^{\ddagger}_{rot}$ > 14.9 kcal mol^{-1} and a Chem3D dihedral calculation suggests a barrier of at least 16.1 kcal mol^{-1}. The observed diastereoselectivity **3.18a$_{cis/trans}$** (1.8:1.0) is similar to that observed in the related enamide system **3.25**, (2.3:1.0), Scheme 3.8, presumably for similar kinetic reasons.[157] However, the formation of the diastereomers being thermodynamically controlled could not be discounted at this stage (although unlikely), as the relative ground state energy between them, calculated by Chem3D at 0.6 kcal mol^{-1}, was very similar to that measured from the ^{1}H NMR (0.7 kcal mol^{-1}, assuming an equilibrium constant of K = 1.8 and $\Delta G = -RT\ln K$). Radical cyclisation would normally be considered to be *5-exo*-selective, however in this case the *6-endo cis* product **3.18a$_{cis}$** is the major

observed product, and the *6-endo* products are clearly in the majority (*6-endo:5-exo* = 4.2) with 6% reduction prior to cyclisation **2.8a**. This can be rationalised as being due to the ground state structure of the starting materials. An X-ray structure of the related enamide **3.29** clearly shows its axially chiral nature (there is a 74˚ angle between the planes of the enamide alkene and the amide groups). This places the *ortho* aromatic hydrogen closer in space, and at the optimal geometry, to the *6-endo* carbon than the *5-exo* carbon. It is likely that in **2.8d** the reacting radical site similarly positions the reacting radical centre closer in space to the *6-endo* carbon than the *5-exo* carbon, explaining the observed regioselectivity.





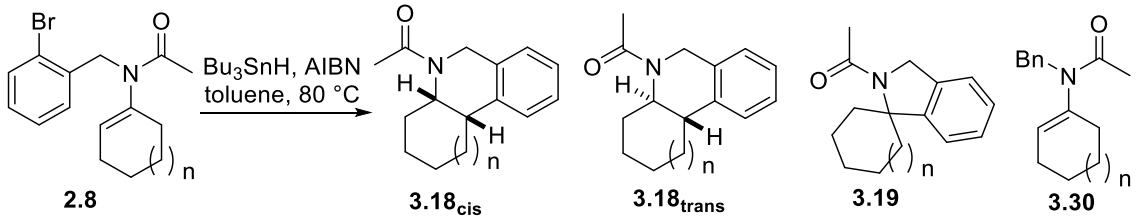
3.29

Figure 3.6: Spatial explanation for the predisposition towards *6-endo* cyclisation.

Finally, in order to discount the possibility that the 6-*endo* cyclisation was arising *via* a neophyl rearrangement of the 5-*exo* intermediate **3.21**, (Scheme 3.7, pg 68) another group member investigated the cyclisation under a variety of Bu_3SnH concentrations.[84] They concluded that the reaction was not proceeding *via* a neophyl rearrangement and measured the rates of 5-*exo* (3.5×10^8 s^{-1}) and 6-*endo* (1.8×10^9 s^{-1}) cyclisation at 110 °C. These are approximately 4 and 2 times greater than the corresponding cyclisations of enamine **3.24a** at the same temperature.

3.4.2 Effect of cycloalkenyl ring expansion

Radical cyclisations of **2.8o** and **2.8t** were next investigated, so as to judge the effect of cycloalkenyl ring expansion on the product ratios by comparison with the cyclisations of **2.8d**. In all cases, the **3.18$_{cis}$** isomers consisted of two rotamers with the major rotamer assigned to that with the C=O pointing towards the benzyl CH_2 protons (**2.8d** 1.00:0.83, **2.8o** 1.00:0.95, **2.8t** 1.00:0.78).



2.8d n = 1, **2.8o** n = 2, **2.8t** n = 3

Scheme 3.10: Cyclisation products: Effect of ring expansion. Major rotamer is shown.

Cyclisation compound	n	Yield	Ratio 3.18_{cis}:3.18_{trans}:3.19:3.30	Ratio 3.18_{cis}:3.18_{trans}	Ratio 6-*endo*:5-*exo*
2.8d	1	100%	48:27:18:6	1.8:1.0	4.2:1.0
2.8o	2	100%	86:0:14:0	*cis* only	6.1:1.0
2.8t	3	74%[a]	50:0:11:13	*cis* only	4.5:1.0

[a] 26% of unreacted starting material was recovered.

Table 3.1: Ratio of products obtained in cyclisations of 2.8d, 2.8o, and 2.8t

As before, reduction of the intermediate radical *via* the β-face is less sterically demanding (red trajectory) and for the cycloheptenyl **2.8o** and cyclooctenyl **2.8t** derivatives leads to only the *cis* diastereomer being observed. An alternative explanation may be that epimerization under the reaction conditions leads to the thermodynamically more stable *cis*-ring junctions. While the thermodynamic ring junction in simple 7:5 bicyclic fused systems is known to be *cis*[158], it is unclear whether 7:6 and 8:6 systems follow this pattern.

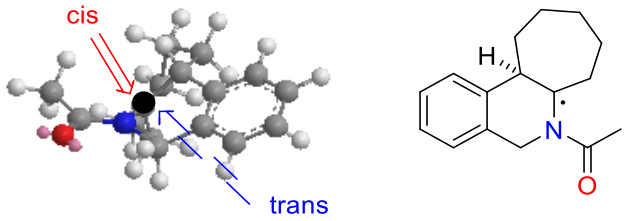
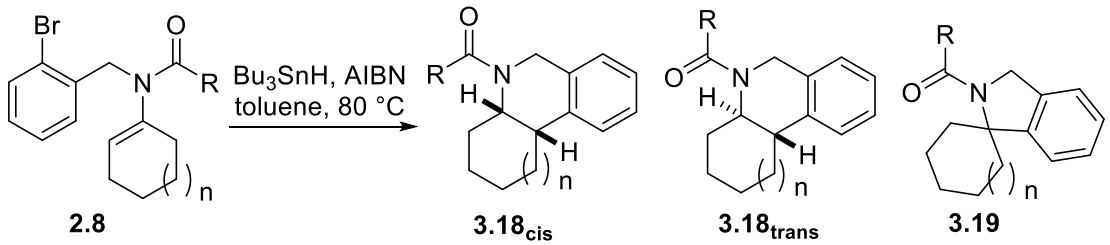


Figure 3.7: Trajectories of reduction of the intermediate radical (black atom).

When the cyclooctenyl substrate **2.8t** was cyclised, however, the reduced product was visible in the crude NMR (13%) indicating a slower cyclisation than **2.8d** or **2.8o**, alongside the expected *6-endo cis* (50%) and *5-exo* (11%) products and 26% of starting material. The TLC used to monitor the reaction was in this case misleading, as the spots for each compound were not sufficiently dissimilar in R_f values. The ratio of **3.18t**$_{cis}$ *6-endo cis* product to **3.19t** *5-exo* product (4.5) was in between the values for the cyclisation's of cyclohexenyl **2.8d** or cycloheptenyl **2.8o** substrates (4.2 and 6.1 respectively), indicating that *6-endo* cyclisation is similarly favoured in the expanded ring systems. The ratios for **2.8d** and **2.8t** are however very similar (4.2 and 4.5 respectively). This can then be correlated to the barrier to rotation: a similar odd trend was seen there, (cf Chapter 2) where cyclohexenyl and cyclooctenyl compounds **2.8d** and **2.8t** had a lower barrier to rotation than cycloheptenyl substrate **2.8o**, presumably due to the folding of the cyclooctenyl ring. It seems that with respect to the size of the cycloalkenyl ring, the higher the barrier to rotation, the more *6-endo* cyclisation takes place, although unfortunately not enough to completely exclude the *5-exo* pathway.

3.4.3 Effect of increased size of acyl group

The study of the acetamides synthesised in Chapter 2 next required the cyclisation of compounds with varying acyl group size R, as depicted in Scheme 3.11. The *6-endo* product **3.18** was expected to remain predominant, in particular the *cis* product; it was also hypothesised that the cyclisation would be harder to initiate and become slower as the *N*-cycloalkenyl bond became more hindered by the increase in size of the acyl group (R), and an increased amount of reduced product **3.30** (figure 3.7, pg 76) and starting material **2.8** was therefore expected, given the disappointing inefficiency of TLC in detecting the end of the reaction observed in the previous section.



2.8d n = 1, R = Me
2.8j n = 1, R = Et
2.8m n = 1, R = iPr
2.8o n = 2, R = Me
2.8q n = 2, R = Et
2.8s n = 2, R = *i*-Pr

Scheme 3.11: Expected cyclisation products of substrates 2.8d-s

Cyclisation compound	Yield	Ratio 3.18_{cis}:3.18_{trans}:3.19:3.30	Ratio 3.18_{cis}:3.18_{trans}	Ratio 6-*endo*:5-*exo*
2.8d	100%	48:27:18:6	1.8:1.0	4.2:1.0
2.8j	71%[a]	41:trace:30:trace	*cis* only	1.4:1.0
2.8m	100%	71:trace:20:9	*cis* only	3.6:1.0
2.8o	100%	86:0:14:0	*cis* only	6.1:1.0
2.8q	71%[a]	40:0:21:10	*cis* only	1.9:1.0
2.8s	70%[b]	50:0:20:trace	*cis* only	2.5:1.0

[a]29% recovered starting material; [b]30% recovered starting material.

Table 3.2: Ratio of products from cyclisation of 2.8d, 2.8j, 2.8m, 2.8o, 2.8q and 2.8s.

When the acyl substituent size was increased from R=Me to R=Et, **2d** → **2j** and **2.8o** → **2q**, the relative amounts of 5-*exo* cyclisation products **3.19** increased in both series

(n = 1 and 2). This trend was reversed somewhat on moving from R=Et to R=*i*-Pr, **2j** → **2m** and **2.8q** → **2s**, but this was less evident for the n = 2 series and the values were still less than the R=Me analogues **2d** and **2o**. The overall effect of the increase in size of the acyl substituents seemed to be to encourage *5-exo* cyclisation to the detriment of *6-endo*, while also slowing the rate of reaction sufficiently that starting material and traces of reduced product were observed in the crude reaction mixtures. The reasons for this change in regioselectivity are unclear and would require further detailed high level modelling studies of the transition states which is not within the remit of this project. However, irreversible radical cyclisations under kinetic control have early transition states and ground-state structures can make good transition-state models.[159] Assuming the cyclisations are irreversible then knowledge of ground state conformations of the radical precursors may give some insight into the observations. Solid state X-ray structure analysis of a functionalised enamides[69,71,72] have shown that the size of the acyl group effects the dihedral angle between CH=C-N-C(O) so that larger acyl groups cause an increase in this angle. This in turn alters the positioning of the aryl radical in relation to the π framework and the regioselectivity.

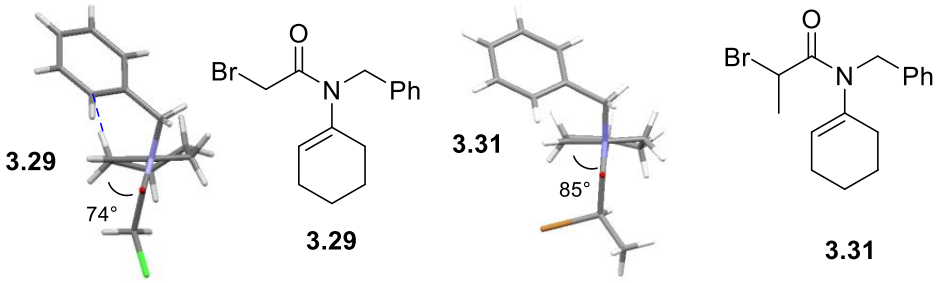


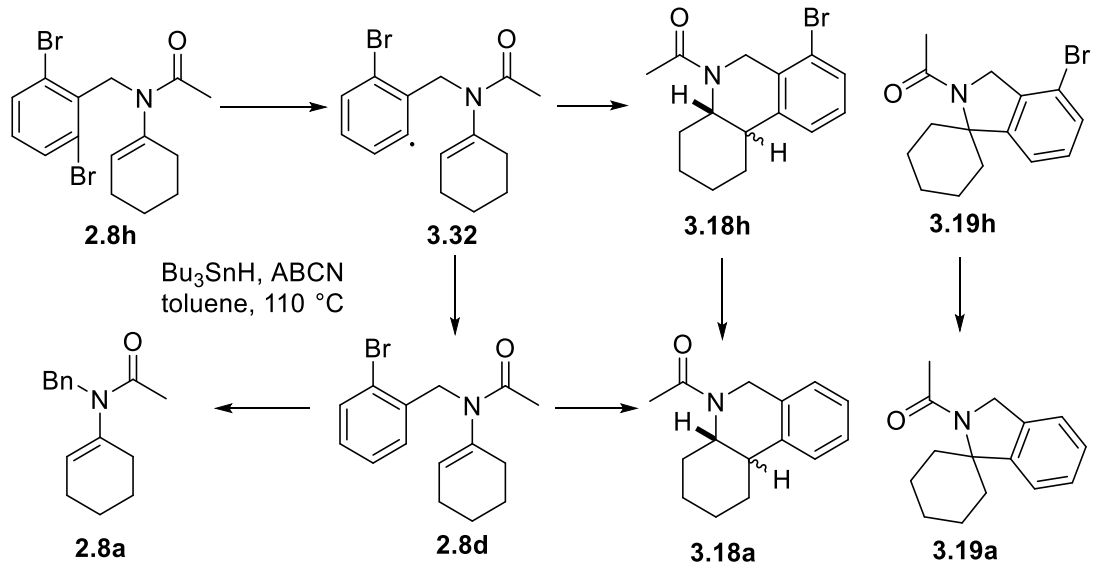
Figure 3.8: Dihedral angles found in X-ray structures of enamides.

However, it seems clear at least that the outcome of the cyclisation can be controlled by alteration of the acyl substituent (R), although not to the exclusion of any particular

pathway. It is unfortunate that despite many attempts it was not possible to make the *t*-butyl substituted analogue **2.8** (R=*t*-Bu), as this could have provided valuable insight.

3.4.4 Effect of 2,6-dibromo aryl substitution

One disadvantage of the Bu_3SnH method is the formation of pre-cyclised reduction products by competitive reduction of the initial aryl radical (**3.30**, Scheme 3.10, pg 75). This amount of reduction was found to increase with ring and acyl group size (cyclised:reduction **2.8d** = 16:1, **2.8m** = 10:1, 2**q** = 6:1). In order to lower these levels the cyclisation of the 2,6-dibromobenzyl derivatives was next investigated, illustrated using **2.8h**, Scheme 3.12.



Scheme 3.12: Tin-mediated cyclisation of 2.8h.

Theoretically, if cyclisation of the dibromide **2.8h** proceeds with a similar selectivity to **2.8d** then the ratio of the corresponding brominated cyclised:reduced products (**3.18h+3.19h**:**2.8d**) will be 93:6. If two equivalents of Bu_3SnH are used during the cyclisation then **3.18h** and **3.19h** will be further reduced to **3.18a** and **3.19a**

respectively but the 6% of reduced **2.8d** will in turn react to give another 93:6 ratio of **3.18a**+**3.19a**:**2.8a**. This would lead ultimately to a reaction that theoretically will only produce 0.4% of pre-cyclised reduction **2.8a**. In order to detect the intermediates **3.18h** and **3.19h**, **2.8h** was reacted with only 1.5 equivalents of Bu_3SnH. Cyclisation of **2.8h** resulted in six cyclised products: the non-brominated products **3.18a**$_{cis}$ (11%), **3.18a**$_{trans}$ (2%) and **3.19a** (10%), and the brominated products **3.18h**$_{cis}$ (21%), **3.18h**$_{trans}$ (17%) and **3.19h** (39%). The reduced products **2.8d** and **2.8a** are not observed in the crude mixture, nor isolated during purification. Assuming no epimerization or reversibility under the reaction conditions the overall *cis*:*trans* ratio for all the 6-*endo* products from **2.h** (1.7:1.0) is similar to the control **2.8d** (1.8:1.0), however the *endo*:*exo* ratio is significantly decreased [**2.h** (1.0:1.0), **2.8d** (4.2:1.0)]. However, the fact that the individual *cis*:*trans* ratios for 2-bromobenzyl derivative **3.18a** (5.5:1.0) and 2,6-dibromobenzyl derivative **3.18h** (1.2:1.0) are different is highly suggestive that **3.18h**$_{cis}$ is reduced to **3.18a**$_{cis}$ significantly faster than **3.18h**$_{trans}$ is reduced to **3.18a**$_{trans}$. The major rotamer of **3.18h**$_{cis}$ is opposite to that for **3.18a**$_{cis}$ while **3.18h**$_{trans}$ exists as one rotamer but **3.18a**$_{trans}$ exists as two at room temperature.

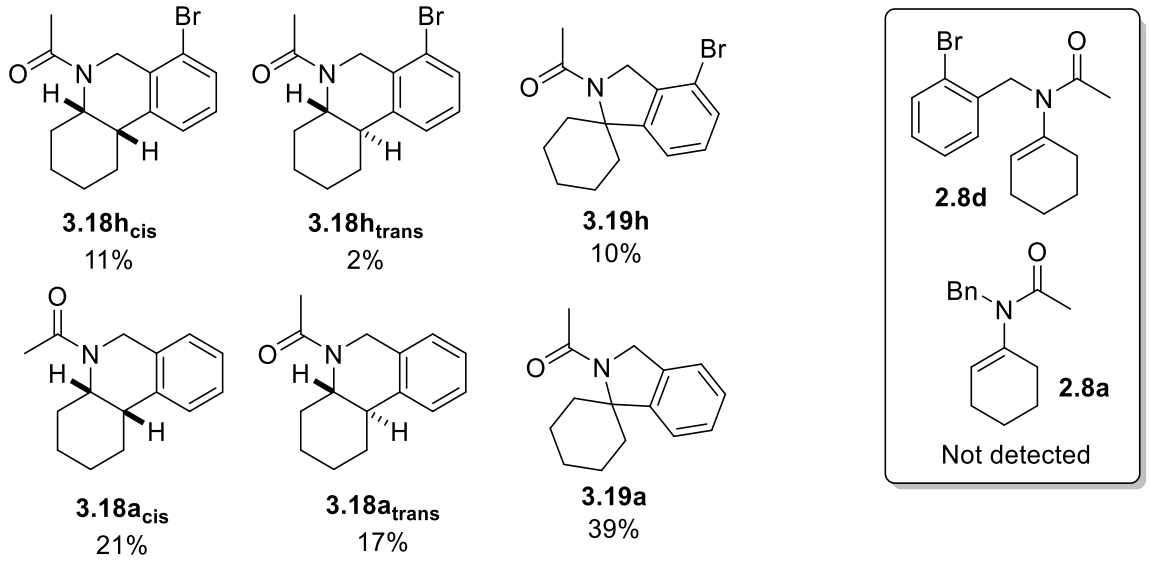
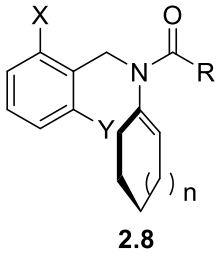


Figure 3.9: Dihedral angles found in X-ray structures of enamides.

These observations were found to be general when comparing the effect of ring size. Thus the corresponding 2,6-dibromobenzyl derivatives all gave significantly more 5-*exo* product compared to their 2-bromobenzyl analogues (*endo*:*exo* = **2.8d** vs **2.8h**, 4.2:1.0 to 1.0:1.0; **2.8o** vs **2.8p**, 6.1:1.0 to 3.3:1.0; **2.8t** vs **2.8u**, 4.5:1.0 to 3.0:1.0), Table 3.3. In addition, cyclisations of 2,6-dibromobenzyl derivatives did not lead to any identified pre-cyclisation aryl radical reduction as theorised in Scheme 3.11.



2.8

n = 1

2.8d X= H, Y = Br, R = Me
2.8h X= Br, Y = Br, R = Me

n = 2

2.8o X= H, Y = Br, R = Me
2.8p X= Br, Y = Br, R = Me

n = 3

2.8t X= H, Y = Br, R = Me
2.8u X= Br, Y = Br, R = Me

Cyclisation compound	**n**	**R**	**X**	**Ratio 3.18_{cis}:3.18_{trans}**	**Reduction % of total mixture**	**Combined Ratio 6-*endo*:5-*exo***
2.8d	1	Me	H	1.8:1.0	6	4.2:1.0
2.8h	1	Me	Br	1.7:1.0	0	1.0:1.0
2.8o	2	Me	H	*cis* only	0	6.1:1.0
2.8p	2	Me	Br	*cis* only[a]	0	3.3:1.0[b]
2.8t	3	Me	H	*cis* only	13[c]	4.5:1.0
2.8u	3	Me	Br	*cis* only[d]	0[e]	3.0:1.0

Unquantifiable trace levels of materials were ignored. [a] **$3.18p_{cis}$:$3.18o_{cis}$** = 2.0:1.0; [b] **$3.19p_{cis}$** only; [c] 27% unreacted starting material; [d] **$3.18u_{cis}$** only [e] 9% unreacted starting material; [f] **$3.19u_{cis}$** only.

Table 3.3: Effect of 2,6-dibromo- vs 2-bromobenzyl derivatives on cyclisation

The effect of the acyl group was also probed and the results compared to the analogous 2-bromobenzyl derivatives, Table 3.4. The same pattern of observation was recorded. In each case the 2,6-dibromobenzyl derivatives provided more 5-*exo* product compared to their 2-bromobenzyl derivatives, so much so that it became the major product for **2.8k**, Table 3.4.

Cyclisation compound	n	R	X	Combined Ratio 6-*endo*:5-*exo*
2.8d	1	Me	H	4.2:1.0
2.8h	1	Me	Br	1.0:1.0
2.8j	1	Et	H	1.4:1.0
2.8k	1	Et	Br	0.6:1.0[a]
2.8m	1	*i*-Pr	H	3.6:1.0
2.8n	1	*i*-Pr	Br	1.4:1.0[b]
2.8o	2	Me	H	6.1:1.0
2.8p	2	Me	Br	3.3[c]:1.0[d]
2.8r	2	*i*-Pr	H	4.0:1.0
2.8s	2	*i*-Pr	Br	2.5:1.0[e]

[a] **3.18k$_{cis}$** and **3.19k** only; [b] 2:1 ratio of **3.18ncis**:**3.18n$_{trans}$**, no **3.18m$_{cis}$** and **3.19m** observed, [c] **3.18p$_{cis}$**:**3.18o$_{cis}$** = 2.0:1.0; [d] **3.19p$_{cis}$** only; [e] **3.18s$_{cis}$** and **3.19s** only.

Table 3.4: Effect of 2,6-dibromobenzyl derivatives on cyclisation (effect of R group)

It seems the extra bromo substituent has a profound effect on the regioselectivity of cyclisation and determines the relative stability of the rotamer products. This is highly suggestive that the extra substituent is crucial in determining the ground state conformation of the substrates.

3.4.5 Cyclisation of substrates with high barriers to rotation around the enamide bond

Cyclisation of substrates with relatively high barriers to rotation around the enamide bond such as **2.16b**, **2.21b, 3.32**[84] and **3.33**[156] and those with sterically congested C-Br bonds (**2.9**) were next investigated. It was expected that a) initiation and/or cyclisation would be difficult due to the substrates being more sterically congested, and that b) 6-*endo* cyclisation would be disfavoured or slowed as there are significant steric clashes as the axially chiral radical moves towards planarity during cyclisation. The higher barriers to rotation, along with larger dihedral angles between the CH=CNC(O) might

be expected to favour 5-*exo* cyclisation with the formation of spiro derivatives. Unfortunately, reaction of **2.9**, **3.32** and **2.16b** with 1.5 eq Bu_3SnH / 0.2 eq AIBN or ACBN in toluene at reflux led to pre-cyclisation reduction only (**2.9** 5%, **3.32** not measured[84], **2.16b** 13%) along with recovered starting material, indicating that cyclisation was particularly slow. This is not surprising as the rate of Bu_3SnH reduction of an aryl radical has been measured at 5.9 x 10^8 M^{-1} s^{-1},[160] indicating that the cyclisation reactions only need to be slowed by 1-2 orders of magnitude for reduction to predominate.

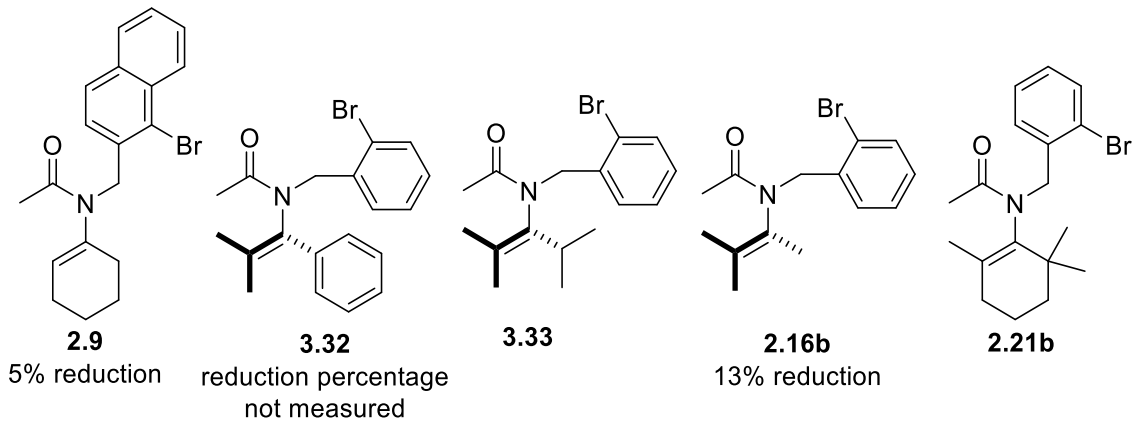
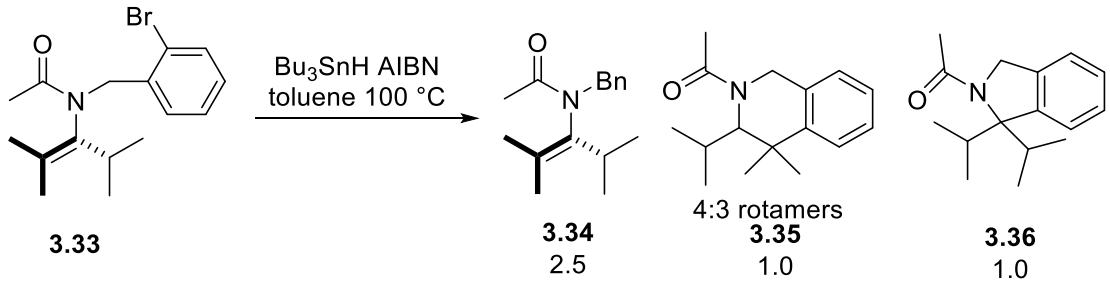


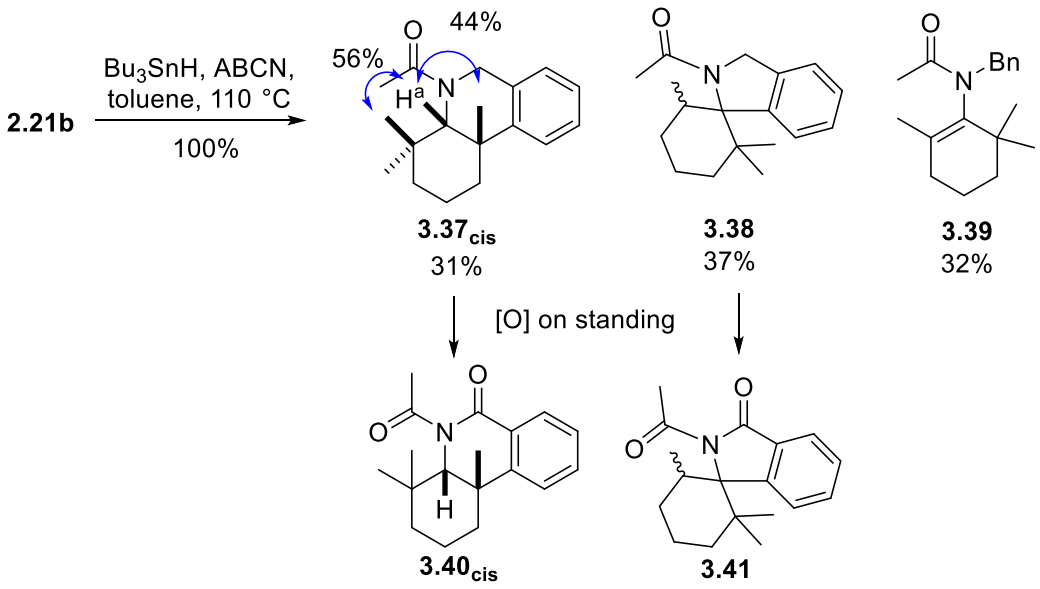
Figure 3.10: Further acetamide substrates for cyclisation

It came as a surprise therefore when it was reported that cyclisation of **3.33** under the same conditions proceeded to give a 5.0:2.5:1.0:1.0 mixture of **3.33**:**3.34**:**3.35**:**3.36** products (1:1 ratio of 6-*endo*:5-*exo* cyclisation).[156]



Scheme 3.13: Cyclisation of 3.33

Encouraged by this result, the cyclisation of **2.21b** was next investigated, which shares a similar substitution pattern around the alkene. A 31:37:32 mixture of the *6-endo* **3.37**$_{cis}$, the *5-exo* **3.38** and the reduced product **3.39** was obtained at the end of the reaction. No *6-endo trans* product **3.37**$_{trans}$ was visible in the crude mixture or recovered after purification. Both cyclized products were found to oxidize in air over time to the corresponding imides **3.40**$_{cis}$ and **3.41** (each as one rotamer as depicted in Scheme 3.14). Amide **3.38** and imide **3.41** were detected as one diastereomer each, but stereochemistry could not be determined.



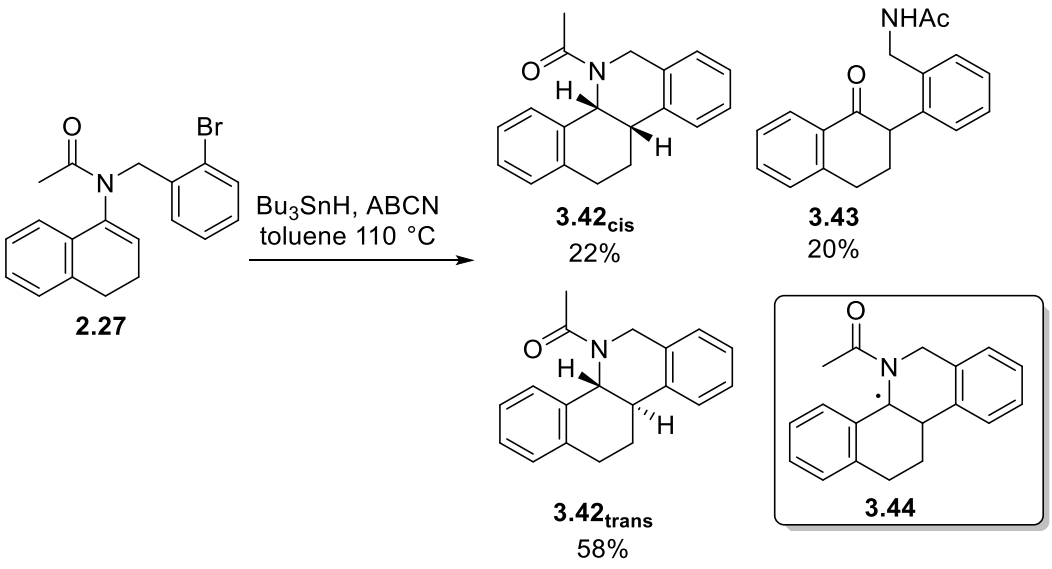
Scheme 3.14: Cyclisation and subsequent oxidation of 2.21b

These findings reinforced what had been observed upon cyclisation of the simpler enamides: increased steric hindrance and higher barriers to rotation led to a larger proportion of both *5-exo* product and pre-cyclisation reduced product, compared to the original enamide **2.8d**. Increased hindrance of the 6-position of the cyclohexene ring rendered *5-exo* cyclisation more favourable. The *6-endo* **3.37**$_{cis}$ cyclisation product was identified by nOe experiments by irradiation of the H^a proton at 4.68ppm. Due to the high barrier to rotation around the *N*-cycloalkenyl bond of this compound ($\Delta G^{\ddagger}$

=30.6 kcal mol^{-1}), as well as the success in separating the individual atropisomers by chiral HPLC ($t_{½}$ = 47.9 years at 298 K), this substrate was a promising candidate to investigate chirality transfer. However, at the reaction temperature for cyclisation (110 °C) this substrate has a half-life of only 3.5 hours. Nevertheless, studies will be carried out by Curran and coworkers, into the possibility of chiral transfer reactions. This work has not been completed at the time of writing.

3.4.6 Stabilising the 6-*endo* cyclized radical intermediate

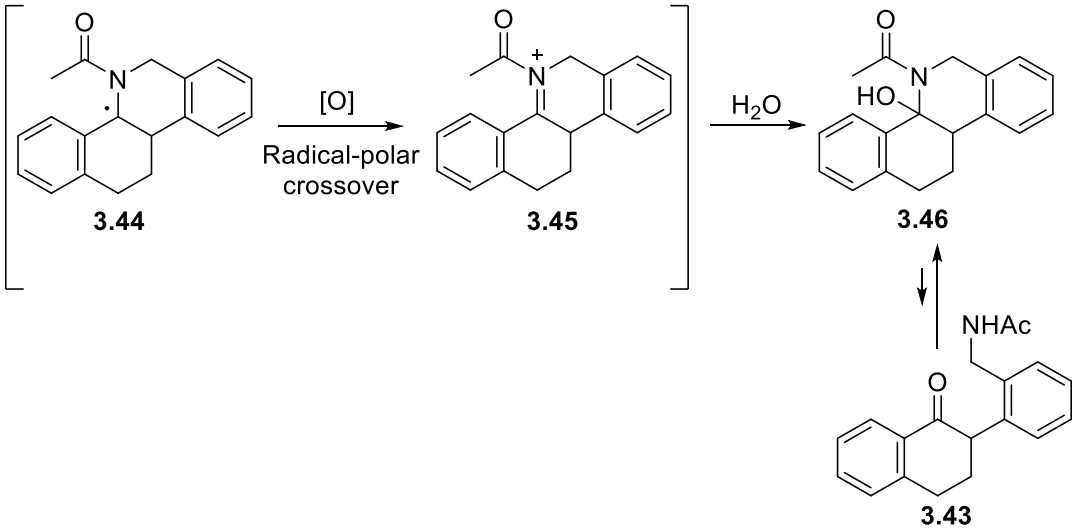
The possibility of cyclising the substrate **2.27** was next investigated, which would generate a particularly stabilised benzylic radical **3.44** upon 6-*endo* cyclisation.



Scheme 3.15: Cyclisation and subsequent oxidation/ring opening of 2.27

The reaction provided a 22:58:20 ratio of three products **3.42$_{cis}$**, **3.42$_{trans}$** and **3.43** respectively but no 5-*exo* product was detected. Both **3.42$_{cis}$** and **3.42$_{trans}$** existed as 1.00:0.89 mixtures of amide rotamers, the major rotamer for each is shown in Scheme

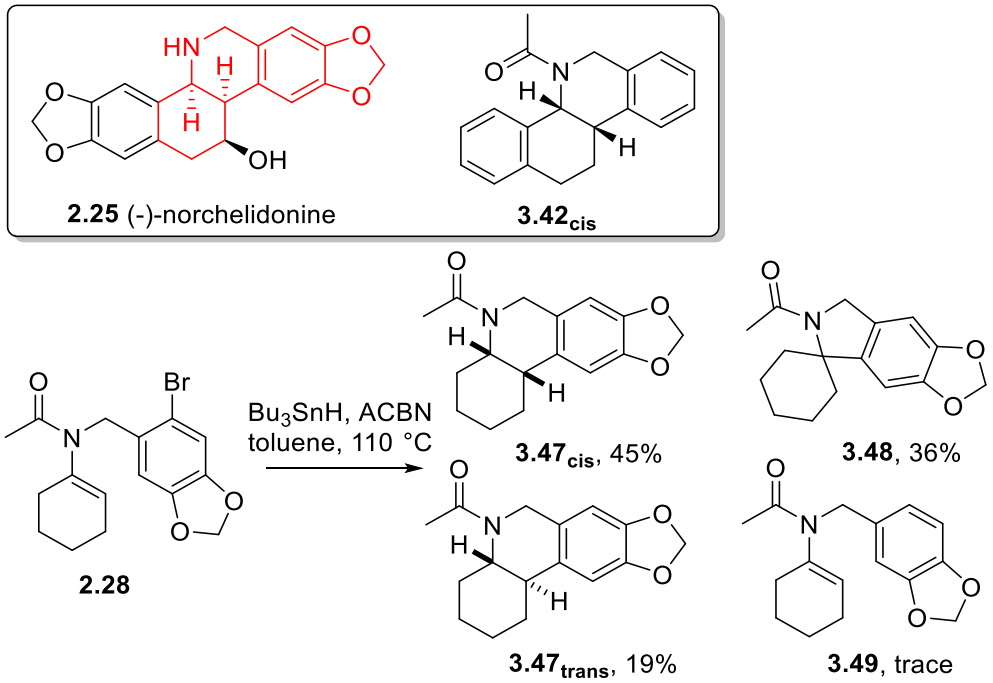
3.15. The **3.42$_{cis}$** and **3.42$_{trans}$** isomers were identified from the coupling constants of the doublets for the H^a signals (**3.42$_{cis}$** major rotamer: 6.28 ppm *J* = 6.0 Hz, minor rotamer: 5.30 ppm, *J* = 6.0 Hz, and **3.42$_{trans}$** minor rotamer: 4.80 ppm *J* = 10.5 Hz, major rotamer: 4.63 ppm, J = 10.5 Hz). The enhanced stability of the radical intermediate **3.44** suggests that either the *5-exo* cyclisation is reversible or the extra aryl group precludes efficient orbital overlap at the *ipso* position. Compound **3.43** is also formed in significant quantities. This could be formed either by trapping of advantageous oxygen by the captodatively stabilized radical **3.44** → **3.46** or by oxidation of the long-lived intermediate **3.44** to the acyl iminium ion **3.45** *via* a polar cross-over process followed by trapping by water to give **3.46**. Once formed aminol **3.46** ring-opens to give the more stable keto-amide **3.43**. Contrary to intuition, oxidation of tertiary radicals to cations under reductive Bu_3SnH conditions has been reported previously.[6] This is therefore the only substrate studied thus far that has exhibited a preference for the *6-endo trans* pathway **3.42$_{trans}$** over the **3.42$_{cis}$.** It is probable that the labile H^a proton of **3.42$_{cis}$** may undergo equilibration to the more thermodynamically stable **3.42$_{trans}$** under the reaction conditions, although this wasn't tested.



Scheme 3.16: Potential mechanism of oxidation/ring opening

3.4.7 Towards natural product skeletons

The 6-*endo* product **3.42**$_{\mathbf{cis}}$ contains the tetracyclic core of the alkaloid (-)-norcheldonine **2.25**. It was next determined whether the addition of electron donating groups to the aryl bromide portion of the molecule was tolerated, as this would provide the right hand portion of the natural product skeleton.

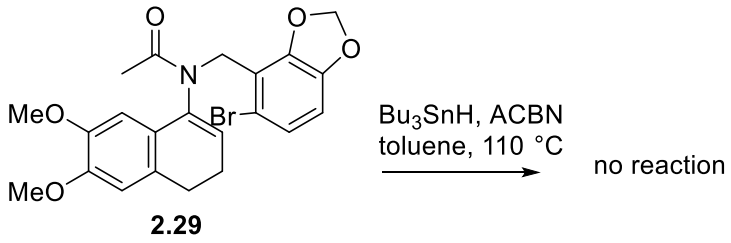


Scheme 3.17: Cyclisation approach towards the (-)-norchelidone skeletal framework

Little difference was expected between the cyclisation results of **2.8d** and **2.28**. The expected range of products **3.47**$_{cis}$, **3.47**$_{trans}$ and **3.48** was obtained in the ratio 45:36:19, with trace amounts of reduced product **3.49** observed in the crude reaction mixture. This was, as expected, similar to the product ratio for the cyclisation of **2.8d** (48:27:18), and therefore it can be concluded that adding electron donating substituents as well as increasing the size of the 2-bromobenzyl group in this manner (extra substitution *meta* to the reacting bromine, rather than *ortho* as it was with **2.9**) does not interfere with cyclisation, but nor does it affect the outcomes of said cyclisation.

Given this success in cyclising **2.27** and **2.28**, it was expected that **2.29** would cyclise at the very least in a *6-endo* fashion (the extra aryl substitution was *para* to the reacting bromine in the 2-bromobenzyl substituent, and it was considered unlikely that the methoxy groups would interfere). This, however, proved not to be the case: compound **2.29** showed no sign of cyclisation or reduction product either in the crude reaction

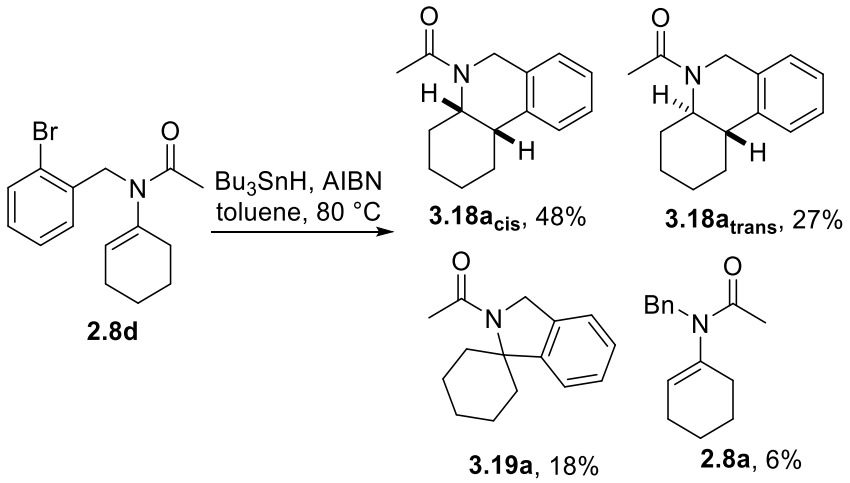
mixture or after repurification of the starting material was attempted by column chromatography. Only starting material was observed. This would indicate that the aryl halide bond in **2.29** is particularly difficult to break under normal radical cyclisation conditions. The reasons for this were unknown and further study and cyclisation attempts would be necessary to fully understand the lack of cyclisation observed.



Scheme 3.18: Attempted cyclisation of 2.29

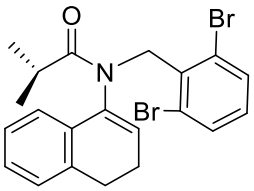
3.5 Summary

In this chapter the effect of an increased barrier to rotation in compounds **2.8**, **2.9**, **2.16**, **2.21**, **2.27**, **2.28** and **2.29** on the efficacy and products of their radical cyclisations has been studied. The amount of reduced starting material formed has been minimised by dibromination of the starting material aryl group, so as to maximise the overall yield of cyclisation products. The ratio of *5-exo-trig* to *6-endo-trig* cyclisation product varies according to the substitution level of the aryl moiety, the acyl group (increased aryl substitution and acyl group size both increase the proportion of *5-exo-trig* product **3.19**) or the cycloalkane ring (significant steric hindrance of the ring can completely remove the *5-exo* pathway).



Scheme 3.19: Cyclisation of 2.8d.

Substitution at the *meta* position of the aryl ring was found to have little effect on the outcome of cyclisation (**2.27**), but *ortho*- and *para*-substitution were found to completely prevent cyclisation. Expansion of the cycloalkenyl ring causes an increase in stereospecificity of the *6-endo* cyclisation so as to only furnish the *cis* isomer of the *6-endo* cyclisation product, while the ratio of *6-endo* cyclisation to *5-exo* follows the same trend as the barriers to rotation (an increase for the cycloheptenyl substrates, followed by a smaller decrease for the cyclooctenyl substrates). Significant steric hindrance of the cycloalkenyl ring (an extra aryl ring, for example) was found to completely prevent *5-exo* cyclisation, although some alternative ring-opened product was isolated instead. It was thought to be possible to conduct chiral transfer experiments on compound **2.21b**, as it cyclised readily to a smaller range of products than observed with initial compound **2.8d** (no 6-*endo-trans* cyclisation product was observed) and had a high barrier to rotation. This compound, along with all cyclised products, were accordingly sent to Curran and co-workers in Pittsburgh, although this work was unfortunately not complete at the time of writing. None of the compounds cyclised in this chapter provided the single reaction pathway that was hoped for, but the results were nonetheless of interest and could merit further investigation.



3.50

Figure 3.11: Possible structure for further investigations into substituent effects on radical cyclisation.

In particular, a combination of a dihydronaphthyl cycloalkenyl moiety, a dibrominated aryl ring and an isopropyl acyl group such as in **3.50** could be used to remove the possibility of the *6-endo trans* and *5-exo* cyclisation pathways and the reduction pathway, and render the reaction regio- and stereospecific despite the reaction conditions. Equally, the synthesis of the natural product skeleton from **2.29** should be reattempted and further investigated.

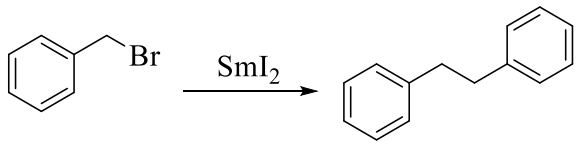
Chapter 4: Alternative Cyclisation Methods for *N*-*o*-Halobenzyl-*N*-acetylenamides

4.1 Introduction

Having established in Chapter 3 that *N*-acetylenamides **2.8** could be cyclised using organostannane radical methods, alternative methods of cyclisation were investigated. The tin method used in Chapter 3 is well known to be toxic, reductive and indiscriminate, as well as leaving an organostannane residue that renders purification extremely difficult. Therefore, several methods were investigated that might remove these difficulties.

4.1.1 Samarium-mediated cyclisation

Effective replacement methods for the generation of aryl radicals without using tin hydrides have in the past included organosilane- and samarium diiodide-mediated reations.[94,121,161–163] The samarium diiodide method has been used to generate radicals from organic halides since its inception[93] by Kagan in 1981 (Scheme 4.1).

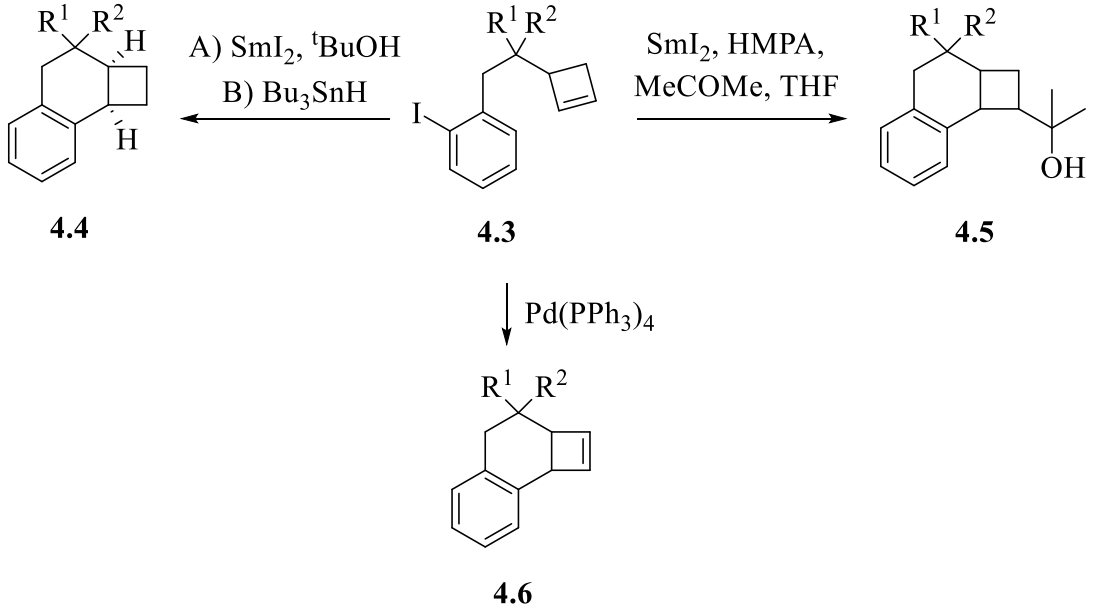


4.1 **4.2**

Scheme 4.1: Dimerisation of benzyl bromide using SmI_2.

The use of SmI_2 to generate aryl radicals is of slightly more recent date: the intramolecular reaction of aryl radicals generated by SmI_2 onto an alkene was reported by Molander and Harring in 1990.[94] Curran *et al*[163] formed the BCD ring system of penitrem D **4.4** from the aryl iodide **4.3**, Scheme 4.2, *via* a 6-*exo*-*trig* cyclisation in 54-90% yield. The addition of HMPA as an additive and co-solvent (acetone) produced

4.5. They also report a palladium Heck cyclisation of the same substrates, resulting in products **4.6** with increased functionality in better yield (78-84%), which will be discussed in greater detail in section 4.1.4.

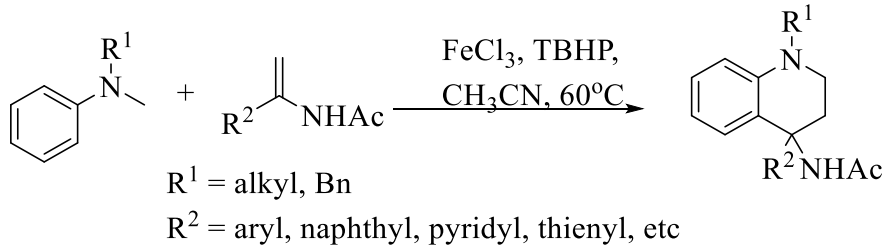


Scheme 4.2: Intramolecular cyclisations mediated by SmI_2 and $Pd(PPh_3)_4$

The 6-*exo*-*trig* cyclisation protocols described for **4.3** in Curran's work should be transferable to compounds **2.8**, as the tin and samarium methods are seen to work almost equally well for compounds **4.3**. In Curran's work HMPA was used as a co-solvent, to enable the reaction to be carried out under milder conditions than would have been necessary in its absence. This was first reported as a way to facilitate SmI_2-mediated reductions by Inanaga[164] but is equally useful for cyclisations.[163] This renders the method more toxic due to the presence of HMPA, a known carcinogen, but the ability to conduct radical cyclisations at lower temperatures would be attractive for these substrates if individual atropisomers were used. This would allow potential chiral transfer from substrates to cyclisation products to occur at a lower temperature than with the tin hydride methods described in the last chapter.

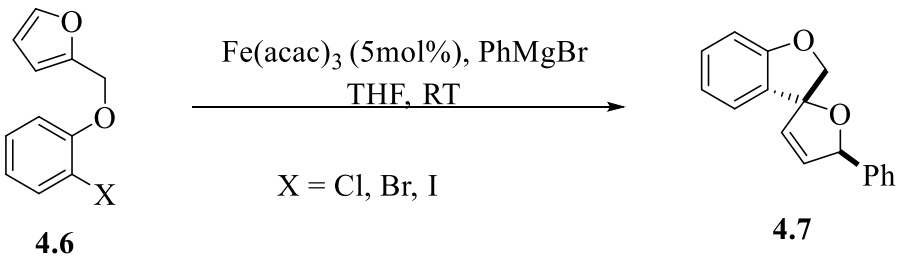
4.1.2 Iron-mediated cyclisation

The use of iron in heterocycle synthesis has been extensively investigated, although at the present time iron catalysts have mostly been used for intermolecular, rather than intramolecular, cyclisation.[165] Guan has recently reported the iron-catalysed dehydrogenative [4+2] intermolecular cycloaddition of a series of enamides and anilines with alkenes, using $FeCl_3$,[166] to furnish a wide array of nitrogen-containing heterocycles (Scheme 4.3) in good yield, with a wide functional group tolerance.



Scheme 4.3: [4+2] Cycloaddition reported by Guan.

In 2016 Sweeney and coworkers reported a "*novel and sustainable iron(III)-catalysed arylative spirocyclization reaction*" using $Fe(acac)_3$ and an aryl Grignard reagent (Scheme 4.4)[167] to generate spirocycles **4.7** from aryl halides such as **4.6**.



4.6 **4.7**

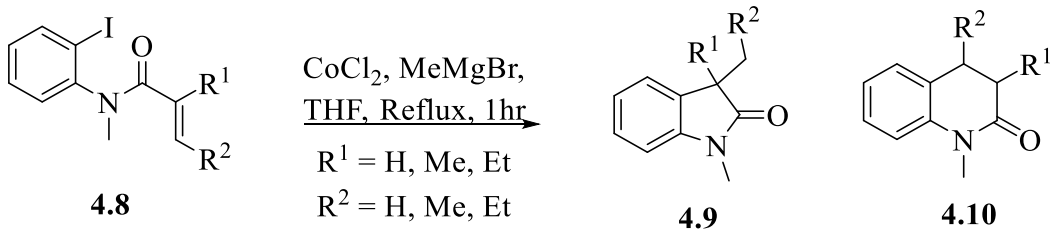
Scheme 4.4: $Fe(acac)_3$-mediated cyclisation reported by Sweeney.

Although this method was found to work best with aryl iodides, the reaction of the aryl bromide furnished 30% of the same 5-*exo-trig* product **4.7**. Replacement of either of the two oxygen atoms with nitrogen was found to yield the corresponding amine

products, also in excellent yield. This can therefore be considered a potentially useful method for obtaining nitrogen-containing heterocycles. Alteration of the Grignard reagent used was also found to affect the outcome of the reaction: aryl Grignard reagents were found to induce superior yields compared to alkyl Grignard reagents, with only EtMgBr furnishing a respectable yield (36%). If the reaction proceeds *via* a free radical (as opposed to a metal complexed radical) this approach would be expected to yield the same 5-*exo*-*trig* and 6-*endo*-*trig* cyclisation products as produced *via* the Bu_3SnH mediated pathway described in the last chapter.

4.1.3 Cobalt-mediated cyclisation

Work done by Jones in 1994 established that cobalt dihalides could be used to mediate aryl radical cyclisations in the presence of a Grignard reagent.[168] Anhydrous cobalt dichloride was used in conjunction with methylmagnesium bromide in THF to accomplish the cyclisation of a group of *ortho*-iodoacryloylanilides **4.8** (Scheme 4.5). The cyclisation of the bromine analogue was also successful, albeit with a lower yield (45% compared to 71%). The ratio of regioisomers was similar to that obtained using conventional reductive Bu_3SnH processes.



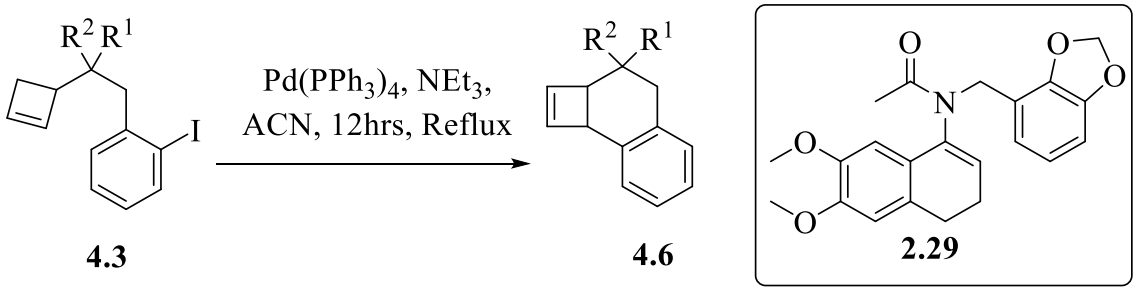
Scheme 4.5: Cobalt-mediated cyclisation of iodoanilides 4.8.

As was predicted, the substitution of the alkene affected the regioisomer obtained as product: unsubstituted alkenes (R^1=R^2=H) or substituted (R^1=H, R^2=Me) favoured the

5-*exo-trig* cyclisation product **4.9**, whereas alkenes with higher substitution at R^1 (R^1=Me, R^2=H) favoured the 6-*endo-trig* cyclisation pathway to give **4.10**. By analogy, therefore, the cyclisation of compounds **2.8** was expected to proceed *via* the 6-*endo-trig* cyclisation pathway.

4.1.4 Heck cyclisation

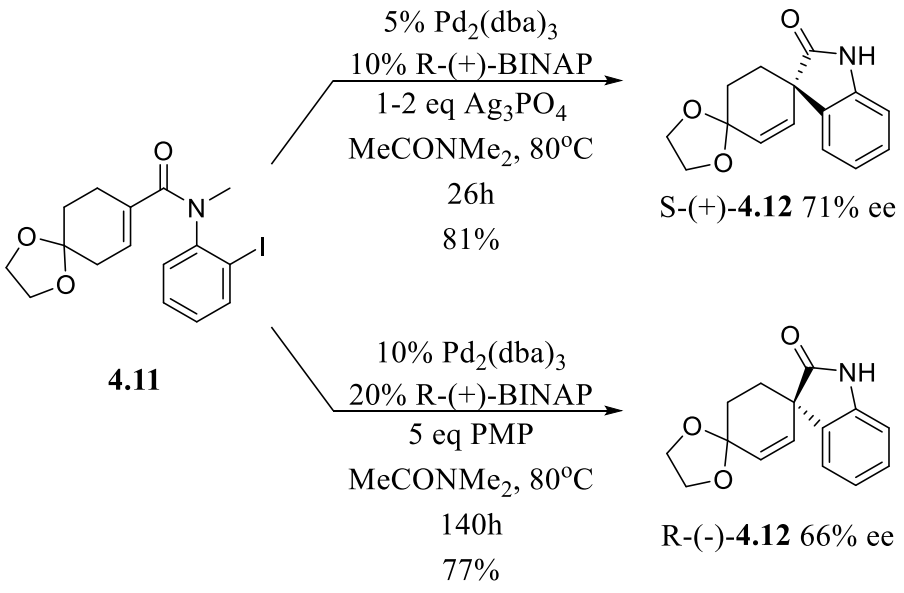
As discussed in section 4.1.1, Curran's work on radical cyclisations using samarium was extended to palladium Heck cyclisations of the same substrates, to yield similar cyclic skeletons (Scheme 4.6).



Scheme 4.6: Palladium Heck cyclisation reported by Curran.

The key difference between the products of radical and of Heck cyclisations was that the Heck reaction product retained a double bond, thereby preserving some of the functionality of the starting material. This would be desirable for further functionalisation of compounds synthesised in this work, particularly in the case of **2.29**. The regiochemistry of the cyclisation was the same as when a samarium-based radical method was used: the lack of 7-*endo-trig* cyclisation product was in this case unremarkable, given the steric constraints of the cyclobutene ring. However, the *exo-trig* cyclisation pathway has been reported to predominate in cases where similar substrates were cyclised.[169,170] More complicated palladium catalysts can also be used

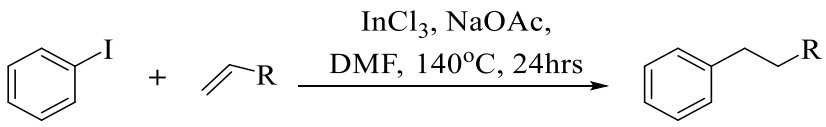
to mediate Heck-type reactions to accomplish stereospecific cyclisations of substrates related to compounds **2.8** with high yields, and have been reported to only generate the 5-*exo-trig* product, as found by Hartwig.[66,123,169,171] Of particular interest is the synthesis of compounds containing quaternary carbons: the first reported asymmetric Heck-type cyclisation using palladium to produce such compounds was reported in 1989.[116] Several combinations of reagents have been reported, with varying degrees of success.[123,169,172,173] Overman and Ashimori reported the asymmetric synthesis of oxindoles[169] using palladium and R-(+)-BINAP, as detailed in scheme 4.7.



Scheme 4.7: Overman's asymmetric oxindole synthesis.[169]

The conditions used by Overman involved, in both cases shown in Scheme 4.7, a chiral ligand. The fact that compound **4.11** exists as a mixture of interconverting anilide atropisomers suggests that chiral induction is produced by kinetic resolution. In other words, one atropisomers cyclises preferentially to give the observed product. It would be preferable to be able to cyclise such aryl halides onto an alkene without the need for chiral catalysts, and compounds **2.8**, with higher barriers to rotation, would seem to be uniquely suited to this if individual atropisomers were isolated. The conditions

used by Curran (Scheme 4.6), or the combination of $Pd(dba)_2$, a ligand and trimethylamine which was found to be effective in reacting aryl bromides with vinyl substrates[66,123,171] would perhaps be more suited to the purposes of this project, without any need for chiral catalysts or ligands. Additionally, in 2013 Wang and Pan reported a palladium- and ligand-free Heck reaction of aryl iodides with alkenes (Scheme 4.8), using $InCl_3$ and NaOAc, which gave 96% conversion to the desired product.[174] If suited to the compounds described in this project, this version of the Heck reaction could provide a much simpler route to the desired cyclised compounds than the palladium method.

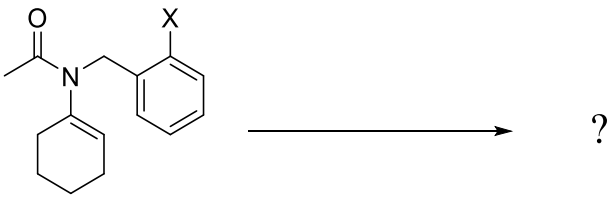


Scheme 4.8: Indium-mediated Heck reaction.

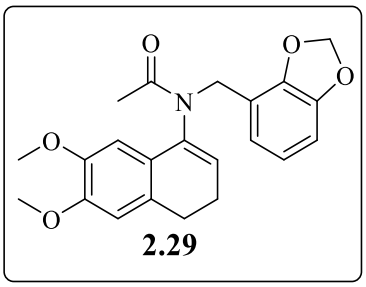
4.2 Aims of chapter

In the previous chapter a range of potentially atropoisomeric enamide substrates were reacted using Bu_3SnH to assess the regiochemical outcome of their cyclization reactions. Investigations into substrates exhibiting varying levels of restricted rotation around the enamide were undertaken in order to determine if cyclization of individual hindered atropisomers would be possible. Unfortunately the high temperatures required to cyclize the more hindered enamides precluded this approach to produce enantiomerically enriched products. In this chapter a number of other protocols were investigated (initially with control substrates **2.8d** and **2.8e**) by with varying reaction conditions, as detailed in section 4.1, with varying degrees of success. The yields, conditions, and regiomeric outcomes of each set of reactions were analysed with

regards to their efficacy and compared to the tin-mediated method used in Chapter 3. Ultimately the best method would be applied to the cyclisation of a selection of the compounds synthesised in Chapter 2, to assess the scope of the process. More specifically it was desirable to address:



2.8d-e



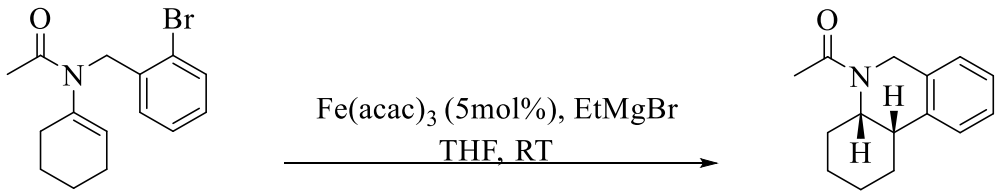
2.29

Scheme 4.9: Compounds used for testing conditions and compound 2.29.

- The effectiveness and differences between cyclisation reactions mediated by samarium, cobalt, iron and palladium.
- The possibility of optimising a method for cyclization of compounds synthesised in Chapter 2 at ambient temperatures.
- The differences between cyclisations undertaken in this chapter and those mediated by tin in Chapter 3.
- Any possible applicability to the construction of a natural product skeleton, particularly from compound **2.29**.

4.3 Preliminary attempts

Initially, compound **2.8d** was cyclised using each of the methods described in section 4.1, so as to determine whether such conditions would furnish any useful results. In each case, compound **2.8d** was subjected to the reaction conditions deemed most likely to be successful from literature research into each method of cyclisation mediation. Unfortunately, the iron, cobalt and indium cyclisation methods proved unsuited, as no reaction was observed in the case of either the indium or cobalt cyclisations, while iron cyclisation produced only trace amounts of **3.18a$_{cis}$** that was not recoverable by column chromatography.



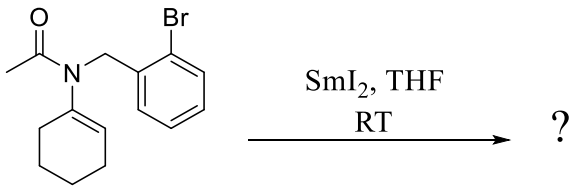
2.8d **3.18a$_{cis}$** trace

Scheme 4.10: Iron-mediated cyclisation of 2.8d.

For example, reaction of **2.8d** with $Fe(acac)_3$ (0.01eq), TMEDA (0.1eq) and EtMgCl (1.2eq) in THF at reflux produced only trace amounts of **3.18a$_{cis}$** (Scheme 4.10), while reaction of **2.8d** with $CoBr_2$ (0.5eq) and MeMgBr (2eq) in THF at room temperature, and with $InCl_3$ (0.05eq) and NaOAc (2eq) in THF at room temperature both resulted in no cyclisation and recovery of starting material. These methods were abandoned due to time constraints. However, samarium and palladium cyclisations proved more fruitful.

4.3.1 Samarium cyclisations

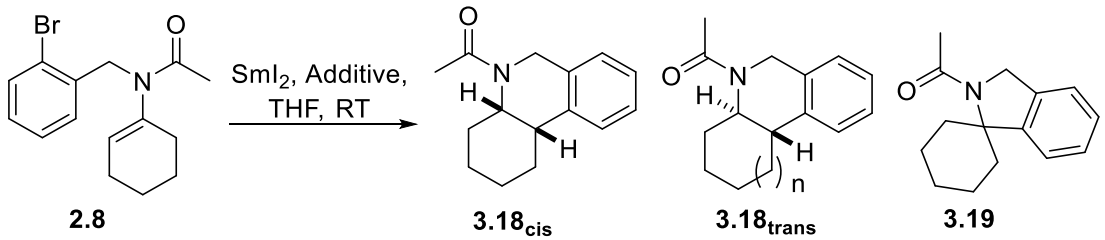
Initially, cyclisation of **2.8d** using a samarium method was attempted without any additives. The regioselectivity of cyclization should be similar to those using the tin hydride method, as the only difference would have been how the radical was generated.



2.8d

Scheme 4.11: Samarium-mediated reaction of 2.8d.

Thus, to a solution of **2.8d** (1eq) in THF (0.08M) was added SmI_2 in THF (1.1eq), dropwise over several minutes. This solution was stirred at room temperature under nitrogen until the SmI_2 was seen to have fully oxidised: the colour of the solution had changed from dark blue to yellow. The reaction mixture was washed with NH_4Cl and brine, extracted into EtOAc and dried. The ^1H NMR of the crude reaction mixture showed no reaction: only starting material was recovered. As some literature reports utilise additives (e.g. HMPA) to mediate reactions the conditions were varied as reported in Table 4.1.



2.8 **3.18$_{cis}$** **3.18$_{trans}$** **3.19**

Scheme 4.12: Samarium diiodide-mediated radical cyclisation of 2.8d, see Table 4.1.

Entry	Eq of SmI_2	Additive	Eq of additive	Temp	Yield
1	1.1	/	0	RT	0
2	2.2	/	0	RT	0
3	2.2	/	0	Reflux	0
4	1.1	DMI	8	RT	0
5	1.1	DMSO	8	RT	0
6	1.1	HMPA	8	RT	0
7	1.1	HMPA	3	RT	0
8	2.2	HMPA	3	Reflux	0
9	5	HMPA	10	RT	66%
10	5	HMPA	10	Reflux	0
11	5	DMI	10	RT	0
12	5	DMSO	10	RT	0
13	2	HMPA	10	RT	0
14	2	HMPA	5	RT	0

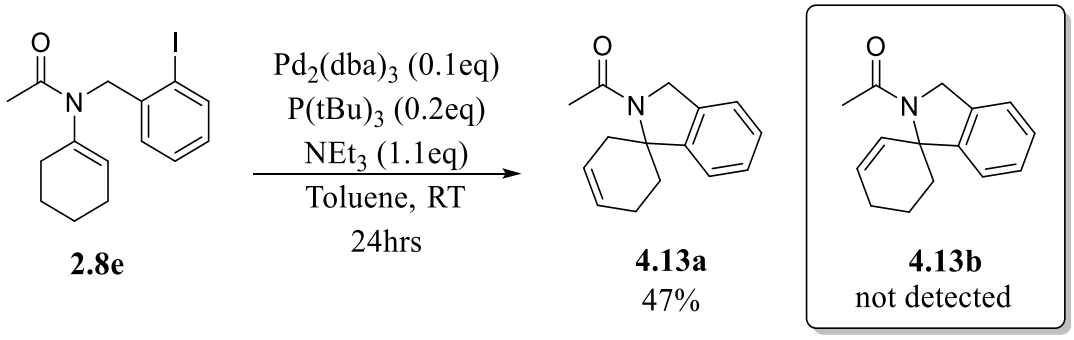
Table 4.1: Screening of samarium diiodide reaction conditions

Initially the reaction was attempted with no additive, with variation of the temperature and the amount of SmI_2 used. These were all unsuccessful and returned quantitative yields of the starting material **2.8d** (entries 1-3). In an attempt to avoid the use of HMPA, commonly used to promote samarium diiodide reactions but known to be extremely toxic, the first additives used were 1,3-dimethyl-2-imidazolidinone (DMI), a common alternative to HMPA, and DMSO (entries 4-5). These were equally unsuccessful and the literature procedure using HMPA was therefore used.[94] This, however, proved futile in the first instance, as the cyclisation remained unsuccessful (entries 6-8) even at reflux. Finally, a successful SmI_2 cyclisation method was found: this used 5 equivalents of SmI_2 and 10 of HMPA, and the reaction was left stirring overnight at room temperature as the blue colour of the SmI_2 had not disappeared after 5 hours (entry 9). The solvent was found to have evaporated overnight, but a ^1H NMR of the crude product obtained after workup showed the reaction to have produced the products **3.1a**$_{cis}$, **3.1a**$_{trans}$, **3.2a** and the starting material **2.8d** in the approximate ratio 14:39:14:33 for an overall yield of cyclised products of 66% (entry 9). This is therefore inferior in conversion to the tributyltin hydride method (100% conversion) and while

the 6-*endo* cyclisation **3.1a** remains prevalent the *trans* product **3.1a$_{trans}$** is now the major one (Bu_3SnH ratio *cis:trans* = 1.8:1.0, SmI_2 *cis:trans* = 1.0:2.8). The regiochemistry 6-endo:5-exo remains similar to that of the Bu_3SnH reaction (Bu_3SnH ratio *endo:exo* = 4.2:1.0, SmI_2 *endo:exo* = 3.8:1.0). Assuming both proceed *via* the same free aryl radical intermediate, the key difference between the two methods was the temperature and the method of termination. The predominance of the **3.1a$_{trans}$** product at room temperature (SmI_2), compared to the predominance of **3.1a$_{cis}$** at 120 ^oC (Bu_3SnH), would seem to confirm that **3.1a$_{trans}$** is the kinetic product of the reaction as postulated in Chapter 3 (page 75). Alternatively, the different termination mechanisms may play a part in determining the stereochemistry. While the Bu_3SnH reaction is terminated by reduction of the intermediate radical by Bu_3SnH, the SmI_2 process is likely terminated *via* a radical-polar crossover reaction to give the corresponding anion (although this will be relatively unstable). Quenching by the addition of a proton would then give rise to the observed products. Attempts to optimise these conditions by refluxing the reaction mixture (entry 10), by replacing HMPA with the equivalent amount of DMI or DMSO (entries 11-12) or by reducing either the amount of SmI_2 or the amount of HMPA used were unsuccessful. The required reaction conditions were deemed to not be an improvement over the tin method, particularly considering the toxicity of HMPA, although the ambient temperature was an advantage.

4.3.2 Palladium Heck cyclisation

Due to the failure of the indium Heck cyclisation method, palladium Heck cyclisation was first attempted with the iodine derivative **2.8e**. A solution of **2.8e** (1eq), $Pd_2(dba)_3$ (0.1eq), $(t\text{-}Bu)_3P$ (0.2eq) and triethylamine (1.1eq) in toluene was stirred at room temperature for 24 hours. The reaction mixture was then poured into saturated LiCl solution and washed with ether. The ether layer was concentrated under vacuum to give a brown oil, which was purified by column chromatography to obtain the 5-*exo* cyclised product **4.13a** as a yellow oil (30mg, 47%). No **4.13b** or 6-*endo* product was observed in the crude reaction mixture by ^1H NMR, confirming that the palladium Heck cyclisation of this and of similar compounds[169,170] prefer the *exo-trig* pathway due to the mechanistic differences of Heck verses radical pathways.



Scheme 4.13: Palladium Heck cyclisation of 2.8e.

The product **4.13a** was identified by ^1H NMR spectroscopy and existed as one amide rotamer at room temperature (H^2_{axial} and $H^{2'}_{axial}$ at 3.1 and 3.9 ppm respectively): this downshift marks the influence of the oxygen on the two protons in question, and therefore indicates that the amide conformer obtained has the oxygen pointing towards the cyclohexenyl ring. The presence of two cyclic alkane signals downshifted rather than one indicates that the preferred conformer is **4.13a**$_1$ (Figure 4.1), as **4.13a**$_2$ would only have one downshifted proton $H^{3'}_{axial}$.

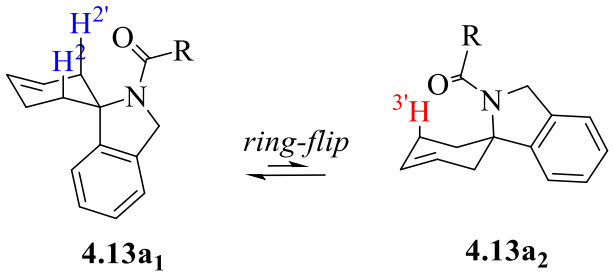
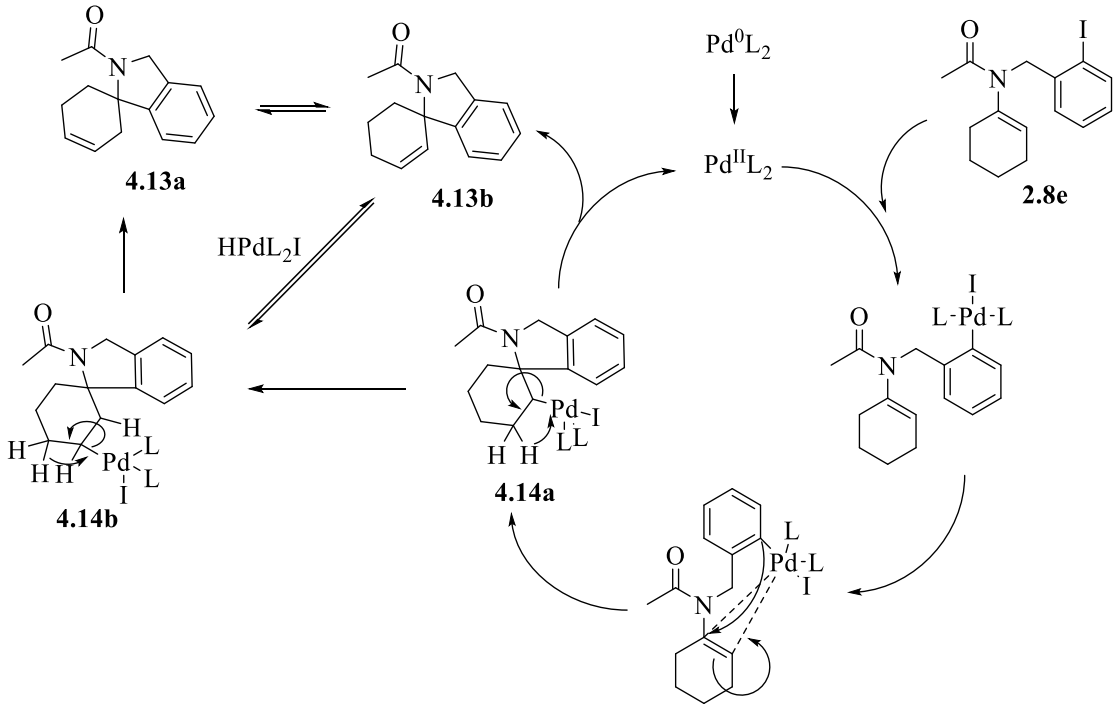


Figure 4.1: Ring flip in product 4.13a.

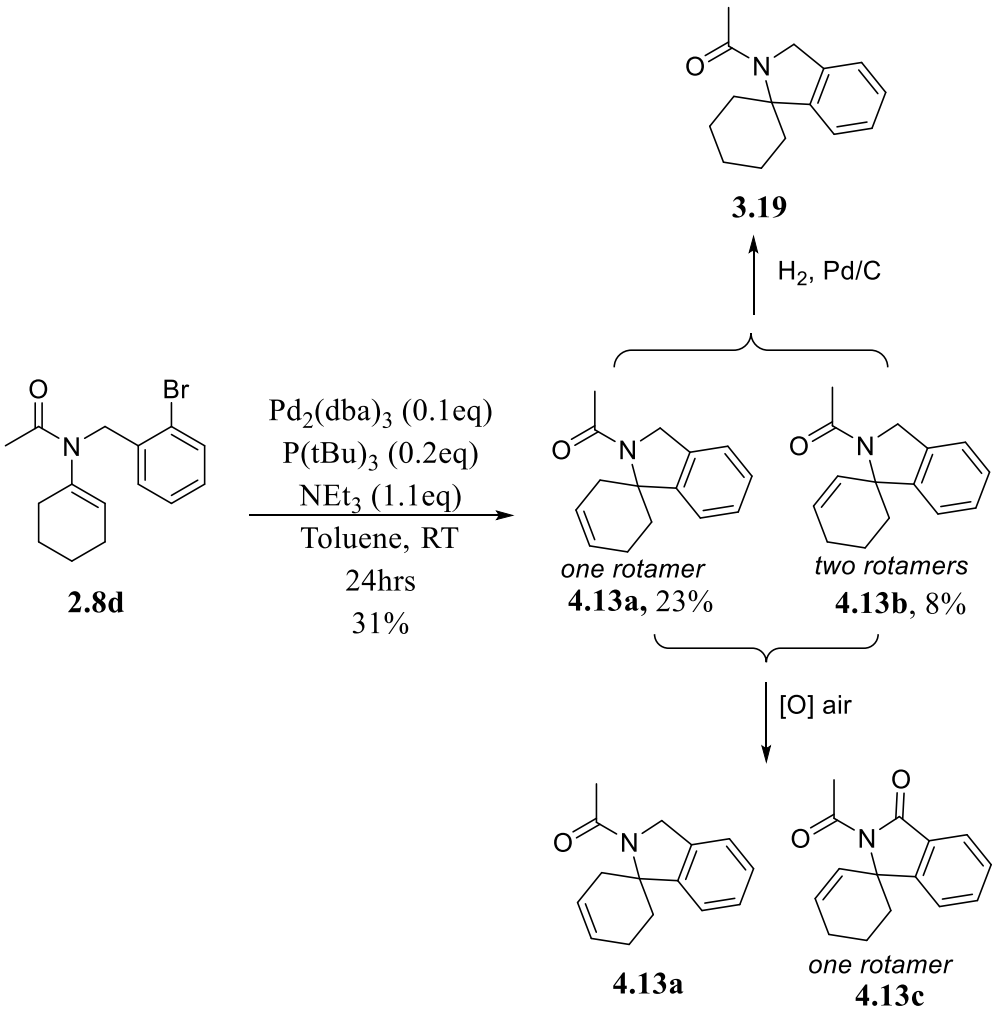
The oxidative nature of the cyclisation and the fact that a single product that was obtained at room temperature from this cyclisation was also encouraging: increased stereo- and regioselectivity at room temperature would be highly useful for other substrates. It must be evident from mechanistic considerations that product **4.13a** cannot be the direct result of the Heck reaction (Scheme 4.14): it must be obtained *via* palladium-mediated olefin migration from either the initial cyclisation product **4.13b** or from the previous intermediate **4.14a** *via* a Pd migration (Scheme 4.14).



Scheme 4.14: Palladium-mediated Heck reaction and olefin migration.

Olefin migration during a Heck reaction has been observed and reported in cycloalkenes for similar compounds, where the product range was also a set of spirocycles.[175]

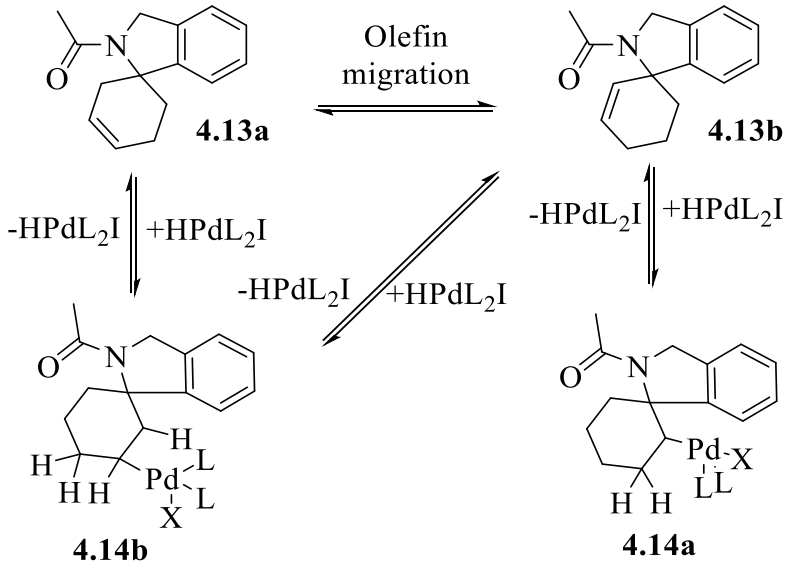
The majority of reactions described in this thesis utilise the less reactive aryl bromides, consequently the reactivity of the bromine analogue **2.8d** was next investigated, so as to have a basis for comparison with the other cyclisations attempted in this chapter, as well as those accomplished in Chapter 3. Reaction using the same conditions as the iodine compound **2.8e**, yielded the products **4.13a**, **4.13b** (ratio 3:1) and the starting material **2.8d** (ratio 2:1 **2.8d**:**4.13**). The reactivity of the starting material is demonstrably lower than that of the iodine analogue, but the reaction still takes place. The palladium Heck cyclisation can therefore be considered as a candidate for further optimisation for the purposes of cyclising compounds **2.8**.



Scheme 4.15: Palladium Heck cyclisation of 2.8d.

The degree of olefin migration in the product is determined by the halogen in the starting material: instead of a single olefin migration product **4.13a**, the isomer **4.13b** is also obtained, albeit in low yield as an inseparable mixture. In order to verify that the compounds **4.13a** and **4.13b** were indeed the structures identified by NMR analysis, a mixture was subjected to reducing conditions (Pd/C, H_2, EtOH) to give quantitative yield of the cyclohexane compound **3.19**, previously identified as the product of 5-*exo-trig* radical cyclisation. Interestingly, **4.13b** underwent slow oxidation in air to imide **4.13c**, while **4.13a** remained stable. Major and minor amide rotamers are visible in the NMR spectra for **4.13b**, in a 1:0.63 ratio: when oxidised to

4.13c, the spectrum is simplified to only one rotamer. This suggests that the preferred conformation of the amide is for the oxygen to point towards the cyclohexenyl ring, as orbital overlap principles would place the carbonyls parallel to each other in **4.13c**.



Scheme 4.16: Migration and oxidation decomposition pathways for 4.13b.

The observed difference in alkene migration between the cyclisation of the bromo and iodo compounds is noteworthy: cyclisation of the iodinated **2.8e** gave the isomerised product **4.13a** only, whereas cyclisation of the brominated **2.8d** produced both **4.13a** and the non-isomerised compound **4.13b**. This may be due to two reasons. The faster the oxidative addition of the C-X bond with the palladium precatalyst, the faster the synthesis of initial kinetic product **4.13b**. Thus for the iodo compound **2.8e** there is more time for equilibration of product **4.13b** ↔ **4.13a** *via* **4.14b**. Alternatively, the rate of migration **4.14a** → **4.14b** may be determined by the Pd-X bond, with the larger Pd-I bond preferring to be further away from the congested spiro center.

The propensity of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ to mediate olefin migration has been reported[176] when used together in a 1:1:1 catalytic system with isobutyryl chloride: it is evident from these test reactions that a similar pre-catalyst and ligand can mediate

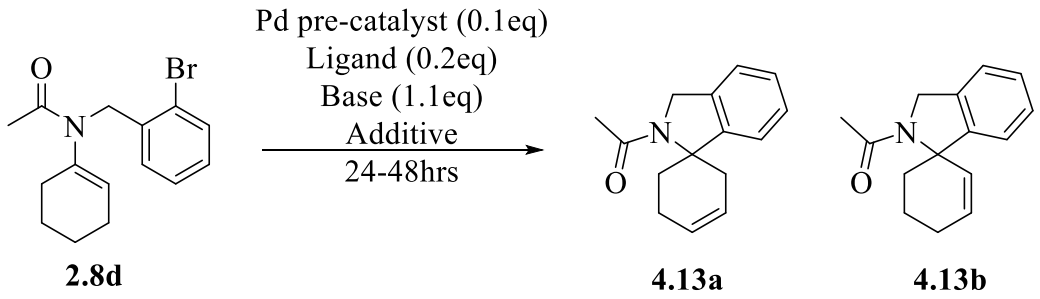
this migration without the chloride. A longer reaction time or higher reaction temperature might be expected to increase the proportion of isomerised product **4.13a**, as "intermediate" compound **4.13b** would have a higher propensity to isomerise to the more stable **4.13a** under such conditions.

4.3.3 Choice of reaction to pursue

Given the lack of initial success experienced with the cyclisation reactions using cobalt, iron and indium reagents, these were not deemed suitable for further investigation. The extreme toxicity of HMPA, as well as the number of equivalents required of samarium diiodide and HMPA, made the samarium-mediated radical cyclisations almost equally unattractive. By comparison, the low catalyst loading, low temperature and relative ease of purification of the palladium Heck reactions made them the logical choice for further investigation. It was therefore decided to attempt the optimisation of this reaction to furnish a single product in better yield than had been observed with the test reaction.

4.4 Palladium Heck reaction screening

Despite the poorer conversion and mixture of products produced **2.8d** was chosen to screen reaction conditions as it was much easier to make than the iodo derivative **2.8e**, comparison with results from chapter 3 would be more meaningful and more insight into the formation of regioisomeric alkene products **4.13a** and **4.13b** might be possible. A series of cyclisation reactions using varying conditions was therefore conducted (Scheme 4.17).



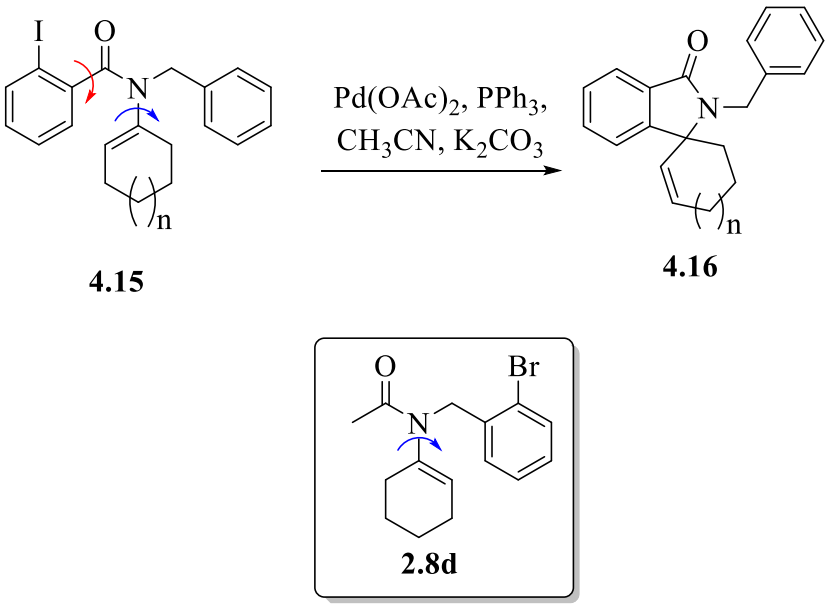
2.8d **4.13a** **4.13b**

Scheme 4.17: Conditions for screening of the palladium Heck cyclisation of 2.8d.

4.4.1 Pre-catalyst and ligand variation

The effect of the pre-catalyst and ligand was first screened. The base, solvent, temperature and time of the reaction were all kept constant while all combinations of the chosen pre-catalysts and ligand were tested. The choice of pre-catalyst and ligand must be considered to make up an important part of the catalytic system: the Pd(0) pre-catalyst must be oxidised to the corresponding Pd(II) compound by the ligand before reaction can take place. The nature of this ligand would therefore be of some importance: it has been reported that phosphine ligands are particularly well-adapted to oxidation of the pre-catalyst. The pre-catalysts and phosphine ligands in this study were chosen as being highly suited to Heck reactions[177,178] from the literature as well as their commercial availability. The combination of $Pd(OAc)_2$ and PPh_3 was expected to work well, given the success experienced by Grigg in cyclising enamides **4.15** (Scheme 4.18).[179] He described the series of iodoenamides **4.15** as undergoing "smooth regiospecific 5-*exo*-*trig* cyclisation" to give the desired spirocycles in good yield. Interestingly structures **4.15** contain two potential atropisomeric bonds, the enamide bond (in blue) similar to substrates **2.8d** but also the *o*-iodo benzamide moiety (in red) giving rise to two diastereomeric atropisomeric intermediates. A recent attempt was made to measure both rotation barriers for the enamide and benzamide rotation in the Grigg compound **4.15** (n = 1) by VT ^{1}H NMR. While the enamide

rotation (blue bond) in **4.15** was similar in magnitude to that in **2.8d** the benzamide rotation (red bond) was too high to measure by this technique (indicating a value of > 20 kcal mol^{-1}). The Grigg compounds therefore have somewhat more complicated rotation dynamics compared to the ones in this study.



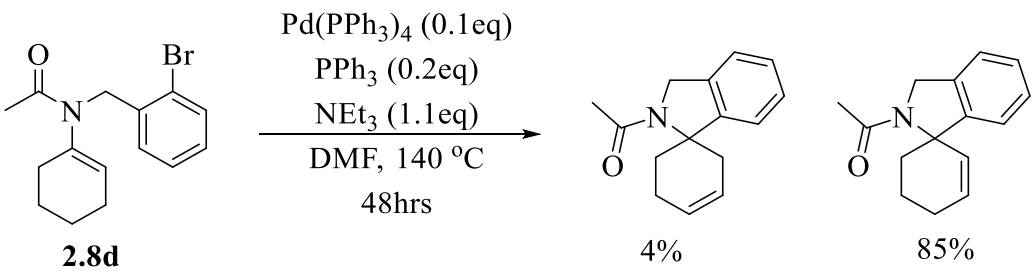
Scheme 4.18: Iodoenamide cyclisation reported by Grigg.

The use of the Grigg conditions ($Pd(OAc)_2$ and PPh_3), however, proved disappointing when applied to compound **2.8d**. An overall yield of 11% was recorded, comprising both possible regioisomers (entry 5, table 4.2) and changing the phosphine ligand did not render the palladium acetate more reactive (entries 4 and 6). $Pd(dba)_2$ gave even poorer conversions (entries 10-12) but $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ provided much more promising results (entries 1-3, 7-9).

Entry	Pre-catalyst	Ligand	Results (%)		
			4.13a	4.13b	Overall yield
1	**$Pd_2(dba)_3$**	**P(*t*-Bu)$_3$**	**23**	**8**	**31**
2	$Pd_2(dba)_3$	PPh_3	2	2	4
3	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	17	9	26
4	$Pd(OAc)_2$	P(*t*-Bu)$_3$	10	7	16
5	$Pd(OAc)_2$	PPh_3	4	7	11
6	$Pd(OAc)_2$	P(*o*-Tol)$_3$	3	2	5
7	**$Pd(PPh_3)_4$**	**P(*t*-Bu)$_3$**	**29**	**45**	**74**
8	**$Pd(PPh_3)_4$**	**PPh_3**	**1**	**30**	**31**
9	$Pd(PPh_3)_4$	P(*o*-Tol)$_3$	0	9	9
10	$Pd(dba)_2$	P(*t*-Bu)$_3$	3	0	3
11	$Pd(dba)_2$	PPh_3	2	0	2
12	$Pd(dba)_2$	P(*o*-Tol)$_3$	9	7	16

Table 4.2: Pre-catalyst (0.1eq) and ligand (0.2eq) variation (Conditions: NEt_3 (1.1eq), Toluene, Reflux, 24hrs).

Interestingly, when pre-catalyst $Pd_2(dba)_3$ was used, the favoured product was the isomerised compound **4.13a**, whereas when $Pd(PPh_3)_4$ was used, the regiochemistry was reversed and product **4.13b** was favoured, albeit in relatively poor conversions. The use of the $Pd(PPh_3)$/ligand combination did not appear to favour olefin migration while some migration was observed with the ligand P(t-Bu)$_3$, minimal was observed with PPh_3 (**4.13a**:**4.13b** = 1:30) and none was seen with P(o-Tol)$_3$, although the yield was low (9%). The combination of $Pd(PPh_3)_4$ and P(t-Bu)$_3$ (entry 7) produced the highest overall yield (74%), but with the lowest regioselectivity in this series (**4.13a**:**4.13b** = 29:45). In an attempt to increase the relative amount of isomerised product **4.13a** the reactions were attempted at higher temperature or for a longer period of time, using the same reagents. However, when the reaction was run in DMF at 140 ^oC for 48 hours, the proportion of isomerised product **4.13a** was actually found to decrease.



2.8d 4% 85%

Scheme 4.19: Increasing the temperature and time of the reaction does not increase the proportion of isomerised product.

On the other hand, while $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ (entry 1) produced the same overall yield as $Pd(PPh_3)_4$ and PPh_3 (entry 8), there was a reversal in regioselectivity (compare entry 1 **4.13a:4.13b** = 23:8 to entry 8 = 1:30). This time reaction at a higher temperature (140 °C in DMF for 48 hours) produced **4.13a** only, and no **4.13b** (*vide infra*). The factors which control the regiochemistry must therefore be a complex interplay of catalyst, ligand, solvent, halide, temperature and time negating the simplistic argument highlighted previously. Lindhardt and Skrydstrup[176] merely noted the need for a bulky pre-catalyst: it is now evident that this cannot be the only requirement. The question of why the choice of the $Pd(PPh_3)_4$ as a pre-catalyst (and as a catalyst, given that the presence of PPh_3 as the ligand discourages the olefin migration almost completely) affects the reaction in this way is unknown, and a survey of the literature indicates that it is not a commonly seen trend. Olefin migration has been reported in systems where $Pd(PPh_3)_4$ has been used as a pre-catalyst, and where PPh_3 has been used as a ligand to other pre-catalysts.[170,180,181] It is possible that the bulkiness of the PPh_3 ligand, combined with the aryl and cyclohexenyl bulk of compound **2.8d**, impedes the isomerisation.

Due to the difficulty of manipulation associated with $Pd(PPh_3)_4$ (air, light and moisture sensitivity), a large proportion of the rest of the screening was carried out with

$Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ instead of the combinations detailed in entries 7 and 8, but with an end goal of applying any yield or selectivity-increasing changes to either combination of reagents once the remaining conditions had been optimised.

4.4.2 Solvent and temperature variation

The next variables studied were the solvent and temperature of the reaction, as reported in Table 4.3. Most of the solvents tested proved to show no improvement over toluene, either at room temperature or at reflux/high temperature. However, dimethylformamide (DMF) proved superior to toluene at low temperature (compare entries 13 and 15, overall yields 1% and 12%) when the pre-catalyst/ligand combination was $Pd_2(dba)_3/P(t\text{-}Bu)_3$, although the overall yield at high temperature was slightly lower than with toluene (29% with DMF, 31% with toluene).

Entry	Pre-catalyst	Ligand	Solvent	Temp.	Results (%)		
					4.13a	4.13b	Overall yield
13	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	Toluene	RT	0	0	1
14	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	THF	RT	0	0	0
15	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	DMF	RT	12	0	12
16	**$Pd_2(dba)_3$**	$P(t\text{-}Bu)_3$	**DMF**	**140**	**29**	**0**	**29**
17	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	CH_3CN	RT	0	0	0
18	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	DCE	RT	0	0	0
19	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	Dioxane	RT	0	0	0
20	$Pd(PPh_3)_4$	$P(t\text{-}Bu)_3$	THF	Reflux	0	0	0
21	$Pd(PPh_3)_4$	$P(t\text{-}Bu)_3$	CH3CN	Reflux	1	10	11
22	**$Pd(PPh_3)_4$**	**$P(t\text{-}Bu)_3$**	**DMF**	**140**	**21**	**79**	**100**
23	**$Pd(PPh_3)_4$**	**PPh_3**	**DMF**	**140**	**4**	**85**	**89**

Table 4.3: Solvent and temperature variation (Conditions: Pre-catalyst (0.1eq), Ligand (0.2eq), NEt_3 (1.1eq), 48hrs).

This prompted a cyclisation attempt using the $Pd(PPh_3)_4/PPh_3$ combination, at 140 °C in DMF, which furnished an overall yield of 89%, 85% of which was **4.13b** (4% **4.13a**), as well as with $Pd(PPh_3)_4/P(tBu)_3$, furnishing 100% product in a 21:79 ratio of

4.13a to **4.13b**. These conditions therefore produced a high product yield combined with a considerably decreased propensity of **4.13b** to isomerise to **4.13a**. DMF was therefore carried forward as the solvent of choice, despite the high temperature needed for high yields to be recorded. While unfortunate, the necessity for high temperature to mediate the Heck reaction of aryl bromides has been well documented[182], particularly in cases where the aryl bromide is electron-rich, as with compound **2.8d**.

4.4.3 Base variation and use of additives.

Other bases that had been reported to work in the Heck reaction were next tested: DABCO (1,4-diazabicyclo[2.2.2]octane)[121,177] and Ag_2CO_3.[180] Neither of these were found to be an improvement on triethylamine, either in overall yield or regioselectivity: the base was concluded to not be mechanistically important, and therefore the cheaper and more commonly used triethylamine was used.

Entry	Base	Results (%)		
		4.13a	4.13b	Overall yield
24	NEt_3	21	79	100
25	DABCO	15	73	88
26	Ag_2CO_3	20	63	83

Table 4.4: Base variation (Conditions: $Pd(PPh_3)_4$ (0.1eq), $P(t\text{-}Bu)_3$ (0.2eq), Base (1.1eq), DMF, 48hrs).

Additives were then employed in a final attempt to suppress alkene migration, while keeping the overall yield as high as possible. Unfortunately, the use of silver nitrate ($AgNO_3$) with either Pd_2dba_3 or $Pd(PPh_3)_4$ as the precatalyst proved ineffectual in improving the reaction, and instead seemed to inhibit it (entries 27-28). Tetrabutylammonium bromide (NBu_4Br) was found to maintain a high overall yield no matter the number of equivalents used, but favoured olefin migration, resulting in an increased proportion of the alkene migration product **4.13a** (entries 29-31). The combinations detailed in entries 22 and 23, Table 4.3 remained therefore the most

effective, as having the highest overall yield of product. Of these, the combination of $Pd(PPh_3)_4/PPh_3$ was the more attractive, due to the increased yield and increased reactivity of the obtained product **4.13b** (notably olefin migration to **4.13a** and oxidation to **4.13c**, neither of which were available with **4.13a**).

Entry	Pre-catalyst	Additive (nº eq)	Results (%)		
			4.13a	4.13b	Overall yield
27	$Pd_2(dba)_3$	$AgNO_3$ (1.1eq)	0	0	0
28	$Pd(PPh_3)_4$	$AgNO_3$ (1.1eq)	6	13	20
29	$Pd(PPh_3)_4$	NBu_4Br (1.1eq)	46	42	87
30	$Pd(PPh_3)_4$	NBu_4Br (3eq)	42	53	95
31	$Pd(PPh_3)_4$	NBu_4Br (10eq)	38	56	94

Table 4.5: Additive variation (Conditions: Pre-catalyst (0.1eq), $P(t\text{-}Bu)_3$ (0.2eq), NEt_3 (1.1eq), DMF, 48hrs).

4.5 Palladium Heck reactions of other compounds

The conditions detailed in Section 4.3.2 were used to attempt the cyclisation of a selection of the compounds synthesised in Chapter 2, to ascertain the degree of influence held by the *N*-alkenyl barrier to rotation in the success or otherwise of palladium-mediated Heck cyclisations.

4.5.1 Cyclisation of substrates with lower barriers to rotation (< 15.0 kcal mol^{-1}).

The compounds in Figure 4.2 were cyclised to give the results detailed in Table 4.6. It was hypothesised, given the bulkiness of the mediating complex $[Pd(PPh_3)_4]^{II}$, that the compounds with higher barriers to rotation, due to steric congestion (> 15 kcal mol^{-1}), would be less likely to cyclise using this method.

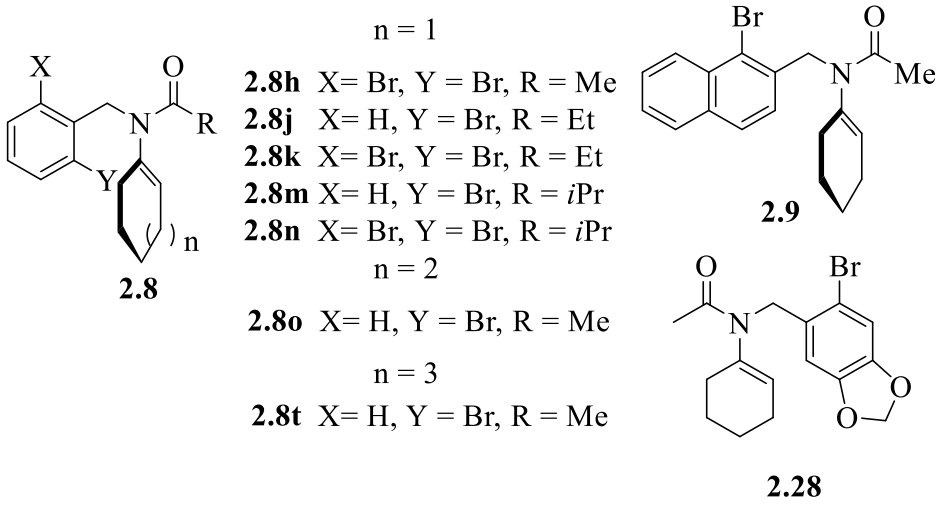
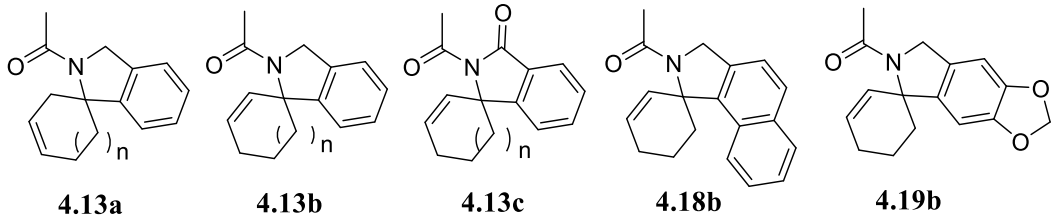


Figure 4.2: Compounds for cyclisation (barriers to rotation < 15 kcal mol^{-1}).

The increase in cycloalkenyl ring size (**2.8d** → **2.8o** → **2.8t**) afforded in an increase in both yield and regioisomeric selectivity. While the regioselectivity for **2.8o** was complete (for **4.13b**, n = 2), the eight membered analogue showed a reversal in selectivity for **4.13a** (n =3, along with some oxidised **4.13c**). Like **2.8d**, the other cyclohexenyl compounds derived from cyclisation of **2.9** and **2.28** were also highly selective for **4.13b**.

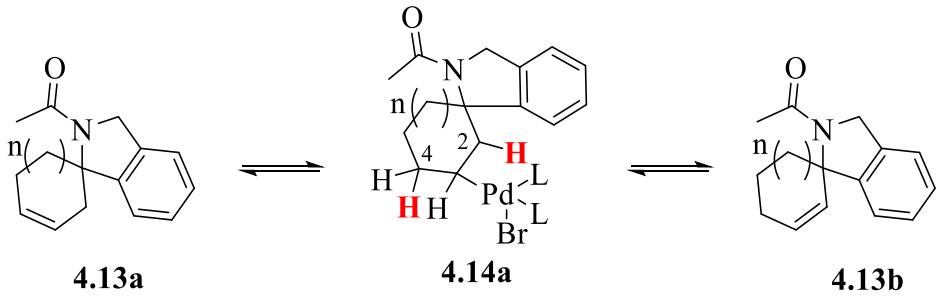


Starting material	n	ΔG (kcal/mol)	4.13b	4.13a	SM	4.13c[3]
2.8d	1	10.5	85	4	11	0
2.8o	2	12.0	100	tr	tr	0
2.8t	3	11.3	tr	83	0	17
2.9	1	10.8	100[1]	tr	tr	0
2.28	1	10.4	89[2]	tr	11	0

[1] Structure **4.18b**. [2] Structure **4.19b.** [3]**4.13c** = oxide.

Table 4.6: Results of palladium-mediated Heck cyclisation. Effect of ring size.

Overman noted that in order to lose the palladium hydride, as happens here in the final step, the palladium and the hydrogen being eliminated must be *syn*.[175] After initial formation of **4.13b** in each case, subsequent re-addition of Pd-H would furnish **4.14a** which may eliminate from either the 2-position (regenerating **4.13b**) or the 4-position on the ring (giving **4.13a**): elimination would occur on whichever hydrogen is *syn* to the palladium.

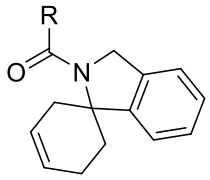


4.13a **4.14a** **4.13b**

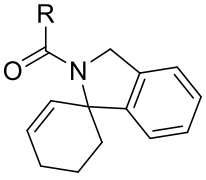
Scheme 4.20: Olefin migration in product 4.13.

According to MM2 calculations, the dihedral angles between the hydrogen and the palladium for the cyclohexene derivative from **2.8d** are in fact very similar: 53.5° for H^4 and 56.8° for H^2. It seems likely, therefore that the preference for **4.13b** in all the cyclohexenyl derived substrates (**2.8d**, **2.9**, **2.28**) originates in a lack of isomerisation due to the bulk of the mediating compound suppressing **4.13b** → **4.14a**. The change in regioisomeric selectivity for the cyclisation of the cyclooctenyl derivative **2.8t** could be rationalised by a difference in the folding pattern of the cycloalkenyl ring facilitating **4.13b** (n = 3) → **4.14a** (n = 3) and preferential elimination of hydrogen in the 4 position. Modelling using the MM2 forcefield bore out this hypothesis: in an energetically minimised configuration of **4.14a** (n = 3), the dihedral angle between H^2 and the palladium was 33.5°, whereas the angle between H^4 and the palladium was 15.1°. This would in all probability be sufficient to account for the change in regioselectivity of the alkene formation.

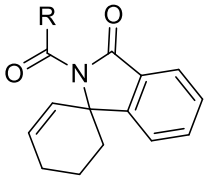
The effect of the bulk of the acyl group on the cyclisation was next examined. The reaction conditions were kept the same so direct comparisons of conversion could be made, Table 4.7. The increase in size of the acyl group (**2.8d** → **2.8j** → **2.8m**) had a strong effect on the yield/conversion of the reaction: the larger the acyl group, the lower the overall yield. In all cases (as observed for the cyclohexenyl derivatives (**2.8o**, **2.8t**, **2.9** and **2.28**) the major product was **4.13b** (presumably for the same reasons).



4.13a



4.13b



4.13c

Starting material	ΔG (kcal/mol)	4.13b	4.13a	SM	4.13c
2.8d (R = Me)	10.5	85	4	11	0
2.8j (R = Et)	11.3	28	3	69	0
2.8m (R = iPr)	12.2	7	tr	93	17

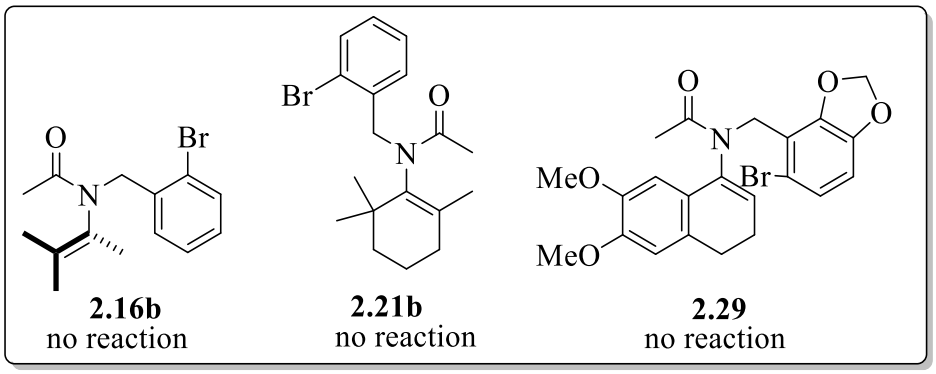
Table 4.7: Results of palladium-mediated Heck cyclisation. Effect of acyl group size.

Further study and mechanistic work would be required to fully understand the reasons for the low conversions in cyclisations of compounds **2.8j** and **m**.

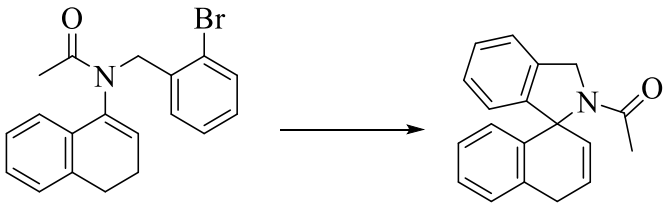
4.5.2 Cyclisation of substrates with greater barriers to rotation (> 15.0 kcal mol^{-1}).

To a certain extent the hypothesis was validated, as the compounds with the highest barriers to rotation, **2.16b**, **2.21b** and **2.29**, underwent no reaction when subjected to the optimised conditions. Given the high level of substitution of the alkene in **2.16b** and **2.21b**, and the bulk of the aryl group in **2.29**, this is unsurprising. Additionally, the compound with the next highest barrier to rotation (**2.27**) showed low conversion

(28%) to the cyclised product **4.20**, indicating that the reaction was indeed inhibited by slower rotation around the *N*-cycloalkenyl bond.



2.16b no reaction | **2.21b** no reaction | **2.29** no reaction



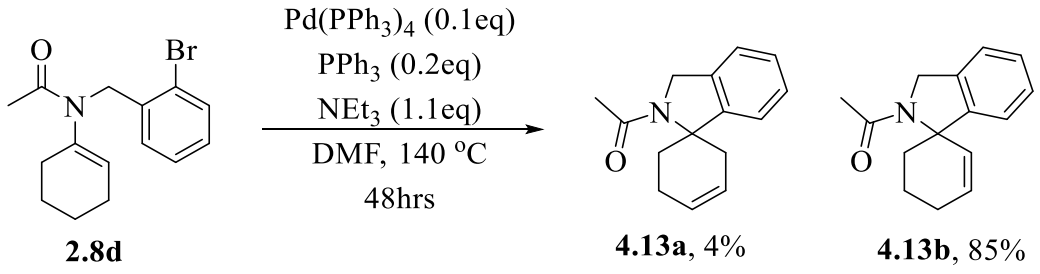
2.27 → **4.20**

Starting material	ΔG (kcal/mol)	
2.16b	19.9	No reaction
2.21b	30.6	No reaction
2.27	17.9	**4.20** (28%), recovered SM (72%)
2.29	>20	No reaction

Table 4.8: Results of palladium-mediated Heck cyclisation, (barriers to rotation > 15 kcal mol^{-1}).

4.6 Summary

In this chapter, the cyclisation of compound **2.8d** was initially studied using different methods in order to attempt to provide a viable alternative to the toxic and reductive tin method. Of the methods tested, two showed promise: samarium diiodide-mediated cyclisation was successful when a large amount of the mediating species was present, along with HMPA. This method produced similar results to the tin hydride cyclisations discussed in Chapter 3, with a difference in product stereoselectivity due to the low temperature of the reaction and a different termination mechanism. Further optimisation of this method was not attempted due to safety and time considerations. The palladium-mediated Heck cyclisation, however, was successful even at low temperature (for aryl iodides), although a different regiochemistry of cyclisation (5-*exo* favoured over 6-*endo* cyclisation) occurred. A high temperature was necessary to optimise the yield and regioselectivity of the reaction with regards to the aryl bromide starting material **2.8d**. Two alkene regioisomers of the 5-*exo-trig* product were isolated (**4.13a** and **4.13b**), confirming the preference of the Heck reaction for the *exo* pathway.[169,170] The reaction conditions were optimised to those depicted in Scheme 4.21.



2.8d **4.13a**, 4% **4.13b**, 85%

Scheme 4.21: Optimised conditions for Heck cyclisation of 2.8d.

The amount of olefin migration product was minimised by the presence of bulky pre-catalyst $Pd(PPh_3)_4$ and ligand PPh_3, which impeded the isomerisation process. These

conditions were then used to attempt the cyclisation of several compounds synthesised in Chapter 2, to assess the effect of the barrier to *N*-cycloalkenyl rotation on the Heck reaction. Increased aryl bulk was found to sterically hinder (in conjunction with the palladium catalyst) the alkene sufficiently to prevent isomerisation, although in cases where the barrier to rotation was above 17.9 kcal mol^{-1} cyclisation was not observed due to the steric constraints around the starting material alkene or around the aryl halide. Palladium Heck conditions were successful in mediating most cyclisations accomplished with the tin method, and the failure to mediate cyclisations with high barriers to rotation was expected given the bulkiness of the mediating species. However, the goal of the palladium cyclisations was not attained, as high temperatures would impede chiral transfer, and the lack of 6-*endo*-*trig* cyclisation product prevents the attempt to cyclise **2.29** into a natural product analogue in any case. Alternative methods must provide the basis for future work, and the copper-based methods studied by Clark[86,183–185] could provide an excellent starting point.

Chapter 5: Experimental

5.1 General Information and Procedures

Unless otherwise stated, the chemicals and solvents used in these syntheses were obtained from commercial suppliers and were used without further purification. 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°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. Flash chromatography was carried out using Merck silica gel 60, 35-75μm as the stationary phase. NMR spectra were obtained at 298 K unless otherwise stated. 1H 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 (δH) are quoted in parts per million (ppm), coupling constants J are quoted in hertz (Hz), and data is quoted as (δH, integration, multiplicity). Proton and carbon NMR assignments were routinely confirmed by 1H-1H (COSY), 1H-13C (HMQC) and 1H-13 C (HMBC) experiments. For variable temperature NMR, samples were submitted to the NMR service and analysed on a Bruker DPX500 spectrometer. Spectra obtained were analysed using Mestrec© and NUTS© software prior to lineshape analysis using WINDNMR or TopSpin. 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

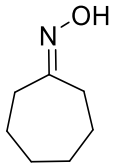
analysis. Only molecular ion fractions from molecular ions and other major peaks are reported as mass/charge (m/z) ratios. IR was recorded using a Perkin-Elmer Avatar 320 FTIR spectrometer. Solids were compressed into a thin tablet and oils/non-volatile liquids were analysed as films over a diamond sensor. Absorption maxima (υmax) 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).

5.2 Compounds synthesised in Chapter 2.

5.2.1 General procedure for the synthesis of oximes 2.10 from ketones

The commercially available cyclohexanone oxime (**2.10a**) was used, but otherwise the oximes were synthesised in the following manner. The ketone (1eq), hydroxylamine hydrochloride (1.1eq) and sodium acetate (1.1eq) were dissolved in methanol and heated at reflux for 24 hours. The solvent was removed from the crude reaction mixture under vacuum, after which the residue was taken up in ethyl acetate and water, washed with brine, dried with magnesium sulphate, the solvent removed under vacuum and the product used without further purification.

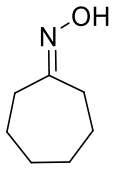
Cycloheptanone oxime (2.10b)[186]



The general procedure for the synthesis of oximes was used: cycloheptanone (5mL, 42.4mmol), hydroxylamine hydrochloride (3.24g, 46.6mmol) and sodium acetate

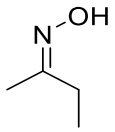
(3.82g, 46.6mmol) were dissolved in methanol (30mL), heated to reflux and stirred for 24 hours. A brown oil was obtained (5.16g, 96%) and immediately used to synthesise the acetamides.

Cyclooctanone oxime (2.10c)[187]



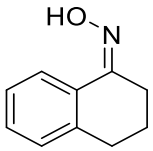
The general procedure for the synthesis of oximes was used: cyclooctanone (5.00g, 40.0mmol), hydroxylamine hydrochloride (3.10g, 44.0mmol) and sodium acetate (3.60g, 44.0mmol) were dissolved in methanol (30mL), heated to reflux and stirred for 24 hours. A dark brown oil was obtained (4.78g, 85%) and immediately used to synthesise the acetamides.

3-Methyl-2-butanone oxime (2.10d)[187]



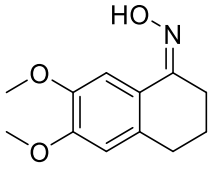
The general procedure for the synthesis of oximes was used: 3-methyl-2-butanone (20mL, 187mmol), hydroxylamine hydrochloride (14.3g, 206mmol) and sodium acetate (16.9g, 206mmol) were dissolved in methanol (100mL), heated to reflux and stirred for 24 hours. A yellow oil was obtained (10.1g, 53%) and immediately used to synthesise the acetamides.

Tetralone oxime (2.10e)[84]



The general procedure for the synthesis of oximes was used: α-tetralone (21.0g, 144mmol), hydroxylamine hydrochloride (11.0g, 158mmol) and sodium acetate (12.96g, 158mmol) were dissolved in methanol (100mL), heated to reflux and stirred for 24 hours. A light brown solid was obtained (23.0g, 99%) and immediately used to synthesise the acetamide.

6,7-Dimethoxy-3,4-dihydronaphthalen-1-one oxime (2.10f)

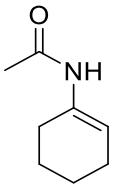


The general procedure for the synthesis of oximes was used: 6,7-dimethoxy-3,4-dihydronaphthalen-1-one (2.00g, 9.7mmol), hydroxylamine hydrochloride (0.76g, 11.0mmol) and sodium acetate (0.90g, 11.0mmol) were dissolved in methanol (20mL), heated to reflux and stirred for 24 hours. A brown oil was obtained (1.69g, 79%) and immediately used to synthesise the acetamide.

5.2.2 General procedure for the synthesis of alkenylacetamides 2.11 from the oximes 2.10.[69]

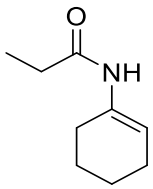
The oxime (1eq), cupper iodide (0.1eq), sodium bisulfite (3eq) and the appropriate anhydride (2eq) were dissolved in 1,2-dichloroethane under nitrogen and reacted together at 120 °C for 24 hours. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (30mL), washed with 2M sodium hydroxide solution (100mL) and brine (saturated solution, 100mL), dried with anhydrous sodium sulphate and the solvent removed under vacuum. A brown oil was obtained, and was used without further purification.

***N*-Cyclohexenylacetamide (2.11a)**[69]



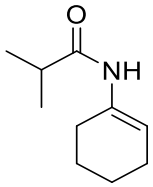
The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cyclohexanone oxime **2.10a** (1.15g, 10.16mmol), copper iodide (0.2g, 1.02mmol), sodium bisulfite (3.17g, 30.5mmol) and acetic anhydride (2.08g, 20.3mmol) were dissolved in 1,2-dichloroethane (30mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.63g, 45%, brown oil. δ_H (300 MHz, $CDCl_3$) 6.43 (1H, br s, NH), 6.06 (1H, s, C=CH), 2.10 (2H, m, cy), 2.02 (3H, s, $COCH_3$), 1.88 (2H, s, cy), 1.74 – 1.62 (2H, m, cy), 1.62 – 1.51 (2H, m, cy).

***N*-(Cyclohex-1-en-1-yl)propionamide (2.11b)**[69,84]



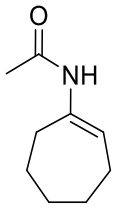
The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cyclohexanone oxime **2.10a** (2.0g, 17.7mmol), copper iodide (0.34g, 1.77mmol), sodium bisulfite (5.62g, 53.1mmol) and propionic anhydride (4.69g, 35.4mmol) were dissolved in 1,2-dichloroethane (40mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.52g, 19%, brown oil. δ_H (400 MHz, $CDCl_3$) 7.44 (1H, br s, NH), 6.07 (1H, br s, C=CH), 2.25 (2H, q, *J* = 8.0 Hz, $COC\underline{H}_2CH_3$), 2.15 (2H, m, cy), 2.08 (2H, m, cy), 1.66 (2H, m, cy), 1.57 (2H, m, cy), 1.15 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$).

***N*-(Cyclohex-1-en-1-yl)isobutyramide (2.11c)**[69,84]



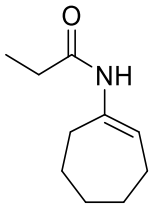
The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cyclohexanone oxime **2.10a** (2.0g, 17.7mmol), copper iodide (0.34g, 1.77mmol), sodium bisulfite (5.62g, 53.1mmol) and isobutyric anhydride (5.59g, 35.4mmol) were dissolved in 1,2-dichloroethane (50mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.61g, 20%, brown oil. δ_H (250 MHz, $CDCl_3$) 7.15 (1H, br s, NH), 6.08 (1H, br s, NC=CH), 2.53 – 2.29 (1H, m, $COC\underline{H}(CH_3)_2$), 2.21-2.11 (2H, m, cy), 2.12 – 2.04 (2H, m, cy), 1.75 – 1.63 (2H, m, cy), 1.61 – 1.51 (2H, m, cy), 1.15 (6H, d, *J* = 7.0 Hz, $COCH(C\underline{H}_3)_2$).

***N*-Cycloheptenylacetamide (2.11d)**



The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cycloheptanone oxime **2.10b** (4.0 g, 31.5mmol), copper iodide (0.60g, 3.15mmol), sodium bisulfite (9.83g, 94.5mmol) and acetic anhydride (6.43, 63.0mmol) were dissolved in 1,2-dichloroethane (200mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 1.36g, 28%, brown oil, identified by comparison with compound **2.11a** spectra. δ_H (300 MHz, $CDCl_3$ 7.05 (1H, s, NH), 6.13 (1H, t, *J* = 7.0 Hz, C=CH), 2.39 – 2.23 (2H, m, cy), 2.10 (2H, d, *J* = 6.5 Hz, cy), 2.05 (1H, s, cy), 2.01 (3H, s, $COCH_3$), 1.72 (2H, d, *J* = 5.5 Hz, cy), 1.54 (2H, dd, *J* = 14.0, 8.0 Hz, cy), 1.26 (1H, t, *J* = 7.0 Hz, cy).

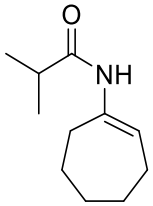
***N*-(Cyclohept-1-en-1-yl)propionamide (2.11e)**



The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cycloheptanone oxime **2.10b** (1.0g, 7.0mmol), copper iodide (0.13g, 0.7mmol), sodium bisulfite (2.19g, 21.0mmol) and propionic anhydride (1.82g, 14.0mmol) were dissolved in 1,2-dichloroethane (20mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.11g, 9%, brown oil, identified by comparison with compound **2.11b** spectra. δ_H (400 MHz, $CDCl_3$) 7.18 (1H, s, NH), 6.14 (1H, t, *J*

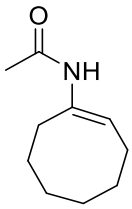
= 6.5 Hz, C=CH), 2.36 – 2.28 (2H, m, cy), 2.24 (2H, q, *J* = 7.5 Hz, COC<u>H</u>$_2$CH$_3$), 2.14 – 2.08 (2H, m, cy), 1.75 – 1.69 (2H, m, cy), 1.62 – 1.56 (2H, m, cy), 1.54 – 1.47 (2H, m, cy), 1.15 (3H, t, *J* = 7.5 Hz, COCH$_2$C<u>H</u>$_3$).

_N_-(Cyclohept-1-en-1-yl)isobutyramide (2.11f)



The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cycloheptanone oxime **2.10b** (0.71g, 5.5mmol), copper iodide (0.10g, 0.55mol), sodium bisulfite (1.72g, 16.5mmol) and propionic anhydride (1.74g, 11.0mmol) were dissolved in 1,2-dichloroethane (20mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.13g, 13%, brown oil, identified by comparison with compound **2.11c** spectra. δ_H (300 MHz, $CDCl_3$) 6.70 (1H, s, NH), 6.14 (1H, t, *J* = 7.0 Hz, C=CH), 2.42 – 2.31 (1H, m, COC<u>H</u>$(CH_3)_2$), 2.35 – 2.27 (2H, m, cy), 2.12 (2H, dd, *J* = 11.0, 6.5 Hz, cy), 1.78 – 1.67 (2H, m, cy), 1.66 – 1.57 (2H, m, cy), 1.57 – 1.46 (2H, m, cy), 1.16 (6H, d, *J* = 7.0 Hz, COCH(C<u>H</u>$_3$)$_2$).

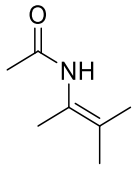
_N_-Cyclooctenylacetamide (2.11g)



The general procedure for the formation of alkenylacetamides (5.2.2) was used. Cyclooctanone oxime **2.10c** (1.50 g, 11mmol), copper iodide (0.21g, 1.1mmol), sodium bisulfite (3.43g, 33mmol) and acetic anhydride (2.24, 22mmol) were dissolved

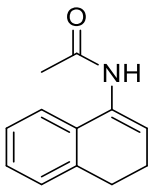
in 1,2-dichloroethane (30mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.76g, 42%, brown oil, identified by comparison with compound **2.11a** spectra. δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s, NH), 6.04 (1H, t, *J* = 8.5 Hz, C=CH), 2.33 (2H, br s, cy), 2.11 (2H, br s, cy), 2.03 (3H, s, $COCH_3$), 1.58 (2H, br s, cy), 1.50 (6H, br s, cy).

***N*-(3-Methylbut-2-en-2-yl)acetamide (2.11h)**[69]



The general procedure for the formation of alkenylacetamides (5.2.2) was used. 3-Methyl-2-butanone oxime **2.10d** (5.0 g, 49.4mmol), copper iodide (0.94g, 4.94mmol), sodium bisulfite (15.4g, 148mmol) and acetic anhydride (10.1g, 98.8mmol) were dissolved in 1,2-dichloroethane (200mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 2.46g, 39%, brown oil. δ_H (300 MHz, $CDCl_3$) 8.08 (1H, s, NH), 1.56 (3H, s, $COCH_3$), 1.38 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.16 (3H, s, CH_3).

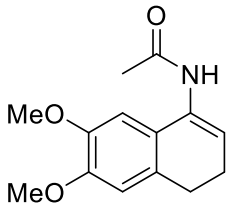
***N*-(3,4-Dihydronaphthalen-1-yl)acetamides (2.11i)**[84]



The general procedure for the formation of alkenylacetamides (5.2.2) was used. Tetralone oxime **2.10e** (15.00 g, 94.0mmol), copper iodide (1.79g, 9.4mmol), sodium bisulfite (29.0g, 280mmol) and acetic anhydride (19.0g, 190mmol) were dissolved in 1,2-dichloroethane (200mL) under nitrogen and reacted together for a period of 24

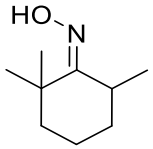
hours at 120 °C. Yield 6.66g, 38%, brown oil. δ_H (400 MHz, $CDCl_3$) 7.45 (1H, s, NH), 7.24 – 7.03 (4H, m, ArH), 6.29 (1H, t, *J* = 4.5 Hz, NC=CH), 2.71 (2H, t, *J* = 8.0 Hz, NC=CHCH$_2$C$\underline{H}_2$) 2.35 – 2.26 (2H, m, NC=CHC$\underline{H}_2$CH$_2$), 2.07 (3H, s, COCH$_3$).

***N*-(6,7-dimethoxy-3,4-dihydronaphthalen-1-yl)acetamide (2.11j)**

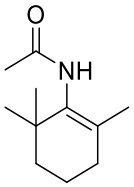


The general procedure for the formation of alkenylacetamides (5.2.2) was used. 6,7-dimethoxy-3,4-dihydronaphthalen-1-one oxime **2.10f** (1.69g, 7.64mmol), copper iodide (0.15g, 0.76mmol), sodium bisulfite (2.39g, 22.9mmol) and acetic anhydride (1.55g, 15.3mmol) were dissolved in 1,2-dichloroethane (50mL) under nitrogen and reacted together for a period of 24 hours at 120 °C. Yield 0.42g, 21%, brown oil identified by comparison to spectra for compound **2.11i**. δ_H (300 MHz, $CDCl_3$) 7.84 (1H, s, NH), 6.70 (1H, s, ArH), 6.62 (1H, s, ArH), 6.09 (1H, t, *J* = 4.5 Hz, NC=CH), 3.83 (3H, s, OCH$_3$), 3.77 (3H, s, OCH$_3$), 2.61 (2H, t, *J* = 8.0 Hz, NC=CHCH$_2$C$\underline{H}_2$), 2.31 – 2.19 (2H, m, NC=CHC$\underline{H}_2$CH$_2$), 2.07 (3H, s, COCH$_3$).

5.2.3 Alternative synthesis of acetamide 2.23 using iron powder[69,84]



The general procedure for the synthesis of oximes was used: 2,2,6-trimethylcyclohexanone (2.00g, 14.3mmol), hydroxylamine hydrochloride (1.09g, 15.7mmol) and sodium acetate (1.29g, 15.7mmol) were dissolved in methanol (50mL), heated to reflux and stirred for 24 hours. An off-white solid was obtained (1.78g, 81%) and immediately used to synthesise the acetamide.

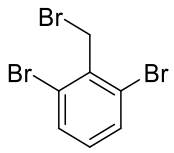


A mixture of 2,2,6-trimethylcyclohexanone oxime (**2.22**) (2.00g, 12.9mmol, 1eq), acetic acid (2.32g, 38.6mmol, 3eq), acetic anhydride (3.94g, 38.6mmol, 3eq) and iron powder (1.44g, 25.8mmol, 2eq) in anhydrous toluene (100mL) was heated to reflux under nitrogen and left to react overnight. The mixture was then cooled, filtered through celite, diluted with dichloromethane and washed with brine (50mL) and sodium hydroxide (50mL), and then dried over magnesium sulphate. The solvent was removed under vacuum to yield a white solid. Yield 0.75g, 32%. δ_H (400 MHz, $CDCl_3$) 6.27 (1H, s, NH), 2.05 (3H, s, $COCH_3$), 1.66 (3H, s, $C{=}CCH_3$), 1.60 – 1.41 (6H, m, cy), 0.90 (3H, s, Me), 0.88 (3H, s, Me).

5.2.4 Synthesis of the aryl moieties 2.12

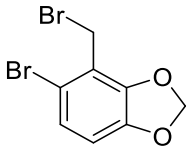
Some benzyl bromides were available commercially and were used without further purification, but those that could not be obtained were synthesised as follows.

2,6-Dibromobenzyl bromide[84,188]



2,6-Dibromotoluene (1.00g, 4.00mmol, 1eq), *N*-bromosuccinimide (783mg, 4.40mmol, 1.1eq), and benzoyl peroxide (65mg, 0.2mmol, 5 mol%) were dissolved in carbon tetrachloride (10mL) under nitrogen and reacted together for a period of 16 hours at 80°C. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (30mL), washed with water (3x50mL), dried with $MgSO_4$ and the solvent removed under vacuum. The product was recrystallised with 10:1 hexane:ethyl acetate to yield an off-white crystalline solid. Yield 0.90g, 69%. δ_H (300 MHz, $CDCl_3$) 7.54 (1H, dd, *J* = 8.0, 1.0Hz, ArH), 7.41 (1H, dd, *J* = 7.5, 1.5Hz, ArH), 7.26 (1H, td, *J* = 7.5, 1.0 Hz, ArH), 7.12 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 4.57 (2H, s, $ArCH_2Br$).

5-Bromo-4-(bromomethyl)benzo[1,3]dioxole



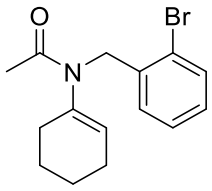
5-Bromo-1,3-benzodioxole-4-carboxaldehyde (0.45g, 1.96mmol, 1eq) was reacted at room temperature for 2 hours with sodium borohydride (89mg, 2.35mmol, 1.2eq) in methanol (20mL). The reaction mixture was then quenched with HCl (20mL), extracted thrice with DCM (30mL), dried with $MgSO_4$ and the solvent was removed under vacuum to furnish 0.40g (1.73mmol, 88%) of the alcohol. This was then reacted

with triphenylphosphine (0.49g, 1.90mmol, 1.1eq) and tetrabromomethane (0.63g, 1.90mmol, 1.1eq) in diethyl ether (20mL) at room temperature for another hour, after which the reaction mixture was filtered and concentrated under vacuum. Purification by flash column chromatography with hexane as eluent produced 0.36g of the desired product (1.22mmol, 71%) as a yellow solid, identified by comparison with the starting material and with 2,6-dibromobenzylbromide. Overall yield 0.36g, 62%. δ_H (300 MHz, $CDCl_3$) 7.03 (1H, d, *J* = 8.5 Hz, ArH), 6.64 (1H, d, *J* = 8.5 Hz, ArH), 6.05 (2H, s, OCH_2O), 4.55 (2H, s, CH_2Br).

5.2.5 General procedure for the synthesis of benzyl-*N*-alkenylacetamides

N-Cycloalkenylacetamide (1eq), sodium hydride (5eq) and the aryl bromide (1.1eq) were dissolved in dry THF (20mL) under nitrogen and refluxed under nitrogen for 20 hours. The reaction mixture was cooled to room temperature, poured into water, extracted thrice with EtOAc (50mL), dried with $MgSO_4$ and concentrated under vacuum. The product was purified by flash column chromatography with 9:1 to 6:1 pet ether:EtOAc. Compounds **2.8a-c**, **2.8f-g**, **2.8i** and **2.8l** have been synthesised by other groups, as referenced. All other syntheses are detailed below.

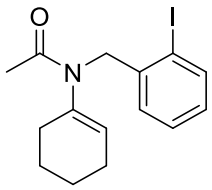
_N_-Cyclohex-1-enyl-_N_-2-bromobenzylacetamide (2.8d)



N-Cyclohexenylacetamide (**2.11a**) (0.40g, 2.85mmol), sodium hydride (0.36g, 14.8mmol) and 2-bromobenzyl bromide (0.82, 3.28mmol) were reacted together as in the general protocol. Yield 0.31g, 35%; Yellow-brown oil; R_f (6:1 pet ether:EtOAc)

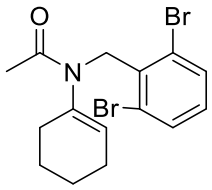
0.54; ν_{max} (film)/cm^{-1} 2928 (C-H), 1647 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.44 (1H, d, *J* = 8.0 Hz, ArH), 7.34 (1H, d, *J* = 7.7 Hz, ArH), 7.20 (1H, t, *J* = 7.5 Hz, ArH), 7.04 (1H, t, *J* = 7.6 Hz, ArH), 5.38 (1H, br s, NC=CH), 4.73 (2H, s, NCH_2), 2.05 (3H, s, $COCH_3$), 2.03 – 1.90 (4H, m, cy), 1.68 – 1.56 (2H, m, cy), 1.54 – 1.42 (2H, m, cy); δ_C (101 MHz, $CDCl_3$) 170.2 (C=O), 138.7 (ArC quaternary), 137.1 (N<u>C</u>=CH), 132.5, 130.4, 128.7, 128.2 (ArCH), 127.5 (NC=<u>C</u>H), 124.0 (ArCBr), 48.8 (NCH_2), 28.0, 24.8, 22.7 (cy), 21.5 ($COCH_3$), 21.4 (cy); *m/z* (ESI) 308.07 ($[M]^+H$); [Found: ($[M]^+H$) 308.0644, $C_{15}H_{19}{}^{79}BrNO$ requires 308.0645].

_N_-Cyclohex-1-enyl-_N_-2-iodobenzylacetamide (2.8e)



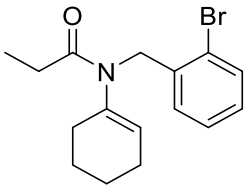
N-Cyclohexenylacetamide (**2.11a**) (90mg, 0.61mmol), sodium hydride (74mg, 3.07mmol) and 2-iodobenzyl bromide (0.20, 0.67mmol) were reacted together as in the general protocol. Yield 97mg, 45%. Yellow oil; R_f (6:1 pet ether:EtOAc) 0.49; ν_{max} (film)/cm^{-1} 2928 (C-H), 1643 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.73 (1H, d, *J* = 7.9 Hz, ArH), 7.32 (1H, d, *J* = 7.7 Hz, ArH), 7.23 (1H, t, *J* = 7.5 Hz, ArH), 6.87 (1H, t, *J* = 8.4 Hz, ArH), 5.38 (1H, br s, NC=CH), 4.68 (2H, s, NCH_2), 2.05 (3H, s, $COCH_3$), 1.99 (4H, s, cy), 1.68 – 1.58 (2H, m, cy), 1.50 (2H, qd, *J* = 11.0, 7.4 Hz, cy); δ_C (101 MHz, $CDCl_3$) 170.3 (C=O), 140.4 (ArC quaternary), 139.3(ArCH), 138.7 (N<u>C</u>=CH), 129.8, 128.9 (ArCH), 128.5 (NC=<u>C</u>H), 99.7 (ArCI), 53.6 (NCH_2), 28.2, 24.9, 22.8 (cy), 21.6 ($COCH_3$), 21.4 (cy); *m/z* (ESI) 356.05 ($[M]^+H$); [Found: ($[M]^+H$) 356.0516, $C_{15}H_{19}INO$ requires 356.0506].

***N*-Cyclohex-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8h)**



N-Cyclohexenylacetamide (2.11a) (0.20g, 1.38mmol), sodium hydride (0.28g, 6.90mmol) and 2,6-dibromobenzyl bromide (0.50, 1.52mmol) were reacted together as in the general protocol. Yield 0.14g, 26%. Yellow-brown oil; R_f (6:1 pet ether:EtOAc) 0.47; ν_{max} (film)/cm^{-1} 2926 (C-H), 1648 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.48 (2H, d, *J* = 8.0 Hz, ArH), 6.95 (1H, t, *J* = 8.0 Hz, ArH), 5.34 (1H, br s, NC=CH), 5.06 (2H, s, NCH_2), 2.02 (3H, s, $COCH_3$), 1.87 (4H, d, *J* = 5.6 Hz, cy), 1.50 (4H, dd, *J* = 11.3, 5.6 Hz, cy), 1.38 (2H, d, *J* = 4.4 Hz, cy); δ_C (101 MHz, $CDCl_3$) 169.9 (C=O), 137.3 (ArC quaternary), 135.7 (N<u>C</u>=CH), 132.5, 130.2 (ArCH), 129.5 (NC=<u>C</u>H), 127.1(ArCBr), 48.8 (NCH_2), 28.7, 24.9, 22.8 (cy), 21.4 ($COCH_3$), 21.3 (cy); *m/z* (ESI) 385.98 ([M]$^+$H); [Found: ([M]$^+$H) 385.9747, $C_{15}H_{18}{}^{79}Br_2NO$ requires 385.9750].

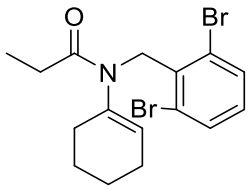
***N*-(2-Bromobenzyl)-*N*-(cyclohex-1-en-1-yl)propionamide (2.8j)**



N-(Cyclohex-1-en-1-yl)propionamide (**2.11b**) (0.20g, 1.30mmol), sodium hydride (0.16g, 6.50mmol) and 2-bromobenzyl bromide (0.35, 1.41mmol) were reacted together as in the general protocol. Yield 0.16g, 38%. Brown oil; ν_{max} (film)/cm^{-1} 2931 (C-H), 1649 (C=O); δ_H (400 MHz, $CDCl_3$) 7.49 (1H, d, *J* = 8.0 Hz, ArH), 7.37 (1H, d,

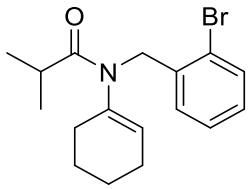
J = 7.5 Hz, ArH), 7.25 (1H, t, *J* = 7.5 Hz, ArH), 7.09 (1H, t, *J* = 7.0 Hz, ArH), 5.41 (1H, br s, NC=CH), 4.78 (2H, s, NCH_2), 2.37 (2H, q, *J* = 7.5 Hz, $COC\underline{H}_2CH_3$), 2.09 – 1.92 (4H, m, cy), 1.73 – 1.59 (2H, m, cy), 1.59 – 1.41 (2H, m, cy), 1.16 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (101 MHz, $CDCl_3$) 173.7 (C=O), 138.2 (ArC quaternary), 137.4 ($N\underline{C}$=CH) 132.5, 130.5, 128.7 (ArCH), 128.2 (NC=$\underline{C}$H), 127.5 (ArCH), 124.1 (ArCBr), 48.9 ($N\underline{C}H_2$), 28.2 ($CO\underline{C}H_2$), 26.8, 24.9, 22.8, 21.4 (cy), 10.2 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 344.06 ($[M]^+Na$); [Found: ($[M]^+Na$) 344.0620, $C_{16}H_{20}{}^{79}BrNNaO$ requires 344.0620].

***N*-(Cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)propionamide (2.8k)**:



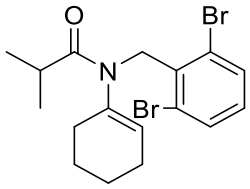
N-(Cyclohex-1-en-1-yl)propionamide (**2.11b**) (0.22g, 1.40mmol), sodium hydride (0.16g, 7.0mmol) and 2,6-dibromobenzyl bromide (0.49, 1.50mmol) were reacted together as in the general protocol. Yield 0.14g, 25%; Brown oil; ν_{max} (film)/cm^{-1} 2940 (C-H), 1646 (C=O); δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* = 8.0 Hz, ArH), 6.98 (1H, t, *J* = 8.0 Hz, ArH), 5.35 (1H, t, *J* = 3.5 Hz, NC=CH), 5.11 (2H, s, NCH_2), 2.37 – 2.23 (2H, m, $COC\underline{H}_2CH_3$), 1.95 – 1.84 (4H, m, cy), 1.60 – 1.52 (2H, m, cy), 1.48 – 1.40 (2H, m, cy), 1.16 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (101 MHz, $CDCl_3$) 173.0 (C=O), 136.8 (ArC quaternary), 135.9 ($N\underline{C}$=CH), 132.4 (NC=$\underline{C}$H), 130.0, 129.3 (ArCH), 127.0 (ArCBr), 48.7 (NCH_2), 28.8, 26.7, 24.9, 22.8 (cy), 21.3 ($COC\underline{H}_2CH_3$), 10.2 ($COCH_2C\underline{H}_3$); *m/z* (ESI) 421.97 ($[M]^+Na$); [Found: ($[M]^+Na$) 421.9728, $C_{16}H_{19}{}^{79}Br_2NNaO$ requires 421.9726].

***N*-(2-Bromobenzyl)-*N*-cyclohexenylisobutyramide (2.8m)**



N-(Cyclohex-1-en-1-yl)isobutyramide (**2.11c**) (0.30g, 1.79mmol), sodium hydride (0.21g, 8.95mmol) and 2-bromobenzyl bromide (0.49, 1.97mmol) were reacted together as in the general protocol. Yield 0.24g, 40%. Yellow oil; ν_{max} (film)/cm^{-1} 2930 (C-H), 1656 (C=O); δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 8.0 Hz, ArH), 7.36 (1H, d, *J* = 7.0 Hz, ArH), 7.25 (1H, dd, app t, *J* = 7.5 Hz, ArH), 7.09 (1H, dd, app t, *J* = 7.5 Hz, ArH), 5.41 (1H, s, C=CH), 4.77 (2H, s, NCH_2), 2.84 (1H, hept, *J* = 6.5 Hz, COCH), 2.08 – 1.92 (4H, m, cy), 1.77 – 1.60 (2H, m, cy), 1.60 – 1.45 (2H, m, cy), 1.14 (6H, d, *J* = 6.5 Hz, $COCH(\underline{C}H_3)_2$); δ_C (101 MHz, $CDCl_3$) 177.2 (C=O), 138.4 (ArC quaternary), 137.7 (N$\underline{C}$=CH), 132.6, 130.5, 128.7, 127.8 (ArCH), 127.6 (NC=$\underline{C}$H), 124.2 (ArCBr), 49.0 (NCH_2), 31.4 ($CO\underline{C}H(CH_3)_2$), 28.8, 24.9, 22.9, 21.5 (cy), 20.4 ($COCH(\underline{C}H_3)_2$); *m/z* (ESI) 358.08 ($[M]^+Na$); [Found: ($[M]^+Na$) 358.0776, $C_{17}H_{22}{}^{79}BrNNaO$ requires 358.0777].

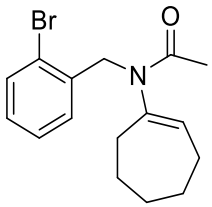
***N*-(Cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide (2.8n)**



N-(Cyclohex-1-en-1-yl)isobutyramide (**2.11c**) (0.31g, 1.82mmol), sodium hydride (0.21g, 9.10mmol) and 2,6-dibromobenzyl bromide (0.66, 2.01mmol) were reacted

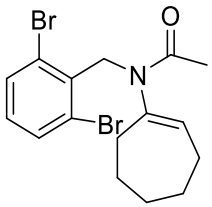
together as in the general protocol. Yield 36mg, 6%; Yellow oil; ν_{max} (film)/cm^{-1} 2929 (C-H), 1649 (C=O); δ_H (300 MHz, $CDCl_3$) 7.53 (2H, d, *J* = 8.0 Hz, ArH), 6.98 (1H, t, *J* = 8.0 Hz, ArH), 5.33 (1H, br s, NC$\underline{H}_a$CH_b), 5.31 (1H, s, C=C$\underline{H}$), 4.89 (1H, s, NCH_aC$\underline{H}_b$), 2.76 (1H, hept, *J* = 7.0 Hz, COC$\underline{H}$(CH_3)$_2$), 1.93 (4H, m, cy), 1.57 (2H, m, cy), 1.47 (2H, m, cy), 1.14 (6H, d, *J* = 7.0 Hz, COCH(C$\underline{H}_3$)$_2$).; δ_C (126 MHz, $CDCl_3$) 176.6 (C=O), 136.9 (ArC quaternary), 136.3 (N$\underline{C}$=CH), 132.5, 130.1 (ArCH), 129.1 (NC=$\underline{C}$H), 127.2 (ArCBr), 48.7 (NCH_2), 31.8 (CO$\underline{C}$H(CH_3)$_2$), 29.4, 25.0, 22.9, 21.4 (cy), 19.9 (COCH($\underline{C}H_3$)$_2$); *m/z* (ESI) 437.99 ([M]$^+$Na); [Found: 437.9866 ([M]$^+$Na), $C_{17}H_{21}{}^{79}Br_2NNaO$ requires 437.9862].

***N*-Cyclohept-1-enyl-*N*-2-bromobenzylacetamide (2.8o):**



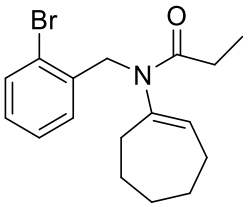
N-Cycloheptenylacetamide (2.11d) (0.60g, 3.9mmol), sodium hydride (0.52g, 19.5mmol) and 2-bromobenzyl bromide (1.07g, 4.30mmol) were reacted together as in the general protocol. Yield 0.31g, 24%. Orange oil; R_f (6:1 pet ether:EtOAc) 0.50; ν_{max} (film)/cm^{-1} 2920 (C-H), 1643 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.36 (1H, d, *J* = 8.0 Hz, ArH), 7.22 (1H, d, *J* = 7.7 Hz, ArH), 7.12 (1H, dd, app t, *J* = 7.5 Hz, ArH), 6.96 (1H, dd, app t, *J* = 7.6 Hz, ArH), 5.47 (1H, t, *J* = 6.4 Hz, NC=CH), 4.66 (2H, s, NCH_2), 2.13 – 2.05 (2H, m, cy), 1.99 (3H, s, $COCH_3$), 1.94 – 1.84 (4H, m, cy), 1.58 – 1.47 (2H, m, cy), 1.36 (2H, dd, *J* = 6.9, 4.1 Hz, cy); δ_C (101 MHz, $CDCl_3$) 170.1 (C=O), 143.6 (ArC quaternary), 136.9 (N<u>C</u>=CH), 132.6, 132.3, 130.7, 128.7 (ArCH), 127.4 (NC=<u>C</u>H), 124.0 (ArCBr), 49.4 (NCH_2), 34.0, 31.1, 27.0, 26.2, 25.9 (cy), 22.0 (CO<u>C</u>H_3); *m/z* (ESI) 322.08 ($[M]^+H$); [Found: ($[M]^+H$) 322.0805, $C_{16}H_{21}{}^{79}BrNO$ requires 322.0801].

***N*-Cyclohept-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8p)**



N-Cycloheptenylacetamide (2.11d) (0.30g, 1.95mmol), sodium hydride (0.23g, 9.8mmol) and 2,6-dibromobenzyl bromide (0.71g, 2.15mmol) were reacted together as in the general protocol. Yield 86mg, 11%. Yellow oil; R_f (6:1 pet ether:EtOAc) 0.45; ν_{max} (film)/cm^{-1} 2921 (C-H), 1647 (C=O); δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* = 8.0 Hz, ArH), 6.97 (1H, t, *J* = 8.0 Hz, ArH), 5.72 (1H, t, *J* = 6.2 Hz, NC=CH), 5.06 (2H, d, *J* = 46.6 Hz, NCH_2), 2.03 (3H, s, $COCH_3$), 1.95 (4H, m, cy), 1.50 (2H, d, *J* = 5.2 Hz, cy), 1.34 (2H, m, cy), 0.86 (2H, dd, *J* = 24.0, 17.6 Hz, cy); δ_C (101 MHz, $CDCl_3$) 169.7 (C=O), 142.3 (ArC quaternary), 135.6 (N<u>C</u>=CH), 133.4, 132.6 (ArCH), 130.3 (NC=<u>C</u>H), 127.2 (ArCBr), 49.7 (NCH_2), 34.6, 30.8, 27.0, 26.2, 25.4 (cy), 21.9 ($COCH_3$); *m/z* (ESI) 399.99 ($[M]^+H$); [Found: ($[M]^+H$) 399.9909, $C_{16}H_{20}{}^{79}Br_2NO$ requires 399.9906].

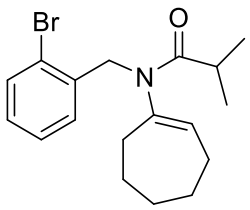
***N*-(2-Bromobenzyl)-*N*-(cyclohept-1-en-1-yl)propionamide (2.8q)**



N-(Cyclohex-1-en-1-yl)propionamide (**2.11e**) (0.10g, 0.60mmol), sodium hydride (0.72g, 5.0mmol) and 2-bromobenzyl bromide (0.17g, 0.70mmol) were reacted together as in the general protocol. Yield 54mg, 27%. Yellow oil; ν_{max} (film)/cm^{-1} 2922 (C-H), 1646 (C=O); δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 7.5 Hz, ArH), 7.35 (1H,

dd, *J* = 7.5, 1.0 Hz, ArH), 7.25 (1H, d, *J* = 7.5 Hz, ArH), 7.09 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 5.58 (1H, t, *J* = 6.5 Hz, NC=CH), 4.79 (2H, s, NCH_2), 2.39 (2H, q, *J* = 7.5 Hz, $COC\underline{H}_2$), 2.28 – 2.12 (2H, m, cy), 2.03 (2H, dd, *J* = 11.0, 6.5 Hz, cy), 1.75 – 1.58 (2H, m, cy), 1.51 (4H, dd, *J* = 6.5, 4.5 Hz, cy), 1.16 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (101 MHz, $CDCl_3$) 173.6 (C=O), 143.2 (ArC quaternary), 137.3 ($N\underline{C}$=CH), 132.7 (ArCH), 132.3 (NC=$\underline{C}$H), 130.9, 128.8, 127.5 (ArCH), 124.1 (ArCBr), 49.6 (NCH_2), 34.3, 31.2 (cy), 27.1 ($CO\underline{C}H_2$), 26.3, 26.0 (cy), 10.1 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 358.08 ($[M]^+Na$); [Found: ($[M]^+Na$) 358.0778, $C_{17}H_{22}{}^{79}BrNNaO$ requires 358.0777].

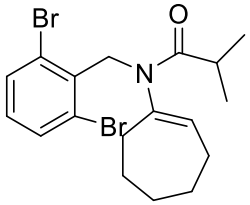
***N*-(2-Bromobenzyl)-*N*-cycloheptenylisobutyramide (2.8r)**:



N-(Cyclohex-1-en-1-yl)isobutyramide (**2.11f**) (0.20g, 1.1mmol), sodium hydride (1.32g, 5.5mmol) and 2-bromobenzyl bromide (0.30g, 1.2mmol) were reacted together as in the general protocol. Yield 0.13g, 33%. Yellow oil; ν_{max} (film)/cm^{-1} 2923, 1646; δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 8.0 Hz, ArH), 7.33 (1H, d, *J* = 8.0 Hz, ArH), 7.25 (1H, dd, app t, *J* = 7.5 Hz, ArH), 7.09 (1H, dd, app t, *J* = 7.5 Hz, ArH), 5.57 (1H, t, *J* = 6.5 Hz, NCC$\underline{H}$), 4.77 (2H, br d, $NC\underline{H}_2$), 3.04 – 2.84 (1H, m, $COC\underline{H}$), 2.21 (2H, s, cy), 2.03 (2H, d, *J* = 4.0 Hz, cy), 1.66 (2H, m, cy), 1.50 (4H, s, cy), 1.14 (6H, d, *J* = 6.5 Hz, $COCH(C\underline{H}_3)_2$); δ_C (101 MHz, $CDCl_3$) 176.9 (C=O), 143.2 (ArC quaternary), 137.2 ($N\underline{C}$=CH), 132.6, 131.9, 130.8, 128.7 (ArCH), 127.5 (NC=$\underline{C}$H), 124.1 (ArCBr), 49.5 (NCH_2), 34.7 (cy), 31.4 ($COCH(\underline{C}H_3)_2$), 31.1, 26.9, 26.2, 25.8 (cy), 20.1

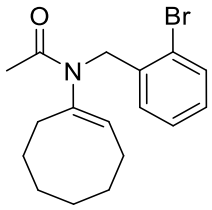
(CO<u>CH</u>$(CH_3)_2$); *m/z* (ESI) 372.09 ($[M]^+$Na); [Found: 372.0932 ($[M]^+$Na), $C_{18}H_{24}{}^{79}BrNNaO$ requires 372.0933].

***N*-(Cyclohept-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide (2.8s)**



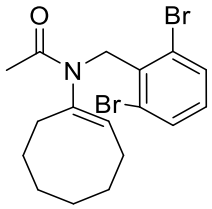
N-(Cyclohex-1-en-1-yl)isobutyramide (**2.11f**) (0.20g, 1.1mmol), sodium hydride (1.32g, 5.5mmol) and 2,6-dibromobenzyl bromide (0.40g, 1.2mmol) were reacted together as in the general protocol. Yield 0.31g, 66%. Off-white solid; ν_{max} (film)/cm^{-1} 2929 1648; δ_H (300 MHz, $CDCl_3$) 7.53 (2H, d, *J* = 8.0 Hz, ArH), 6.98 (1H, t, *J* = 8.0 Hz, ArH), 5.33 (1H, br s, NC<u>H_a</u>CH_b), 5.31 (1H, s, C=C<u>H</u>), 4.89 (1H, s, NCH_aC<u>H_b</u>), 2.76 (1H, hept, *J* = 7.0 Hz, COC<u>H</u>$(CH_3)_2$), 1.93 (4H, m, cy), 1.57 (2H, m, cy), 1.47 (2H, m, cy), 1.14 (6H, d, *J* = 7.0 Hz, COCH(C<u>H_3</u>$)_2$).; δ_C (126 MHz, $CDCl_3$) 176.6 (C=O), 136.9 (ArC quaternary), 136.3 (N<u>C</u>=CH), 132.5, 130.1 (ArCH), 129.1 (NC=<u>C</u>H), 127.2 (ArCBr), 48.7 (NCH_2), 31.8 (COCH(<u>C</u>$H_3)_2$), 29.4, 25.0, 22.9, 21.4 (cy), 19.9 (CO<u>CH</u>$(CH_3)_2$); *m/z* (ESI) 452.00 ($[M]^+$Na); [Found: 452.0017 ($[M]^+$Na), $C_{18}H_{23}{}^{79}Br_2NNaO$ requires 452.0019].

***N*-Cyclooct-1-enyl-*N*-2-bromobenzylacetamide (2.8t)**



N-Cyclooctenylacetamide (**2.11g**) (0.40g, 2.4mmol), sodium hydride (0.28g, 12.0mmol) and 2-bromobenzyl bromide (0.65g, 2.6mmol) were reacted together as in the general protocol. Yield 0.34g, 42%. Yellow oil; ν_{max} (film)/cm^{-1} 2926 (C-H), 1630 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.49 (1H, d, *J* = 8.0 Hz, ArH), 7.26 (2H, m, ArH), 7.08 (1H, dd, app t, *J* = 8.0 Hz, ArH), 5.51 (1H, t, *J* = 8.5 Hz, NC=C<u>H</u>), 4.81 (2H, s, NCH_2), 2.31 (2H, d, *J* = 5.5 Hz, cy), 2.19 (3H, s, $COC\underline{H}_3$), 2.15 – 2.02 (2H, m, cy), 1.60 – 1.32 (8H, m, cy); δ_C (101 MHz, $CDCl_3$) 170.7 (C=O), 141.5 (ArC quaternary), 136.6 (N<u>C</u>=CH), 132.5 (ArCH), 129.8 (NC=<u>C</u>H), 129.0, 128.4, 127.3 (ArCH), 123.1 (ArCBr), 50.3 ($N\underline{C}H_2$), 30.6, 28.9, 28.8, 26.2, 25.9 (cy), 22.1 ($CO\underline{C}H_3$); *m/z* (ESI) 336.10 ([M]$^+$H); [Found: ([M]$^+$H) 336.0955, $C_{17}H_{23}{}^{79}BrNO$ requires 336.0958].

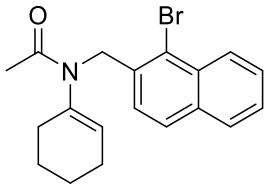
***N*-Cyclooct-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8u)**



N-Cyclooctenylacetamide (**2.11g**) (0.20g, 1.2mmol), sodium hydride (0.14g, 6.0mmol) and 2,6-dibromobenzyl bromide (0.43g, 1.3mmol) were reacted together as in the general protocol. Yield 0.10g, 20%. Brown oil; ν_{max} (film)/cm^{-1} 2929 (C-H), 1648 (C=O); δ_H (500 MHz, $CDCl_3$) 7.51 (2H, d, *J* = 8.0 Hz, ArH), 6.97 (1H, t, *J* = 8.0

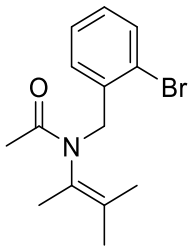
Hz, ArH), 5.53 (1H, t, *J* = 8.5 Hz, NC=CH), 5.16 (2H, s, NCH_2), 2.22 (2H, m, cy), 2.13 (3H, s, $COCH_3$), 1.99 (2H, dd, *J* = 13.0, 8.0 Hz, cy), 1.53 – 1.44 (2H, m, cy), 1.46 – 1.29 (6H, m, cy); δ_C (126 MHz, $CDCl_3$) 170.2 (C=O), 140.2 (ArC quaternary), 135.9 (N<u>C</u>=CH), 132.7, 132.6 (ArCH), 131.2 (NC=<u>C</u>H), 130.2 (ArCH), 127.2, 127.1 (ArCBr), 49.3 (NCH_2), 31.9, 28.2, 28.1, 26.2, 25.7, 25.5 (cy), 22.2 ($COCH_3$); *m/z* (ESI) 435.99 ($[M]^+Na$); [Found: ($[M]^+Na$) 435.9879, $C_{17}H_{21}{}^{79}Br_2NNaO$ requires 435.9882].

_N_-((3-Bromonaphthalen-2-yl)methyl)-_N_-(cyclohex-1-en-1-yl)acetamide (2.9)



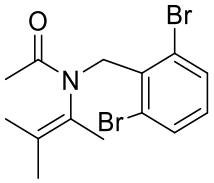
N-Cyclohexenylacetamide (**2.11a**) (0.42g, 3.0mmol), sodium hydride (0.36g, 15.0mmol) and 1-bromo-2-bromomethylnaphthalene (1.0g, 3.3mmol) were reacted together as in the general protocol. Yield 0.31g, 29%. Yellow oil; ν_{max} (film)/cm^{-1} 2927 (C-H), 1649 (C=O); δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* = 8.5 Hz, ArH), 7.76 (2H, dd, *J* = 8.5, 8.0 Hz, ArH), 7.62 – 7.43 (3H, m, ArH), 5.34 (1H, s, NC=CH), 5.06 (2H, s, NCH_2), 2.12 (3H, s, $COCH_3$), 2.04 (2H, d, *J* = 6.5 Hz, cy), 1.91 (2H, dd, *J* = 5.5, 2.5 Hz, cy), 1.64 (2H, dd, *J* = 7.5, 4.0 Hz, cy), 1.48 (2H, dd, *J* = 7.5, 4.0 Hz, cy); δ_C (101 MHz, $CDCl_3$) 170.4 (C=O), 138.5, 135.5, 133.8 (ArC quaternary), 132.2 (N<u>C</u>=CH), 128.3, 128.1, 127.8, 127.5, 127.4 (ArCH), 126.4 (NC=<u>C</u>H), 124.0 (ArCBr), 49.4 (NCH_2), 28.0, 24.8, 22.8 (cy), 21.6 (CO<u>C</u>H_3), 21.4 (cy); *m/z* (ESI) 380.06 ($[M]^+Na$); [Found: 380.0620 ($[M]^+Na$), $C_{19}H_{20}B^{79}BrNNaO$ requires 380.0620].

***N*-(2-Bromobenzyl)-*N*-(3-methylbut-2-en-2-yl)acetamide (2.16b)**



N-(3-Methylbut-2-en-2-yl)acetamide (**2.11h**) (1.0g, 7.86mmol), sodium hydride (0.94g, 39.3mmol) and 2-bromobenzyl bromide (2.16g, 8.65mmol) were reacted together as in the general protocol. Yield 0.66g, 28%. Yellow oil; ν_{max} (film)/cm^{-1} 2919 (C-H), 1642 (C=O); δ_H (250 MHz, $CDCl_3$) 7.52 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.47 (1H, dd, *J* = 8.0, 1.0 Hz, ArH), 7.23 (1H, td, *J* = 7.5, 1.0 Hz, ArH), 7.08 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 4.78 (2H, s, NCH_2), 1.97 (3H, s, $COCH_3$), 1.70 (3H, br s, CH_3), 1.63 (3H, br s, CH_3), 1.31 (3H, br s, CH_3); δ_C (75 MHz, $CDCl_3$) 170.8 (C=O), 137.2 (ArC quaternary), 132.7, 132.1 (ArCH), 131.7 (N<u>C</u>=CH), 129.5 (NC=<u>C</u>H), 129.1, 127.7 (ArCH), 124.5 (ArCBr), 48.3 (NCH_2), 21.3, 19.9, 19.5, 17.8 (Me); *m/z* (ESI) 318.05 ([M]$^+$Na); [Found: 318.0466 ([M]$^+$Na), $C_{14}H_{18}B^{79}BrNNaO$ requires 318.0464].

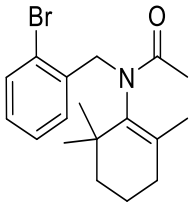
***N*-(2,6-Dibromobenzyl)-*N*-(3-methylbut-2-en-2-yl)acetamide (2.16c)**



N-(3-Methylbut-2-en-2-yl)acetamide (**2.11h**) (1.0g, 7.86mmol), sodium hydride (0.94g, 39.3mmol) and 2,6-dibromobenzyl bromide (2.83g, 8.65mmol) were reacted together as in the general protocol. Yield 0.59g, 20%. Brown oil; ν_{max} (film)/cm^{-1} 2914

(C-H), 1651 (C=O); δ_H (300 MHz, $CDCl_3$) 7.52 (2H, d, *J* = 8.0 Hz, ArH), 6.99 (1H, t, *J* = 8.0 Hz, ArH), 5.21 (1H, d, *J* = 14.0 Hz, $NC\underline{H}_aCH_b$), 4.92 (1H, d, *J* = 14.0 Hz, $NCH_aC\underline{H}_b$), 1.97 (3H, s, $COCH_3$), 1.60 (3H, s, $NCC\underline{H}_3$), 1.48 (3H, s, $NC{=}CC\underline{H}_3CH_3$), 1.46 (3H, s, $NC{=}CCH_3C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.1 (C=O), 135.6 (ArC quaternary), 133.3 ($N\underline{C}$=C), 132.6, 130.3 (ArCH), 128.5 (NC=$\underline{C}$), 127.5 (ArCBr), 48.4 (NCH_2), 21.3, 20.0, 19.6, 18.4 (Me); *m/z* (ESI) 395.96 ($[M]^+$Na); [Found: 395.9567 ($[M]^+$Na), $C_{14}H_{17}{}^{79}Br_2NNaO$ requires 395.9569].

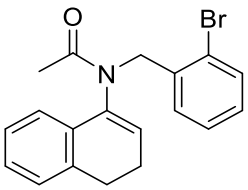
_N_-(2-Bromobenzyl)-_N_-(2,6,6-trimethylcyclohex-1-en-1-yl)acetamide (2.21b)



N-(2,6,6-Trimethylcyclohex-1-en-1-yl)acetamide (**2.23**) (0.5g, 2.8mmol), sodium hydride (0.33g, 14.0mmol) and 2-bromobenzyl bromide (0.77g, 3.1mmol) were reacted together as in the general protocol. Yield 0.23g, 24%. Off-white solid; ν_{max} (film)/cm^{-1} 2948 (C-H), 1657 (C=O); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, d, *J* = 8.0 Hz, ArH), 7.48 (1H, d, *J* = 8.0 Hz, ArH), 7.27 (1H, dd, app t, *J* = 7.5 Hz, ArH), 7.07 (1H, dd, app t, *J* = 7.6 Hz, ArH), 4.88 (1H, d, *J* = 15.5 Hz, $NC\underline{H}_aCH_b$), 4.53 (1H, d, *J* = 15.5 Hz, $NCH_aC\underline{H}_b$), 2.06 (3H, s, $COC\underline{H}_3$), 1.80 – 1.49 (4H, m, cy), 1.37 (3H, s, $NC{=}CC\underline{H}_3$), 1.30 – 1.18 (2H, m, cy), 1.09 (3H, s, $CC\underline{H}_3CH_3$), 0.98 (3H, s, $CCH_3C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 173.3 (C=O), 141.5 (ArC quaternary), 137.3 ($N\underline{C}{=}CCH_3$), 133.6 ($NC{=}\underline{C}CH_3$), 132.7, 132.5, 130.7, 130.6, 128.7, 128.3, 127.5, 127.4 (ArCH, maj and min rotamers), 123.1 (ArCBr), 53.5 (NCH_2), 40.6, 38.6, 36.3, 34.6, 32.1 (cy, major and minor rotamers), 28.6, 28.0, 27.9 (methyl groups), 24.8 (quaternary alkyl carbon),

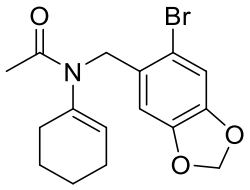
22.6, 22.0 ($COCH_3$, major and minor rotamers); *m/z* (ESI) 372.09 ($[M]^+Na$); [Found: 372.0934 ($[M]^+Na$), $C_{18}H_{24}{}^{79}BrNNaO$ requires 372.0933].

_N_-(2-Bromobenzyl)-_N_-(3,4-dihydronaphthalen-1-yl)acetamide (2.27)



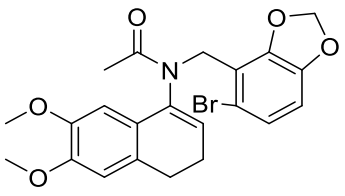
N-(3,4-Dihydronaphthalen-1-yl)acetamide (2.11i) (0.25g, 1.34mmol), sodium hydride (0.16g, 6.7mmol) and 2-bromobenzyl bromide (0.73g, 2.9mmol) were reacted together as in the general protocol. Yield 0.23g, 24%; Orange solid; ν_{max} (film)/cm^{-1} 2973 (C-H), 1664 (C=O); δ_H (400 MHz, $CDCl_3$) 7.46 (1H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, d, *J* = 7.5 Hz, ArH), 7.27 – 7.13 (4H, m, ArH), 7.12 – 6.99 (2H, m, ArH), 5.69 (1H, t, *J* = 4.5 Hz, C=C<u>H</u>), 5.51 (1H, d, *J* = 15.0 Hz, N<u>CH$_a$</u>CH$_b$), 4.26 (1H, d, *J* = 15.0 Hz, NCH$_a$<u>CH$_b$</u>), 2.78 – 2.68 (2H, m, cy), 2.39 – 2.13 (2H, m, cy), 2.05 (3H, s, $COCH_3$); δ_C (101 MHz, $CDCl_3$) 171.3 (C=O), 138.3, 136.9, 136.9 (ArC quaternary), 132.6 (ArCH), 131.4 (N<u>C</u>=CH), 130.8, 128.9, 128.3, 128.2, 128.0, 127.5, 126.9 (ArCH), 124.3 (ArCBr), 121.8 (NC=<u>C</u>H), 49.7 (NCH_2), 27.0, 22.8 (cy), 21.6 ($COCH_3$); *m/z* (ESI) 378.05 ($[M]^+Na$); [Found: ($[M]^+Na$) 378.0461, $C_{19}H_{18}{}^{79}BrNNaO$ requires 378.0464].

***N*-((6-Bromobenzo[1,3]dioxol-5-yl)methyl)-*N*-(cyclohex-1-en-1-yl)acetamide (2.28)**



N-Cyclohexenylacetamide (**2.11a**) (0.43g, 3.10mmol), sodium hydride (0.37g, 15.5mmol) and 5-bromo-6-(bromomethyl)benzo[1,3]dioxole (1.0g, 3.4mmol) were reacted together as in the general protocol. Yield 0.25g, 23%. Yellow oil; ν_{max} (film)/cm^{-1} 2972 (C-H), 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 6.86 (2H, s, ArH), 5.88 (2H, s, O-$\underline{CH_2}$-O), 5.32 (1H, s, NC$\underline{CH}$), 4.61 (2H, s, N$\underline{CH_2}$), 2.00 (3H, s, $COCH_3$), 1.96 (4H, m, cy), 1.61 (2H, m, cy), 1.48 (2H, m, cy); δ_C (101 MHz, $CDCl_3$) 170.2 (C=O), 147.6, 138.5, 130.6 (ArC quaternary), 128.3 (NC=$\underline{C}$H), 114.4 (N$\underline{C}$=CH), 112.2, 110.0 (ArCH), 101.7 (ArCBr), 48.3 (NCH_2), 28.0, 24.8, 22.8 (cy), 21.5 ($COCH_3$), 21.4 (cy); *m/z* (ESI) 374.04 ($[M]^+$Na); [Found: 374.0366 ($[M]^+$Na), $C_{16}H_{18}{}^{79}BrNNaO_3$ requires 374.0362].

***N*-((5-Bromobenzo[1,3]dioxol-4-yl)methyl)-*N*-(6,7-dimethoxy-3,4-dihydronaphthalen-1-yl)acetamide (2.29)**



N-(6,7-Dimethoxy-3,4-dihydronaphthalen-1-yl)acetamide (**2.11j**) (0.10g, 0.40mmol), sodium hydride (50mg, 2.0mmol) and 5-bromo-4-(bromomethyl)benzo[1,3]dioxole (0.13g, 0.44mmol) were reacted together as in the general protocol. Yield 0.18g, 99%. Brown oil; ν_{max} (film)/cm^{-1} 2936 (C-H), 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* = 8.5 Hz, ArH), 6.65 (1H, s, ArH), 6.56 (1H, s, ArH), 6.54 (1H, d, *J* = 8.5 Hz, ArH), 5.82 (1H, d, *J* = 1.0 Hz, OC$\underline{H}_aH_bO$), 5.73 (1H, dd, *J* = 5.5, 4.0 Hz, NC=CH), 5.70 (1H, d, *J* = 1.0 Hz, OC$H_a\underline{H}_bO$), 5.18 (1H, d, *J* = 14.0 Hz, NC$\underline{H}_aH_b$), 4.78 (1H, d, *J* = 14.0 Hz, NC$H_a\underline{H}_b$), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.68 – 2.45 (2H, m, cy), 2.36 – 2.12 (2H, m, cy), 2.03 (3H, s, $COCH_3$); δ_C (101 MHz, $CDCl_3$) 170.8 (C=O), 148.4, 148.1, 147.5, 146.6 (ArCO), 137.4 (ArC quaternary), 129.3 (N$\underline{C}$=CH), 126.1 (NC=$\underline{C}$H), 125.2 (ArCH), 124.8, 118.4 (ArC quaternary), 116.6 (ArCBr), 111.3, 108.9, 106.2 (ArCH), 101.6 (O$\underline{C}H_2O$), 56.3, 56.0 (OCH_3), 44.0 (NCH_2), 27.0, 23.0 (cy), 21.8 (CO$\underline{C}H_3$); *m/z* (ESI) 482.06 ([M]$^+$Na); [Found: ([M]$^+$Na) 482.0570, $C_{22}H_{22}{}^{79}BrNNaO_5$ requires 482.0574].

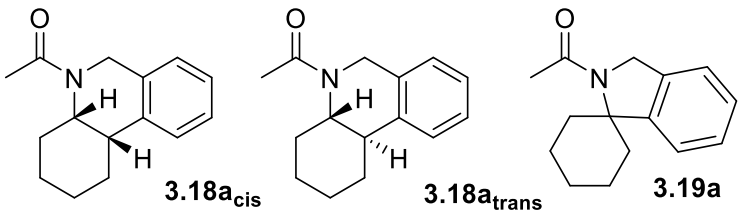
5.3 Tin Cyclisations discussed in Chapter 3

General Procedure:

The enamide (1 eq) was heated to reflux in toluene (0.02M), to which Bu_3SnH (1.5 eq) and ABCN (0.2 eq) were added over the course of two hours *via* syringe pump, and the reaction mixture heated at reflux overnight. The solvent was then removed *in vacuo*, and the product taken up in acetonitrile and washed with hexane. The acetonitrile phase was concentrated *in vacuo* to give the crude product. Products were purified by column chromatography.

Cyclisation of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (2.8d)

To a solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide **2.8d** (90mg, 0.29mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.12mL, 0.44mmol) and ABCN (14.3mg, $5.84x10^{-2}$mmol) in toluene (4.5mL). After standard work-up, the crude product was obtained as a yellow oil (0.12g). The mixture was purified by column chromatography (14:1 to 6:1 pet ether/EtOAc) to obtain products **3.18a$_{cis}$, 3.18a$_{trans}$, 3.19a**, and the reduced starting material **2.8a**, which were present in a 48:27:18:6 ratio in the crude mixture.



***Cis*-1- (1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (3.18a$_{cis}$) (1:0.83 mixture of rotamers)** : Yield 17mg, 25%. ν_{max} (film)/cm^{-1} 2930 (C-H), 1686 (C=O). δ_H ($CDCl_3$, 300 MHz) 6.93-7.96 (4H maj + 4H min, m, ArH), 5.04 (1H maj, d, *J* = 18.0Hz, N$\underline{CH_a}H_b$), 4.76-4.89 (1H min, m, NCH), 4.66 (1H min, d, *J* = 16.5Hz, N$\underline{CH_a}H_b$), 4.55 (1H min, d, *J* = 16.5Hz, N$CH_a\underline{H_b}$), 4.35 (1H maj, d, *J* = 18.0Hz,

NCH_aH_b), 3.88-4.04 (1H maj, m, NCH), 3.24 (1H maj, br s, NCHCH), 3.13 (1H min, br s, NCHCH), 2.35-2.72 (1H maj +1H min, m, cy), 2.21 (1H maj, s, $COCH_3$), 2.18 (1H min, s, $COCH_3$), 1.07-1.86 (7H maj + 7H 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 (ArC, quaternary), 127.2, 126.8, 126.7, 126.4, 126.2, 126.1, 126.0, 125.9 (ArCH), 55.7 (NCH maj), 49.9 (NCH min), 45.9 (NCH_2 min), 42.6 (NCH_2 maj), 37.2 (NCHCH maj), 36.4 (NCHCH min), 27.6, 27.3, 27.2, 25.7, 25.6, 25.4 (cy), 22.4, 21.7 ($COCH_3$), 19.8, 19.5 (cy); *m/z* (ESI) 252.14 ($[M]^+Na$); [Found: ($[M]^+Na$) 252.1357, $C_{15}H_{19}NONa$ requires 252.1359].

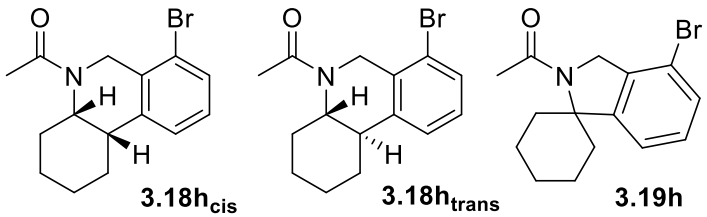
***Trans*-1-(1,2,3,4,4a,10b-Hexahydrophenanthridin-5(6H)-yl)ethanone (3.18a$_{trans}$) (1:0.54 mixture of rotamers)** : Yield 4mg, 6%. ν_{max} (film)/cm^{-1} 2927 (C-H), 1686 (C=O). δ_H ($CDCl_3$, 300 MHz) 7.03-7.46 (4H maj + 4H min, m, ArH), 5.57 (1H min, d, *J* = 14.1Hz, NCH_aH_b), 4.46 (1H maj, d, *J* = 14.8Hz, NCH_aH_b), 4.30 (1H maj, d, *J* = 14.7Hz, NCH_aH_b), 3.76 (1H min, d, *J* = 14.5Hz, NCH_aH_b), 3.38 (1H maj, t, *J* = 10.5Hz, NCH), 3.10 (1H min, m, NCH), 2.37-2.69 (2H maj + 2H min, m, cy), 2.15 (3H maj, s, $COCH_3$), 2.05 (3H min, s, $COCH_3$), 1.15-2.08 (6H maj + 6H min, m, cy) ; δ_C (100 MHz, $CDCl_3$) 170.6 (C=O min), 169.8 (C=O maj), 139.9, 139.2, 137.7, 136.3 (ArC quaternary), 127.9, 127.5, 126.3, 126.2, 125.6, 124.4, 123.1, 122.6 (ArCH), 60.2, 58.3 (NCH min), 53.8 (NCH maj), 47.1 (NCH min), 43.2 (NCH_2 maj), 42.1 (NCH_2 maj), 41.8 (NCHCH), 33.9, 31.0, 27.8, 26.0, 25.8, 25.3, 25.2 (cy), 22.9 (CH_3), 22.5, 22.4 (cy), 21.8 (CH_3); *m/z* (ESI) 252.14 ($[M]^+Na$); [Found: ($[M]^+Na$) 252.1351, $C_{15}H_{19}NONa$ requires 252.1359].

1-(Spiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (3.19a): Yield 9mg, 13%. ν_{max} (film)/cm^{-1} 2927 (C-H), 1626 (C=O). δ_H ($CDCl_3$, 300 MHz) 7.68 (1H, m, ArH),

7.20-7.29 (3H, m, ArH), 4.78 (2H, s, NCH_2), 3.10 (2H, td, *J* = 12.9, 5.6, ortho-cy), 2.16 (3H, s, $COCH_3$), 1.70-1.88 (4H, m, cy), 1.46-1.70 (4H, m, cy); δ_C (100 MHz, $CDCl_3$) 169.4 (C=O), 147.0, 134.0 (ArC), 127.3, 127.2, 124.0, 122.4 (ArCH), 70.7 (NC quaternary), 53.8 (NCH_2), 32.1, 27.8 (cy), 25.3 (CH_3), 24.3, 22.4 (cy); *m/z* (ESI) 252.14 ($[M]^+Na$); [Found: ($[M]^+Na$) 252.1372, $C_{15}H_{19}NONa$ requires 252.1359].

Cyclisation of *N*-cyclohex-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8h)

To a solution of *N*-cyclohex-1-enyl-*N*-2,6-dibromobenzylacetamide **2.8h** (100mg, $2.58x10^{-4}$mol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.10mL, $3.87x10^{-4}$mol) and ABCN (12.6mg, $5.16x10^{-5}$mol) in toluene (3mL). After standard work-up, the crude product was obtained as a yellow oil with tin residue (0.20g).The mixture was purified by column chromatography (14:1 to 1:1 pet ether/EtOAc) which led to the isolation of **3.18h$_{cis}$**, **3.18h$_{trans}$** and **3.19h**, as well as the non-brominated products **3.18a$_{cis}$, 3.18a$_{trans}$** and **3.19a.** Products **3.18a$_{cis}$, 3.18a$_{trans}$**, **3.19a, 3.18h$_{cis}$**, **3.18h$_{trans}$** and **3.19h** were present in the crude product in the approximate ratio 11:2:10:21:17:39.



***Cis*-1-(7-Bromo-1,2,3,4,4a,10b-hexahydrophenanthridin-5(6H)-yl)ethanone (3.18h$_{cis}$) (1:0.71 mixture of rotamers)**: Yield 10mg, 12%. ν_{max} (film)/cm^{-1} 2929 (C-H), 1632 (C=O). δ_H ($CDCl_3$, 700 MHz) 7.45 (1H maj, d, *J* = 7.9Hz, ArH) 7.44 (1H min, d, *J* = 7.8 Hz, ArH), 7.37 (1H min, d, *J* = 7.8Hz, ArH), 7.32 (1H maj, d, *J* = 7.9Hz, ArH), 7.16 (1H maj, dd, app t, *J* = 7.9Hz, ArH), 7.12 (1H min, dd, app t, *J* = 7.9Hz,

ArH), 5.17 (1H min, d, *J* = 18.8 Hz, N$\underline{CH_a}H_b$), 4.87 (1H maj, dt, *J* = 12.5, 4.5 Hz, NCH), 4.62 (1H maj, d, *J* = 17.3 Hz, N$\underline{CH_a}H_b$), 4.45 (1H maj, d, *J* = 17.3 Hz, $NCH_a\underline{H_b}$), 4.14 (1H min, d, *J* = 18.8Hz, $NCH_a\underline{H_b}$), 3.95 (1H min, dt, *J* = 12.1, 4.4 Hz, NCH), 3.23 (1H min, br s, NCHC$\underline{H}$), 3.12 (1H maj, br s, NCHC$\underline{H}$), 2.59 – 2.40 (2H maj + 2H min, m, cy), 2.22 (1H min, s, $COCH_3$), 2.21 (1H maj, s, $COCH_3$), 2.18 – 2.10 (1H maj + 1H min, m, cy), 2.10 – 1.00 (5H maj + 5H min, m, cy); δ_C (176 MHz, $CDCl_3$) 169.4 (C=O maj), 169.2 (C=O min), 138.7, 137.1, 132.6, 131.7 (ArC quaternary), 130.6, 130.2, 128.5, 128.0, 125.7, 125.2 (ArCH), 123.0, 122.5 (ArCBr), 55.1 (NCH maj), 48.9 (NCH min), 46.9 (NCH_2 min), 43.5 (NCH_2 maj), 37.6(NCHCH maj), 36.6 (NCHCH min), 28.0, 27.8, 27.6, 26.6, 25.5, 25.3 (cy), 22.4 ($COCH_3$ maj), 21.7 ($COCH_3$ min), 19.8, 19.5(cy); *m/z* (ESI) 330.05 ($[M]^+Na$); [Found: ($[M]^+Na$) 330.0458, $C_{15}H_{18}BrNONa$ requires 330.0464].

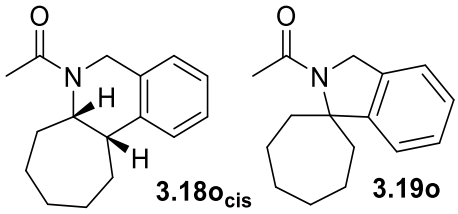
***Trans-1*-(7-Bromo-1,2,3,4,4a,10b-hexahydrophenanthridin-5(6H)-yl)ethanone (3.18h$_{trans}$) (one rotamer only)**: Yield 5mg, 6%. ν_{max} (film)/cm^{-1} 2926 (C-H), 1630 (C=O). δ_H ($CDCl_3$, 300 MHz) 7.40-7.46 (1H, m, ArH), 7.11-7.21 (2H, m, ArH), 5.08 (1H, d, *J* = 15.2Hz, N$\underline{CH_a}H_b$), 4.13 (1H, d, *J* = 15.0Hz, $NCH_a\underline{H_b}$), 3.35 (1H, t, *J* = 10.2Hz, NCH), 2.34-2.57 (3H, m, cy), 2.23 (3H, s, $COCH_3$), 1.20-2.05 (6H, m, cy); δ_C (151 MHz, $CDCl_3$) 170.3 (C=O), 142.5, 136.3 (ArC quaternary), 129.9, 129.0, 122.3 (ArCH), 119.9 (ArCBr), 58.0 (NCH), 45.7 (NCH_2), 42.5 (NCHCH), 32.1, 30.9, 25.9, 25.0 (cy), 22.9 ($COCH_3$); *m/z* (ESI) 330.05 ($[M]^+Na$); [Found: ($[M]^+Na$) 330.0457, $C_{15}H_{18}BrNONa$ requires 330.0464].

1-(4'-Bromospiro[cyclohexane-1,1'-isoindoline]-2'-yl)ethanone (3.19h): Yield 40mg, 50%. ν_{max} (film)/cm^{-1} 2922 (C-H), 1629 (C=O). δ_H ($CDCl_3$, 400 MHz) 7.61 (1H, d, *J* = 7.8 Hz, ArH), 7.44 (1H, d, *J* = 7.9 Hz, ArH), 7.16 (1H, dd, app t, *J* = 7.9 Hz, ArH), 4.71 (2H, s, NCH_2), 3.18 – 2.98 (2H, m, cy), 2.17 (3H, s, $COCH_3$), 1.89 – 1.70

(5H, m, cy), 1.70 – 1.44 (3H, m, cy); δ_C (101 MHz, $CDCl_3$) 169.5 (C=O), 148.8, 134.8 (ArC), 130.4, 129.2, 122.9 (ArCH), 117.5 (ArCBr), 72.1 (NC quaternary), 55.2 (NCH_2), 32.2(cy), 25.4(CH_3), 24.2, 22.3 (cy); *m/z* (ESI) 330.05 ($[M]^+Na$); [Found: ($[M]^+Na$) 330.0459, $C_{15}H_{18}BrNONa$ requires 330.0464].

Cyclisation of *N*-cyclohept-1-enyl-*N*-2-bromobenzylacetamide (2.8o)

To a solution of *N*-cyclohept-1-enyl-*N*-2-bromobenzylacetamide **2.8o** (150mg, $4.80x10^{-1}$mmol) in toluene (20mL) at reflux was added a mixture of Bu_3SnH (0.19mL, $7.22x10^{-1}$mmol) and ABCN (6.3mg, $2.58x10^{-2}$mmol) in toluene (4mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (6:1 to 1:1 pet ether/EtOAc) which led to the isolation of products **3.18o$_{cis}$** and **3.19o** (combined yield 25mg, 21%, as the products were inseparable by column chromatography), present in the crude product in the approximate ratio 86:14.



3.18o$_{cis}$ **3.19o**

***Cis*-1-(7,8,9,10,11,11a-Hexahydro-5H-cyclohepta[c]isoquinolin-6(6aH)-yl)ethanone (3.18o$_{cis}$) (1:0.95 mixture of rotamers)**: Approx. yield 22mg, 19%. ν_{max} (film)/cm^{-1} 2927 (C-H), 1693 (C=O). δ_H ($CDCl_3$, 250 MHz) 7.36 – 7.03 (4H maj + 4H min, m, ArH), 5.19 (1H maj, d, *J* = 17.5 Hz, N$\underline{CH_a}H_b$), 4.99 (1H min, dd, *J* = 11.6, 6.5 Hz, NCH), 4.57 (1H min, d, *J* = 16.4 Hz, N$\underline{CH_a}H_b$), 4.49 (1H min, d, *J* = 16.5 Hz, $NCH_a\underline{H_b}$), 4.16 (1H maj, d, *J* = 17.4 Hz, $NCH_a\underline{H_b}$), 4.11 – 4.04 (1H maj, m, NCH), 3.27 (1H maj + 1H min, dt, *J* = 14.3, 6.5 Hz, cy), 2.19 (3H min, s, $COCH_3$), 2.12 (3H

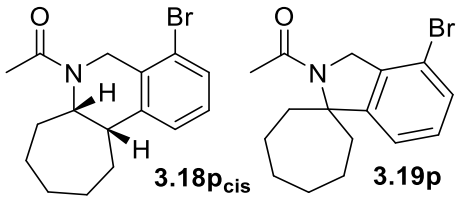
maj, s, $COCH_3$), 1.95 – 1.43 (8H maj + 8H min, m, cy), 1.42 – 1.14 (2H maj + 2H min, m, cy); δ_C (151 MHz, $CDCl_3$) 168.8, 168.7 (C=O), 141.3, 139.4, 132.2, 131.5 (ArC), 130.2, 129.8, 128.4, 127.8, 126.7, 126.0 (ArCH), 122.6, 121.8 (ArCBr), 57.7, 51.5 (NCH), 45.9, 42.0 (NCH_2), 39.9, 39.1 (NCHCH), 30.8, 30.4, 30.0, 29.5, 29.2, 29.1, 26.8, 26.5, 23.2, 22.7 (cy), 22.1, 21.7 ($COCH_3$); *m/z* (ESI) 266.15 ($[M]^+Na$); [Found: ($[M]^+Na$) 266.1512, $C_{16}H_{21}NONa$ requires 266.1515].

1-(Spiro[cycloheptane-1,1'-isoindoline]-2'-yl)ethanone (3.19o): Approx 3mg, 2%. ν_{max} (film)/cm^{-1} 2926 (C-H), 1686 (C=O). δ_H ($CDCl_3$, 250 MHz) 7.37-7.45 (1H, m, ArH), 7.03-7.35 (3H, m, ArH), 4.71 (2H, s, NCH_2), 2.57-2.78 (2H, m, cy), 2.03 (3H, s, $COCH_3$), 1.12-1.97 (12H, m, cy); δ_C (151 MHz, $CDCl_3$) 169.9 (C=O), 153.9, 142.1 (ArC quaternary), 133.6, 129.2, 126.7, 126.0 (ArCH), 72.1 (NC quaternary), 39.2 (NCH_2), 31.1, 30.3, 28.4 (cy), 27.8 ($COCH_3$), 25.2, 24.8, 22.1 (cy); *m/z* (ESI) 266.15 ($[M]^+Na$); [Found: ($[M]^+Na$) 266.1512, $C_{16}H_{21}NONa$ requires 266.1515].

Cyclisation of *N*-cyclohept-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8p)

To a solution of *N*-cyclohept-1-enyl-*N*-2-bromobenzylacetamide **2.8p** (128mg, $3.19x10^{-1}$mmol) in toluene (12mL) at reflux was added a mixture of Bu_3SnH (0.13mL, $4.79x10^{-1}$mmol) and ABCN (16mg, $6.38x10^{-2}$mmol) in toluene (4mL). After standard work-up, the crude product was obtained as a yellow oil (0.33g). The mixture was purified by column chromatography (6:1 to 1:1 pet ether/EtOAc) which led to the isolation of compounds **3.18p$_{cis}$** and **3.19p**, as well as the non-brominated products **3.18o$_{cis}$** and **3.19o**. Products **3.18o$_{cis}$, 3.19o, 3.18p$_{cis}$, 3.19p** were present in the crude product in the approximate ratio 22:55:tr:23. Unfortunately no carbon data could be

obtained for compounds **3.18p$_{cis}$** and **3.19p** due to inseparability and weakness of the samples (combined yield 0.01g, organotin residue still present).



3.18p$_{cis}$ **3.19p**

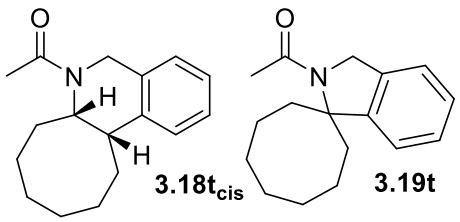
***Cis*-1-(4-Bromo-7,8,9,10,11,11a-hexahydro-5H-cyclohepta[c]isoquinolin-6(6aH)-yl)ethanone (3.18p$_{cis}$) (1:0.63 mixture of rotamers)**: ν_{max} (film)/cm^{-1} 2924 (C-H), 1624 (C=O). δ_H ($CDCl_3$, 300 MHz) 7.06-7.57 (3H, m, ArH), 5.36 (1H min, d, J = 18.5 Hz, N$\underline{CH_a}H_b$), 5.01 (1H maj, m, NCH), 4.69 (1H maj, d, J = 17.5 Hz, N$\underline{CH_a}H_b$), 4.33 (1H maj, d, J = 17.5Hz, N$CH_a\underline{H_b}$), 4.03-4.14 (1H min, m, NCH), 3.96 (1H min, d, J = 18.5Hz, N$CH_a\underline{H_b}$), 3.21-3.38 (1H maj + 1H min, m, cy), 2.23-2.50 (2H maj + 2H min, m, cy), 2.21 (3H min, s, $COCH_3$), 2.18 (3H maj, s, $COCH_3$), 1.10-1.94 (8H maj + 8H min, m, cy); *m/z* (ESI) 344.06 ([M]$^+$Na); [Found: ([M]$^+$Na) 344.0612, $C_{16}H_{20}BrNONa$ requires 344.0620].

1-(4'-Bromospiro[cycloheptane-1,1'-isoindoline]-2'-yl)ethanone (3.19p): ν_{max} (film)/cm^{-1} 2923 (C-H), 1635 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.07-7.59 (3H, m, ArH), 4.67 (2H, s, NCH_2), 2.70 (2H, dd, J = 13.6, 8.6Hz, cy), 2.17 (3H, s, $COCH_3$), 1.05-1.87 (10H, m, cy); *m/z* (ESI) 344.06 ([M]$^+$Na); [Found: ([M]$^+$Na) 344.0616, $C_{16}H_{20}BrNONa$ requires 344.0620].

Cyclisation of *N*-cyclooct-1-enyl-*N*-2-bromobenzylacetamide (2.8t)

To a solution of *N*-cyclooct-1-enyl-*N*-2-bromobenzylacetamide **2.8t** (200mg, 5.90x10^{-1}mmol) in toluene (26mL) at reflux was added a mixture of Bu_3SnH (0.24mL, 8.90x10^{-1}mmol) and ABCN (30mg, 1.2x10^{-1}mmol) in toluene (4mL). After standard work-up,

the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (6:1 to 1:1 pet ether/EtOAc) which led to the isolation of products **3.18t$_{cis}$** and **3.19t** present in the crude product in the approximate ratio 50:11, with 13% of reduced product and 27% of starting material.



3.18t$_{cis}$ **3.19t**

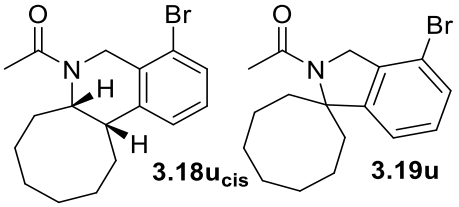
***Cis*-1-((6aS,12aS)-6a,7,8,9,10,11,12,12a-Octahydrocycloocta[c]isoquinolin-6(5H)-yl)ethan-1-one (3.18t$_{cis}$) (1:0.78 mixture of rotamers):** Yield 17mg, 11%. ν_{max} (film)/cm^{-1} 2920 (C-H), 1640 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.41 – 7.03 (4Hmaj + 4H min, m, ArH), 5.23 (1H min, d, *J* = 5.0 Hz, NCH), 4.99 (1H maj, d, *J* = 18.0 Hz, NC$\underline{H}_a$H$_b$), 4.62 (1H min, d, *J* = 16.0 Hz, NC$\underline{H}_a$H$_b$), 4.54 (1H min, d, *J* = 16.0 Hz, NCH$_a\underline{H}_b$), 4.41 (1H min, m, NCH), 4.37 (1H maj, d, *J* = 18.0 Hz, NCH$_a\underline{H}_b$), 3.13 – 3.03 (1H maj, m, NCHC$\underline{H}$), 3.03 – 2.93 (1H min, m, NCHC$\underline{H}$), 2.51 – 2.29 (1H maj + 1H min, m, cy), 2.25 (3H maj, s, $COCH_3$), 2.16 (3H min, s, $COCH_3$), 1.90 – 1.17 (11H maj + 11H min, m, cy + organotin residue); δ_C (75 MHz, $CDCl_3$) 178.1 (C=O), 127.2, 126.8 (ArC quaternary), 126.4, 126.3, 125.7(ArCH), 53.2, 46.2 (N$\underline{C}H_2$), 43.5, 43.0 (N$\underline{C}$H), 41.9 (NCH$\underline{C}$H), 40.9, 29.8, 26.9, 26.0 (cy), 25.2, 24.0 ($\underline{C}H_3$); *m/z* (ESI) 280.17 ([M]$^+$Na); [Found: ([M]$^+$Na) 280.1680, $C_{17}H_{23}NONa$ requires 280.1677].

1-(Spiro[cyclooctane-1,1'-isoindolin]-2'-yl)ethan-1-one (3.19t): Yield 5mg, 3%. ν_{max} (film)/cm^{-1} 2921 (C-H), 1634 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.44 (1H, br s, ArH), 7.40 – 7.03 (3H, m, ArH), 4.74 (2H, s, NCH_2), 2.91 – 2.77 (2H, m, cy), 2.33 (2H, br s, cy), 2.15 (3H, s, $COCH_3$), 1.92 – 1.42 (11H, m, cy); *m/z* (ESI) 280.17 ([M]$^+$Na);

[Found: ([M]$^{+}$Na) 280.1676, $C_{17}H_{23}NONa$ requires 280.1677]. Sample was too weak to obtain carbon NMR.

Cyclisation of *N*-cyclooct-1-enyl-*N*-2,6-dibromobenzylacetamide (2.8u)

To a solution of *N*-cyclooct-1-enyl-*N*-2,6-dibromobenzylacetamide **2.8u** (300mg, 7.2x10^{-1}mmol) in toluene (30mL) at reflux was added a mixture of Bu_3SnH (0.31mL, 1.08 mmol) and ABCN (35mg, 1.44 x10^{-1}mmol) in toluene (6mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (6:1 to 1:1 pet ether/EtOAc) which led to the identification of products **3.18u$_{cis}$** and **3.19u** present in the crude product in the approximate ratio 68:23, with 9% of starting material.



3.18u$_{cis}$ **3.19u**

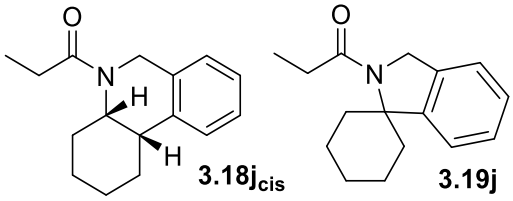
***Cis*-1-((6aS,12aS)-4-Bromo-6a,7,8,9,10,11,12,12a-octahydrocycloocta[c]isoquinolin-6(5H)-yl)ethan-1-one (3.18u$_{cis}$) (1:0.80 mixture of rotamers):** ν_{max} (film)/cm^{-1} 2919 (C-H), 1624 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.65 (1Hmaj, d, *J* = 7.5 Hz, ArH), 7.58 – 7.42 (3H maj/min, m, ArH), 7.20 – 7.07 (2H maj/min, m, ArH), 5.13 (1H min, d, *J* = 19.0 Hz, NC$\underline{H}_aH_b$), 4.76 – 4.70 (1H min, m, NCH), 4.60 (1H maj, d, *J* = 17.5 Hz, NC$\underline{H}_aH_b$), 4.49 (1H maj, d, *J* = 17.5 Hz, NCH$_a\underline{H}_b$), 4.42 – 4.35 (1H maj, m, NCH), 4.20 (1H min, d, *J* = 18.5 Hz, NCH$_a\underline{H}_b$), 3.11 – 3.04 (1H min, m, NCHC$\underline{H}$), 2.99 (1H maj, m, NCHC$\underline{H}$), 2.25 (3H min, s, $COCH_3$), 2.20 (3H maj, s, $COCH_3$), 1.95 – 1.34 (12H maj + 12H min, m, cy); δ_C (126 MHz, $CDCl_3$)

171.8, 169.0 (C=O), 144.5, 143.0, 140.7, 139.0 (ArC quaternary), 131.2, 130.3, 128.6, 128.1, 126.0, 125.1 (ArCH), 117.3, 117.2 (ArCBr), 55.5, 55.0 (NCH), 47.0, 46.9 (NCH_2), 41.1, 41.0 (NCHCH), 29.5, 29.3, 28.7, 28.4, 27.9, 27.6, 27.4, 26.2, 25.9, 25.7, 25.2, 25.0 (cy), 13.8, 13.5 ($COCH_3$); *m/z* (ESI) 358.08 ($[M]^+Na$); [Found: ($[M]^+Na$) 358.0778, $C_{17}H_{22}BrNONa$ requires 358.0777].

1-(4'-Bromospiro[cyclooctane-1,1'-isoindolin]-2'-yl)ethan-1-one (3.19u): ν_{max} (film)/cm^{-1} 2920 (C-H), 1622 (C=O); δ_H ($CDCl_3$, 500 MHz) 7.45 (1H, d, *J* = 8.0 Hz, ArH), 7.41 – 7.32 (1H, m, ArH), 7.11 (1H, dd, app t, *J* = 8.0 Hz, ArH), 4.61 (2H, s, NCH_2), 2.82 – 2.68 (2H, m, cy), 2.11 (3H, s, $COCH_3$), 1.96 – 1.43 (12H, m, cy); δ_C (126 MHz, $CDCl_3$) 169.4 (C=O), 135.15 (ArC quaternary), 134.3, 130.3, 122.6 (ArCH), 120.8 (ArC quaternary), 117.2 (ArCBr), 70.4 (NC quaternary), 55.0 (NCH_2), 35.7, 35.1, 29.1, 28.9, 25.0, 23.7, 23.4 (cy), 13.8 ($COCH_3$); *m/z* (ESI) 358.08 ($[M]^+Na$); [Found: ($[M]^+Na$) 358.0777, $C_{17}H_{22}BrNONa$ requires 358.0777].

Cyclisation of *N*-*(*2-bromobenzyl)-*N*-(cyclohex-1-en-1-yl)propionamide (2.8j)

To a solution of *N*-*(*2-bromobenzyl)-*N*-(cyclohex-1-en-1-yl)propionamide **2.8j** (50mg, $1.6x10^{-1}$mmol) in toluene (6mL) at reflux was added a mixture of Bu_3SnH ($6.5x10^{-2}$ mL, $2.4x10^{-1}$ mmol) and ABCN (8mg, $3.2x10^{-2}$ mmol) in toluene (2mL). After standard work-up, the crude product was obtained as a yellow oil with tin residue (0.104g). The mixture was purified by column chromatography (8:1 to 1:1 pet ether/EtOAc) which led to the identification of products **3.18j$_{cis}$** and **3.19j** present in the crude product in the approximate ratio 41:30 (17 mg combined isolated yield, 44%), with 29% of starting material.



3.18j$_{cis}$ **3.19j**

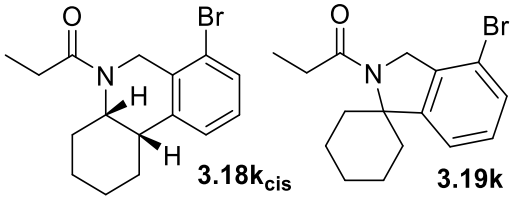
***Cis*-1-(2,3,4,4a,6,10b-Hexahydrophenanthridin-5(1H)-yl)propan-1-one (3.18j$_{cis}$) (1:0.75 mixture of rotamers):** Yield 10 mg, 25%. ν_{max} (film)/cm^{-1} 2938 (C-H), 1680 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.39, (1H min, d, *J* = 8.0Hz, ArH), 7.34 (1H maj, d, *J* = 7.5 Hz, ArH), 7.23 – 7.06 (3H maj + 3H min, m, ArH), 5.09 (1H maj, d, *J* = 18.0 Hz, NC$\underline{H}_a$H$_b$), 4.88 – 4.81 (1H min, m, NCH), 4.67 (1H min, d, *J* = 16.5 Hz, NC$\underline{H}_a$H$_b$), 4.53 (1H min, d, *J* = 16.5 Hz, NCH$_a\underline{H}_b$), 4.33 (1H maj, d, *J* = 18.0 Hz, NCH$_a\underline{H}_b$), 4.00 (1H maj, m, NCH), 3.25 – 3.20 (1H min, m, NCHC$\underline{H}$), 3.16 – 3.10 (1H maj, m, NCHC$\underline{H}$), 2.67 – 2.29 (2H maj + 2H min + 2H maj + 2H min, m, $COCH_2$ + cy), 1.77 – 1.50 (2H maj + 2H min, m, cy), 1.45 – 1.11 (4H maj + 4H min, m, cy + organotin residue), 0.92 (3H, t, J = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (101 MHz, $CDCl_3$) 168.6 (C=O maj), 168.0 (C=O min), 136.8, 135.3, 133.2, 131.9 (ArC, quaternary), 127.1, 126.8, 126.7, 126.5, 126.2, 126.1, 125.9, 125.8 (ArCH), 56.0 (NCH maj), 50.1 (NCH min), 45.8 (NCH_2 min), 43.5 (NCH_2 maj), 37.7 (N$\underline{C}$HCH maj), 37.3 (N$\underline{C}$HCH min), 28.7, 28.4, 26.2, 26.0, 25.4, 25.3, 25.1, 24.9 (cy), 19.4, 19.2 ($CO\underline{C}H_2CH_3$), 18.6, 18.5 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 266.15 ([M]$^+$Na); [Found: ([M]$^+$Na) 266.1523, $C_{16}H_{21}NONa$ requires 266.1521].

1-(spiro[cyclohexane-1,1'-isoindolin]-2'-yl)propan-1-one (3.19j): Yield 7mg, 19%. ν_{max} (film)/cm^{-1} 2932 (C-H), 1675 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.43 – 7.08 (4H, m, ArH), 4.76 (2H, s, NCH_2), 3.13 (2H, td, *J* = 13.0, 5.1 Hz, cy), 2.38 (2H, q, *J* = 7.5 Hz, $CO\underline{C}H_2CH_3$), 1.70 – 1.52 (4H, m, cy), 1.41 – 1.21 (6H, m, cy), 1.17 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_c (101 MHz, $CDCl_3$) 167.5 (C=O), 129.6, 128.2 (ArC quaternary),

127.4, 127.3, 124.1, 122.5 (ArCH), 73.9 (NC quaternary), 52.8 (NCH_2), 32.3, 29.8, 28.4, 22.6 (cy), 17.44 ($CO\underline{C}H_2CH_3$), 13.7 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 266.15 ($[M]^+Na$); [Found: ($[M]^+Na$) 266.1522, $C_{16}H_{21}NONa$ requires 266.1521].

Cyclisation of *N*-(cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)propionamide (2.8k)

To a solution of *N*-(cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)propionamide **2.8k** (104mg, $2.0x10^{-1}$mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.103 mL, $3.9x10^{-1}$ mmol) and ABCN (15mg, $5.2x10^{-2}$ mmol) in toluene (3mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (9:1 to 6:1 pet ether/EtOAc) which led to the identification of products **3.18k$_{cis}$** and **3.19k** present in the crude product in the approximate ratio 17:29 (combined yield 22mg, 35%), with 40% of starting material and 14% of another unidentified compound.



3.18k$_{cis}$ **3.19k**

***Cis*-1-((4aS,10bS)-7-Bromo-2,3,4,4a,6,10b-hexahydrophenanthridin-5(1H)-yl)propan-1-one (3.18k$_{cis}$) (1:0.77 mixture of rotamers):** Yield 8mg, 12%. ν_{max} (film)/cm^{-1} 2930 (C-H), 1624 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.45 (1H maj + 1H min, d, *J* = 8.0 Hz, ArH), 7.34 (1H min + 1H maj, m, ArH), 7.14 (1H maj + 1H min, m, ArH), 5.22 (1H min, d, *J* = 19.0 Hz, $NC\underline{H}_aH_b$), 4.96 – 4.83 (1H maj, m, NCH), 4.66 (1H maj, d, *J* = 17.5 Hz, $NC\underline{H}_aH_b$), 4.41 (1H maj, d, *J* = 17.5 Hz, $NCH_a\underline{H}_b$), 4.13 (1H min, d, *J* = 19.0 Hz, $NCH_a\underline{H}_b$), 4.05 – 3.94 (1H min, m, NCH), 3.22 (1H min, br s, NCHC$\underline{H}$), 3.13 (1H maj, br s, NCHC$\underline{H}$), 2.48 (2H maj + 2H min, q, *J* = 7.5 Hz, $COC\underline{H}_2CH_3$), 1.91 – 1.38 (8H maj + 8H min, m, cy), 1.21 (3H maj + 3H min, t, *J* =

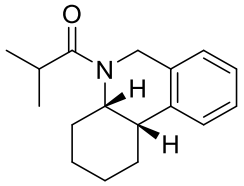
7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.6, 170.1 (C=O), 132.7, 132.6, 131.1, 131.0 (ArC quaternary), 130.6, 130.3, 128.5, 128.0, 125.8, 125.2 (ArCH), 123.0, 122.2 (ArCBr), 54.1, 49.2 (NCH), 46.1, 43.6 (NCH_2), 37.6, 36.7 ($NCH\underline{C}H$), 28.2, 27.7, 27.0, 26.8, 25.7, 25.4, 23.9, 23.4 (cy), 19.9, 19.6 ($CO\underline{C}H_2CH_3$), 17.8, 17.4 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 344.06 ($[M]^+Na$); [Found: ($[M]^+Na$) 344.0627, $C_{16}H_{20}NONaBr$ requires 344.0626].

1-(4'-Bromospiro[cyclohexane-1,1'-isoindolin]-2'-yl)propan-1-one (3.19k): Yield 13mg, 20%. ν_{max} (film)/cm^{-1} 2925 (C-H), 1620 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.62 (1H, d, *J* = 8.0 Hz, ArH), 7.44 (1H, d, *J* = 7.5 Hz, ArH), 7.17 (1H, dd, app t, *J* = 8.0 Hz, ArH), 4.70 (2H, s, NCH_2), 3.12 (2H, m, cy), 2.41 (2H, q, *J* = 7.5 Hz, $COC\underline{H}_2CH_3$), 1.85 – 1.68 (4H, m, cy), 1.65 – 1.46 (4H, m, cy), 1.18 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 169.3 (C=O), 132.6, 130.5 (ArC quaternary), 128.4, 127.6, 124.8 (ArCH), 119.2 (ArCBr), 70.5 (NC quaternary), 50.4 (NCH_2), 29.8, 28.7, 27.7, 23.5 (cy), 19.8 ($CO\underline{C}H_2CH_3$), 12.6 ($COCH_2\underline{C}H_3$)*m/z* (ESI) 344.06 ($[M]^+Na$); [Found: ($[M]^+Na$) 344.0626, $C_{16}H_{20}NONaBr$ requires 344.0626].

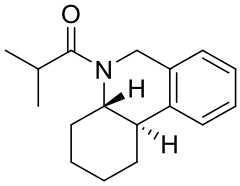
Cyclisation of *N*-(2-bromobenzyl)-*N*-cyclohexenylisobutyramide (2.8m)

To a solution of *N*-(2-bromobenzyl)-*N*-cyclohexenylisobutyramide (**2.8m**) (100mg, $2.9x10^{-1}$mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.13mL, $4.4x10^{-1}$mmol) and ABCN (14mg, $5.7x10^{-2}$mmol) in toluene (4.5mL). After standard work-up, the crude product was obtained as a yellow oil. Purification of the mixture was attempted by column chromatography (14:1 to 1:1 pet ether/EtOAc) which led to the identification of compounds **3.18m$_{cis}$**, **3.18m$_{trans}$**, **3.19m** and reduced product **2.8l**, present in the crude product in the approximate ratio 71:trace:20:10. The products were

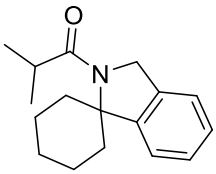
inseparable by column chromatography and no carbon NMR spectrum could be obtained from the mixture. Combined yield 23mg, 31%.



3.18m$_{cis}$



3.18m$_{trans}$



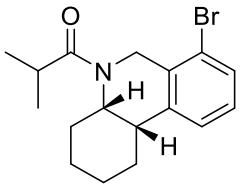
3.19m

***Cis*-1-((4aS,10bS)-2,3,4,4a,6,10b-Hexahydrophenanthridin-5(1H)-yl)-2-methylpropan-1-one (3.18m$_{cis}$) (1:0.80 mixture of rotamers)**: ν_{max} (film)/cm^{-1} 2922 (C-H), 1654 (C=O); δ_H (300 MHz, $CDCl_3$) 7.49 – 7.07 (4H, m, ArH), 5.10 (1H maj, d, *J* = 18.0 Hz, NC$\underline{H}_aH_b$), 4.93 – 4.81 (1H min, m, NCH), 4.77 (1H min, d, *J* = 16.5 Hz, NC$\underline{H}_aH_b$), 4.59 (1H min, d, *J* = 16.0, NC$H_a\underline{H}_b$), 4.31 (1H maj, d, *J* = 18.0 Hz, NC$H_a\underline{H}_b$), 4.15 – 3.97 (1H maj, m, NCH), 3.24 (1H maj, br s, NCHC$\underline{H}$), 3.13 (1H min, br s, NCHC$\underline{H}$), 2.90 (1H maj +1H min, m, COC$\underline{H}$), 2.04 – 1.01 (14H maj + 14H min, m, alkyl protons); *m/z* (ESI) 280.17 ([M]$^+$Na); [Found: ([M]$^+$Na) 280.1677, $C_{17}H_{23}NONa$ requires 280.1677].

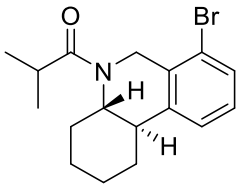
2-Methyl-1-(spiro[cyclohexane-1,1'-isoindolin]-2'-yl)propan-1-one (3.19m): ν_{max} (film)/cm^{-1} 2922 (C-H), 1654 (C=O); δ_H (300 MHz, $CDCl_3$) 7.45 – 7.04 (4H, m, ArH), 4.84 (2H, s, NCH_2), 3.10 (2H, td, *J* = 13.0, 6.0 Hz, meta-cy), 2.75 (1H, dq, *J* = 29.0, 6.5 Hz, COCH), 1.96 – 1.32 (8H, m, cy), 1.14 (3H, d, *J* = 6.5 Hz, COCH(C$\underline{H}_3)_a(CH_3)_b$), 1.10 (3H, d, *J* = 6.5 Hz, COCH($CH_3)_a$(C$\underline{H}_3)_b$); *m/z* (ESI) 280.17 ([M]$^+$Na); [Found: ([M]$^+$Na) 280.1678, $C_{17}H_{23}NONa$ requires 280.1677].

Cyclisation of *N*-(cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide (2.8n)

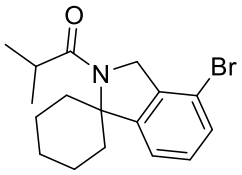
To a solution of *N*-(cyclohex-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide **(2.8n)** (80mg, $1.9x10^{-1}$mmol) in toluene (5mL) at reflux was added a mixture of Bu_3SnH (0.078mL, $2.9x10^{-1}$mmol) and ABCN (10mg, $3.8x10^{-2}$mmol) in toluene (4.5mL). After standard work-up, the crude product was obtained as a yellow oil containing the products **3.18n$_{cis}$**, **3.18n$_{trans}$**, **3.19n** and the reduced product **2.8l** in the ratio 32:14:32:22. Combined yield 35mg, 53%.



3.18n$_{cis}$



3.18n$_{trans}$



3.19n

***Cis*-1-(7-Bromo-2,3,4,4a,6,10b-hexahydrophenanthridin-5(1H)-yl)-2-methylpropan-1-one (3.18n$_{cis}$) (1:0.88 mixture of rotamers):** Yield 11mg, 17%. ν_{max} (film)/cm^{-1} 2941 (C-H), 1628 (C=O); δ_H (400 MHz, $CDCl_3$) 7.45 (1H maj + 1H min, d, *J* = 8.0 Hz, ArH), 7.37 (1H min, d, *J* = 8.0 Hz, ArH), 7.32 (1H maj, d, *J* = 8.0 Hz, ArH), 7.23 – 7.08 (1H maj + 1H min, m, ArH), 5.26 (1H min, d, *J* = 19.0 Hz, NC$\underline{H}_a$H$_b$), 4.91 (1H min, dt, *J* = 12.0, 4.5 Hz, NCH), 4.77 (1H maj, d, *J* = 17.5 Hz, NC$\underline{H}_a$H$_b$), 4.44 (1H maj, d, *J* = 17.5 Hz, NCH$_a\underline{H}_b$), 4.11 (1H min, d, *J* = 19.0 Hz, NCH$_a\underline{H}_b$), 4.11 – 4.03 (1H maj, m, NCH), 3.24 (1H min, br s, NCHC$\underline{H}$), 3.13 (1H maj, br s, NCHC$\underline{H}$), 2.92 (1H maj + 1H min, sept, *J* = 7.0 Hz, COC$\underline{H}$), 2.55 (1H min, d, *J* = 14.5 Hz, cy), 2.47 (1H maj, d, *J* = 14.5 Hz, cy), 1.59 – 1.51 (3H maj + 3H min, m, cy), 1.45 (4H maj + 4H min, m, cy), 1.18 (3H min, d, *J* = 7.0 Hz, COCH(C$\underline{H}_3$)(CH$_3$)), 1.14 (3H maj, d, *J* = 7.0 Hz, COCH(CH$_3$)(C$\underline{H}_3$)); δ_C (101 MHz, $CDCl_3$) 168.7, 168.0 (C=O), 137.7, 135.3, 134.9, 134.3 (ArC quaternary), 130.3, 130.2, 129.7, 128.4, 122.2, 121.8

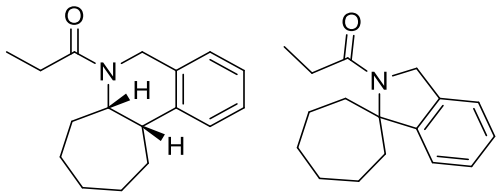
(ArCH), 118.1, 117.6 (ArCBr), 55.7, 54.5 (NCH), 53.2, 52.9 (NCH_2), 52.8, 52.0 (NCH<u>C</u>H), 32.5, 30.9, 30.6, 29.9, 25.04, 24.3, 23.9, 22.5 (cy), 19.7, 19.4 (CO<u>C</u>H(CH_3)$_2$), 18.5, 18.3 COCH(<u>C</u>H_3)$_2$; *m/z* (ESI) 358.08 ([M]$^+$Na); [Found: ([M]$^+$Na) 358.0776, $C_{17}H_{22}$BrNONa requires 358.0777].

***Trans*-1-(7-Bromo-2,3,4,4a,6,10b-hexahydrophenanthridin-5(1H)-yl)-2-methylpropan-1-one (3.18n$_{trans}$):** Yield 6mg, 9%. ν_{max} (film)/cm^{-1} 2936 (C-H), 1620 (C=O); δ_H (400 MHz, $CDCl_3$) 7.44 – 7.40 (1H, m, ArH), 7.19 – 7.13 (2H, m, ArH), 5.21 (1H, d, *J* = 15.0 Hz, NC<u>H$_a$</u>H$_b$), 4.12 (1H, d, *J* = 13.0 Hz, NCH$_a$<u>H$_b$</u>), 3.48 – 3.29 (1H, m, NCH), 2.99 (1H, m, COCH), 2.58 - 2.36 (2H, m, NCHC<u>H</u>), 2.07 – 1.78 (8H, m, cy), 1.20 (3H, d, *J* = 7.0 Hz, COCH(C<u>H$_3$</u>)(CH$_3$)), 1.08 (3H, d, *J* = 6.0 Hz, COCH(CH$_3$)(C<u>H$_3$</u>)); *m/z* (ESI) 336.10 ([M]$^+$H); [Found: ([M]$^+$Na) 336.0944, $C_{17}H_{23}$BrNO requires 336.0958]. Insufficient material for carbon NMR.

1-(4'-Bromospiro[cyclohexane-1,1'-isoindolin]-2'-yl)-2-methylpropan-1-one (3.19n): Yield 10mg, 16%. ν_{max} (film)/cm^{-1} 2929 (C-H), 1620 (C=O); δ_H (400 MHz, CDCl3) 7.62 (1H, d, *J* = 8.0 Hz, ArH), 7.44 (1H, d, *J* = 8.0 Hz, ArH), 7.17 (1H, dd, app t, *J* = 8.0 Hz, ArH), 4.80 (2H, s, NCH_2), 3.18 – 3.04 (2H, m, cy), 2.77 (1H, dt, *J* = 13.5, 6.5 Hz, COC<u>H</u>), 1.90 – 1.84 (2H, m, cy), 1.83 – 1.71 (2H, m, cy), 1.64 – 1.51 (4H, m, cy), 1.18 (6H, d, *J* = 6.5 Hz, COCH(C<u>H$_3$</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 169.1 (C=O), 136.5, 134.3 (ArC quaternary), 130.3, 129.4, 122.6 (ArCH), 117.2 (ArCBr), 62.3 (NC quaternary), 54.0 (NCH_2), 32.2, 31.1, 24.3, 23.2, 22.5 (cy), 19.3, 19.3 (COCH(<u>C</u>H_3)$_2$), 18.5 (CO<u>C</u>H(CH_3)$_2$; *m/z* (ESI) 358.08 ([M]$^+$Na); [Found: ([M]$^+$Na) 358.0783, $C_{17}H_{22}$BrNONa requires 358.0777].

Cyclisation of *N*-*(*2-bromobenzyl)-*N*-(cyclohex-1-en-1-yl)propionamide (2.8q)

To a solution of *N*-*(*2-bromobenzyl)-*N*-(cyclohex-1-en-1-yl)propionamide **2.8q** (204mg, $6.1x10^{-1}$mmol) in toluene (30mL) at reflux was added a mixture of Bu_3SnH (0.247mL, $9.2x10^{-1}$ mmol) and ABCN (30mg, $1.2x10^{-1}$ mmol) in toluene (5.5mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (8:1 to 1:1 pet ether/EtOAc) which led to the identification of products **3.18q$_{cis}$** and **3.19q** present in the crude product in the approximate ratio 40:21, with 10% reduced product and 29% of starting material. Combined yield 84mg, 57%.



3.18q$_{cis}$ **3.19q**

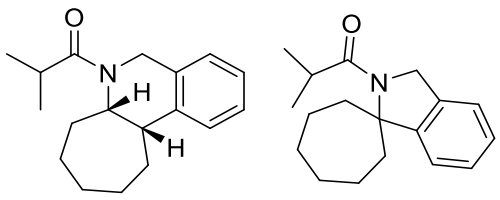
***Cis*-1-(5,6a,7,8,9,10,11,11a-Octahydro-6H-cyclohepta[c]isoquinolin-6-yl)propan-1-one** (**3.18q$_{cis}$**) **(1:0.91 mixture of rotamers)**: Yield 47mg, 32% ν_{max} (film)/cm^{-1} 2918 (C-H), 1664 (C=O); δ_H (300 MHz, $CDCl_3$) 7.38 – 7.02 (4H maj + 4H min, m, ArH), 5.24 (1H min, d, *J* = 17.5 Hz, NC$\underline{H}_aH_b$), 5.00 (1H min, br s, NCH), 4.61 (1H maj, d, *J* = 16.0 Hz, NC$\underline{H}_aH_b$), 4.47 (1H maj, d, *J* = 16.5 Hz, NC$H_a\underline{H}_b$), 4.23 – 4.06 (1H maj + 1H min, m, NCH + NC$H_a\underline{H}_b$), 3.28 (1H maj + 1H min, dt, *J* = 8.0, 7.0 Hz, NCHC$\underline{H}$), 2.39 (1H maj + 1H min, m, COCH), 2.29 (2H maj + 2H min, m, cy), 1.76 (4H maj + 4H min, m, cy), 1.60 (4H maj + 4H min, m, cy), 1.21 (3H maj + 3H min, d, *J* = 5.5 Hz, COCH($C\underline{H}_3$)(CH_3)), 1.17 (3H maj + 3H min, d, *J* = 5.5 Hz, COCH(CH_3)($C\underline{H}_3$)); δ_C (75 MHz, $CDCl_3$) 169.2, 167.6 (C=O), 136.8, 135.0, 134.4, 134.2 (ArC quaternary), 127.4, 127.2, 126.8, 126.6, 126.3, 126.0, 125.7, 125.5 (ArCH), 57.2, 56.0 (NCH), 44.2, 41.1 (NCH_2), 39.9, 38.9 (NCH$\underline{C}$H), 30.8, 30.4, 29.7,

29.2, 27.1, 26.8, 25.2, 24.7, 23.3, 22.9 (cy), 18.5, 18.4 ($CO\underline{C}H_2CH_3$), 17.1, 16.8 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 280.18 ($[M]^+Na$); [Found: ($[M]^+Na$) 280.1678, $C_{17}H_{23}NONa$ requires 280.1677].

1-(Spiro[cycloheptane-1,1'-isoindolin]-2'-yl)propan-1-one (3.19q): Yield 25mg, 17%. ν_{max} (film)/cm^{-1} 2926 (C-H), 1667 (C=O); δ_H (300 MHz, $CDCl_3$) 7.43 – 7.24 (4H, m, ArH), 4.71 (2H, s, NCH_2), 3.24 (2H, m, cy), 1.82 – 1.47 (4H, m, cy), 1.44 – 1.05 (6H, m, cy), 0.91 (2H, q, *J* = 7.5 Hz, $COC\underline{H_2}CH_3$), 0.87 (3H, t, *J* = 7.5 Hz, $COCH_2C\underline{H_3}$); δ_C (75 MHz, $CDCl_3$) 170.6 (C=O), 132.4, 130.5 (ArC quaternary), 128.8, 127.1, 123.2, 122.5 (ArCH), 65.6 (NC quaternary), 51.3 (NCH_2), 29.4, 27.4, 26.8, 26.4, 24.8, 23.7 (cy), 17.3 ($CO\underline{C}H_2CH_3$), 13.7 ($COCH_2\underline{C}H_3$); *m/z* (ESI) 280.18 ($[M]^+Na$); [Found: ($[M]^+Na$) 280.1684, $C_{17}H_{23}NONa$ requires 280.1677].

Cyclisation of *N*-(2-bromobenzyl)-*N*-cycloheptenylisobutyramide (2.8r)

To a solution of *N*-(2-bromobenzyl)-*N*-cycloheptenylisobutyramide (**2.8r**) (240mg, $7.1x10^{-1}$mmol) in toluene (30mL) at reflux was added a mixture of Bu_3SnH (0.28mL, 1.1 mmol) and ABCN (35mg, $1.42x10^{-1}$mmol) in toluene (6mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (14:1 to 1:1 pet ether/EtOAc) which led to the isolation of compounds **3.18r$_{cis}$** and **3.19r**, present in the crude product in the approximate ratio 80:20. Combined yield 153mg, 80%.



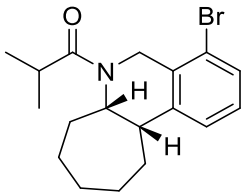
3.18r$_{cis}$ **3.19r**

***Cis*-2-Methyl-1-((6aS,11aS)-5,6a,7,8,9,10,11,11a-octahydro-6H-cyclohepta[c]isoquinolin-6-yl)propan-1-one (3.18r$_{cis}$) (1:0.87 mixture of rotamers)**: Yield 122mg, 64%. ν_{max} (film)/cm^{-1} 2925 (C-H), 1677 (C=O); δ_H (300 MHz, $CDCl_3$) 7.45 – 6.92 (4H maj + 4H min, m, ArH), 5.21 (1H min, d, *J* = 17.5 Hz, NC$\underline{H}_a$H$_b$), 4.97 (1H min, m, NCH), 4.62 (1H maj, d, *J* = 16.5 Hz, NC$\underline{H}_a$H$_b$), 4.43 (1H maj, d, *J* = 16.5 Hz, NCH$_a\underline{H}_b$), 4.20 – 4.11 (1H maj, m, NCH), 4.06 (1H min, d, *J* = 17.5 Hz, NCH$_a\underline{H}_b$), 3.32 – 3.07 (1H maj + 1H min, m, NCHC$\underline{H}$), 2.81 (1H maj + 1H min, ddt, *J* = 20.0, 13.5, 6.5 Hz, COCH), 2.33 – 2.18 (1H maj + 1H min, m, cy), 1.89 – 1.20 (9H maj + 9H min, m, cy), 1.12 (3H maj, d, *J* = 6.5 Hz, COCH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 1.00 (3H min, d, *J* = 6.5 Hz, COCH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); δ (126 MHz, $CDCl_3$) 175.3, 175.2 (C=O), 138.9, 137.0, 133.2, 132.5 (ArC quaternary), 127.6, 127.3, 126.9, 126.8, 126.4, 126.1, 125.8, 125.6 (ArCH), 57.0, 52.3 (NCH), 44.2, 41.1 (NCH_2), 40.1, 38.9 (NCH$\underline{C}$H), 31.0, 30.7, 30.6, 29.9, 29.6, 29.4, 27.0, 26.9, 23.5, 23.0 (cy), 19.9, 19.7 (CO$\underline{C}$H), 19.5, 19.3 (COCH($\underline{C}H_3$)$_2$); *m/z* (ESI) 294.18 ([M]$^+$Na); [Found: ([M]$^+$Na) 294.1830, $C_{18}H_{25}NONa$ requires 294.1834].

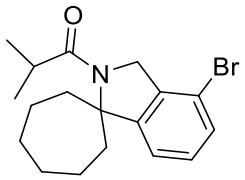
2-Methyl-1-(spiro[cycloheptane-1,1'-isoindolin]-2'-yl)propan-1-one (3.19r): Yield 31mg, 16%. ν_{max} (film)/cm^{-1} 2928 (C-H), 1666 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.47 – 7.10 (4H, m, ArH), 4.78 (2H, s, NCH_2), 2.76 – 2.56 (1H, m, COCH), 2.17 – 2.04 (2H, m, meta-cy), 1.91 – 1.44 (8H, m, cy), 1.15 (6H, d, *J* = 6.5 Hz, COCH(CH$_3$)$_2$); δ_C (126 MHz, $CDCl_3$) 167.8 (C=O), 134.5, 133.0 (ArC quaternary), 128.4, 127.3, 124.3, 122.2 (ArCH), 72.5 (NC quaternary), 52.2 (NCH_2), 31.7, 31.1, 25.1, 25.1, 24.9, 23.2 (cy), 19.2 (CO$\underline{C}$H(CH$_3$)$_2$), 19.2, 19.1 (COCH($\underline{C}H_3$)$_2$); *m/z* (ESI) 294.18 ([M]$^+$Na); [Found: ([M]$^+$Na) 294.1830, $C_{18}H_{25}NONa$ requires 294.1834].

Cyclisation of *N*-(cyclohept-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide (2.8s)

To a solution of *N*-(cyclohept-1-en-1-yl)-*N*-(2,6-dibromobenzyl)isobutyramide **(2.8s)** (124mg, $2.9x10^{-1}$mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.12mL, $4.4x10^{-1}$mmol) and ABCN (14mg, $5.7x10^{-2}$mmol) in toluene (4.5mL). After standard work-up, the crude product was obtained as a yellow oil. Purification of the mixture was attempted by column chromatography (14:1 to 1:1 pet ether/EtOAc), however the products **3.18s$_{cis}$** and **3.19s** obtained were impure. Key peaks are listed.



3.18s$_{cis}$



3.19s

Cis- 1-((6aS,11aS)-4-Bromo-5,6a,7,8,9,10,11,11a-octahydro-6H-cyclohepta[c]isoquinolin-6-yl)-2-methylpropan-1-one (3.18s$_{cis}$) (1:0.83 mixture of rotamers): ν_{max} (film)/cm^{-1} 2923 (C-H), 1625 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.42 (1H maj+ 1H min, d, *J* = 8.0 Hz, ArH), 7.26 (1H maj + 1H min, t, *J* = 12.0 Hz, ArH), 7.11 (1H maj + 1H min, m, ArH), 5.44 (1H min, d, *J* = 18.5 Hz, NC$\underline{H}_aH_b$), 5.04 (1H maj, m, NCH), 4.83 (1H maj, d, *J* = 17.5 Hz, NC$\underline{H}_aH_b$), 4.31 (1H maj, d, *J* = 17.5 Hz, $NCH_a\underline{H}_b$), 4.22 (1H min, m, NCH), 3.93 (1H min, d, *J* = 18.5 Hz, $NCH_a\underline{H}_b$), 3.38 – 3.19 (1H maj + 1H min, m, NCHC$\underline{H}$), 2.87 (1H maj + 1H min, dt, *J* = 13.5, 7.0 Hz, COCH), 2.35 (1H maj + 1H min, m, cy), 1.94 – 0.77 (16H, m, alkyl + organotin residues); *m/z* (ESI) 372.09 ($[M]^+Na$); [Found: ($[M]^+Na$) 372.0932, $C_{18}H_{24}NBrONa$ requires 372.0939]. Impure and insufficient material to obtain carbon NMR.

1-(4'-Bromospiro[cycloheptane-1,1'-isoindolin]-2'-yl)-2-methylpropan-1-one (3.19s): ν_{max} (film)/cm^{-1} 2920 (C-H), 1621 (C=O); δ_H ($CDCl_3$, 400 MHz) 7.51 – 7.00 (3H, m, ArH), 4.67 (2H, s, NCH_2), 2.72 – 2.48 (2H, m, COCH + 2H, m, meta-cy), 2.13 – 0.60 (16H, m, alkyl + organo tin residues); *m/z* (ESI) 372.09 ([M]$^+$Na); [Found: ([M]$^+$Na) 372.0935, $C_{18}H_{24}NBrONa$ requires 372.0939]. Impure and insufficient material to obtain carbon NMR.

Cyclisation of *N*-((3-bromonaphthalen-2-yl)methyl)-*N*-(cyclohex-1-en-1-yl)acetamide (2.9)

To a solution of *N*-((3-bromonaphthalen-2-yl)methyl)-*N*-(cyclohex-1-en-1-yl)acetamide (**2.9**) (100mg, 2.8x10^{-1}mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.12mL, 4.26x10^{-1}mmol) and ABCN (14mg, 5.6x10^{-2}mmol) in toluene (4mL). After standard work-up, the crude product was obtained as a yellow oil with tin residue (0.15g). Purification of the mixture was attempted by column chromatography (14:1 to 1:1 pet ether/EtOAc), resulting in the isolation of one unidentified product, which was not seen upon subsequent attempts. Subsequent attempts showed the crude reaction mixture as a 95:5 mixture of starting material to the presumed reduced product, which however could not be separated for full analysis.

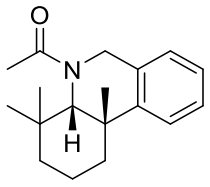
Cyclisation of *N*-(2-bromobenzyl)-*N*-(3-methylbut-2-en-2-yl)acetamide (2.16b)

To a solution of *N*-(2-bromobenzyl)-*N*-(3-methylbut-2-en-2-yl)acetamide **(2.16b)** (100mg, 3.4x10^{-1}mmol) in toluene (12mL) at reflux was added a mixture of Bu_3SnH (0.14mL, 5.1x10^{-1}mmol) and ABCN (17mg, 6.8x10^{-2}mmol) in toluene (5mL). After standard work-up, the crude product was obtained as a yellow oil with tin residue

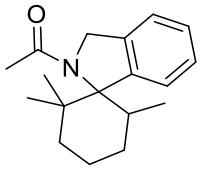
(0.12g). No cyclisation products were observed in the crude mixture, only 13% of the reduced starting material, identified by comparison to data obtained in a paper by Clark.[69]

Cyclisation of *N*-(2-bromobenzyl)-*N*-(2,6,6-trimethylcyclohex-1-en-1-yl)acetamide (2.21b)

To a solution of *N*-(2-bromobenzyl)-*N*-(2,6,6-trimethylcyclohex-1-en-1-yl)acetamide (**2.21b**) (100mg, $2.9x10^{-1}$mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.115mL, $4.28x10^{-1}$mmol) and ABCN (14mg, $5.7x10^{-2}$mmol) in toluene (4.25mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (14:1 to 1:1 pet ether/EtOAc) which led to the isolation of compounds **3.37$_{cis}$**, **3.38** and the reduced product **3.39**, present in the crude mixture in the approximate ratio 31/37/32. Combined yield 70mg, 89%.



3.37$_{cis}$



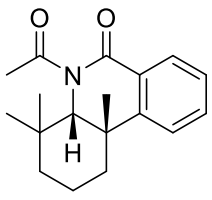
3.38

***Cis*-1-((4aS,10bS)-4,4,10b-Trimethyl-2,3,4,4a,6,10b-hexahydrophenanthridin-5(1H)-yl)ethan-1-one (3.37$_{cis}$) (1:1 mixture of rotamers):** Yield 20mg, 25%. ν_{max} (film)/cm^{-1} 2920 (C-H), 1684 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.30 (1H maj+min, d, *J* = 8.0 Hz, ArH), 7.21 (1H maj+min, dd, app t, *J* = 8.5 Hz, ArH), 7.14 (1H maj+min, m, ArH), 7.07 (1H maj+min, dd, app t, *J* = 8.0 Hz, ArH), 5.17 (1H min, d, *J* = 18.5 Hz, NC$\underline{H_a}H_b$), 4.78 (1H maj, d, *J* = 16.5 Hz, NC$\underline{H_a}H_b$), 4.70 (1H maj, d, *J* = 16.5 Hz, NC$H_a\underline{H_b}$), 4.53 (1H min, s, NCH), 4.48 (1H min, d, *J* = 18.5 Hz, NC$H_a\underline{H_b}$), 3.52 (1H

maj, s, NCH), 2.57 (1H maj+min, m, cy), 2.28 (3H maj + 3H min, s, $COCH_3$), 1.62 – 1.19 (5H maj + 5H min, m, cy), 1.10 (3H min, s, $C(C\underline{H}_3)(CH_3)$), 1.05 (3H maj, s, $C(C\underline{H}_3)(CH_3)$), 0.98 (3H min, s, $C(CH_3)(C\underline{H}_3)$), 0.90 (3H maj, s, $C(CH_3)(C\underline{H}_3)$), 0.35 (3H maj, s, $CC\underline{H}_3$), 0.25 (3H min, s, $CC\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 171.9 (C=O), 140.9, 139.4, 133.7, 132.6 (ArC quaternary), 127.3, 126.8, 126.5, 126.4, 126.2, 126.0, 123.6, 123.3 (ArCH), 68.6, 62.1 ($N\underline{C}H$), 48.7, 46.2 ($N\underline{C}H_2$), 42.5, 41.7 (cy), 39.4, 38.5, 38.3, 37.8 (quaternary C), 36.9, 36.3 (cy), 32.7, 32.1, 32.0, 31.9 ($C(\underline{C}H_3)_2$), 23.0, 22.7, 22.7, 22.2 ($CO\underline{C}H_3$ and $C\underline{C}H_3$), 18.7, 18.6 (cy); *m/z* (ESI) 294.18 ($[M]^+Na$); [Found: ($[M]^+Na$) 294.1827, $C_{18}H_{25}NNaO$ requires 294.1828].

1-(2,2,6-Trimethylspiro[cyclohexane-1,1'-isoindolin]-2'-yl)ethan-1-one (3.38) : Yield 26mg, 33%. ν_{max} (film)/cm^{-1} 2918 (C-H), 1678 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.34 (1H, d, *J* = 7.0 Hz, ArH), 7.30 – 7.20 (2H, m, ArH), 7.21 – 7.10 (1H, m, ArH), 4.67 (2H, s, NCH_2), 2.70 – 2.52 (1H, m, NCH), 2.50 – 2.31 (2H, m, cy), 2.22 (3H, s, $COCH_3$), 1.77 – 1.49 (4H, m, cy), 0.94 (3H, s, Me), 0.92 (3H, s, Me), 0.69 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 172.2 (C=O), 139.5, 136.4 (ArC quaternary), 127.4, 126.4, 125.7, 121.2 (ArCH), 57.3 ($N\underline{C}H_2$), 37.6 (NC quaternary), 36.7 ($NC\underline{C}H$), 36.0 ($NC\underline{C}$ quaternary), 30.5 (cy), 27.7 (Me), 27.4 (Me), 26.1 (Me), 21.1 (cy), 17.4 (cy), 17.3 (Me); *m/z* (ESI) 294.18 ($[M]^+Na$); [Found: ($[M]^+Na$) 294.1828, $C_{18}H_{25}NNaO$ requires 294.1828].

5-Acetyl-4,4,10b-trimethyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2H)-one ($\mathbf{3.40_{cis}}$): $\mathbf{3.37_{cis}}$ decomposes in air to give **$\mathbf{3.40_{cis}}$** over a period of weeks.

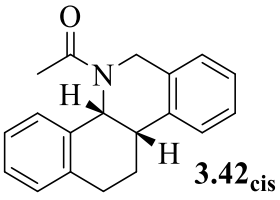


$\mathbf{3.40_{cis}}$

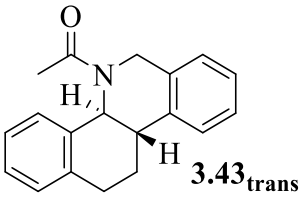
Yield 20 mg, 95%. ν_{max} (film)/cm^{-1} 2924 (C-H), 1690 (C=O); δ_H ($CDCl_3$, 600 MHz) 8.15 (1H, d, *J* = 8.0 Hz, ArH), 7.55 (1H, dd, app t, *J* = 7.5 Hz, ArH), 7.38 (1H, dd, app t, *J* = 7.5 Hz, ArH), 7.31 (1H, d, *J* = 8.0 Hz, ArH), 4.66 (1H, s, NCH), 2.71 (3H, s, COC<u>H</u>$_3$), 2.52 (1H, dd, *J* = 14.0, 3.0 Hz, cy), 1.58 – 1.52 (2H, m, cy), 1.50 – 1.43 (2H, m, cy), 1.42 – 1.36 (2H, m, cy), 1.18 (3H, s, Me), 0.84 (3H, s, Me), 0.23 (3H, s, Me); δ_C (151 MHz, $CDCl_3$) 174.2, 166.6 (C=O), 145.9 (ArC quaternary), 134.0 (ArCH), 130.0 (ArC quaternary), 129.7, 127.0, 123.2 (ArCH), 65.6 (N<u>C</u>H), 41.0 (cy), 38.2, 37.5 (quaternary C), 35.7 (cy), 33.1, 31.4, 27.7, 23.3 (Me), 18.6 (cy); *m/z* (ESI) 302.16 ($[M]^+$Na); [Found: ($[M]^+$Na) 308.1617, $C_{18}H_{23}NNaO_2$ requires 308.1621].

Cyclisation of *N*-(2-bromobenzyl)-*N*-(3,4-dihydronaphthalen-1-yl)acetamide (2.27)

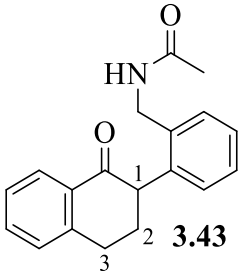
To a solution of *N*-(2-bromobenzyl)-*N*-(3,4-dihydronaphthalen-1-yl)acetamide **(2.27)** (100mg, 2.8x10^{-1}mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.12mL, 4.26x10^{-1}mmol) and ABCN (14mg, 5.6x10^{-2}mmol) in toluene (4mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (pet ether, then 10:1 to 1:1 pet ether/EtOAc) which led to the isolation of compounds **3.42$_{cis}$**, **3.42$_{trans}$** and **3.43**, present in the crude product in the approximate ratio 22:58:20. Combined yield 54mg, 69%.



3.42$_{cis}$



3.43$_{trans}$



3.43

Cis-1-((4bR,10bS)-6,10b,11,12-Tetrahydrobenzo[c]phenanthridin-5(4bH)-yl)ethan-1-one ($\mathbf{3.42_{cis}}$) (1:0.89): Yield 8mg, 10%. ν_{max} (film)/cm^{-1} 2935 (C-H), 1682 (C=O); δ_H ($CDCl_3$, 500 MHz) 7.53 – 6.88 (8H maj + 8H min, m, ArH), 6.28 (1H maj, d, *J* = 6.0 Hz, NCH), 5.37 (1H min, d, *J* = 17.5 Hz, NC$\underline{H}_aH_b$), 5.30 (1H min, d, *J* = 6.0 Hz, NCH), 4.57 (1H maj, d, *J* = 16.5 Hz, NC$\underline{H}_aH_b$), 4.27 (1H maj, d, *J* = 16.5 Hz, NC$H_a\underline{H}_b$), 3.84 (1H min d, *J* = 17.4 Hz, NC$H_a\underline{H}_b$), 3.58 (1H min, br s, NCHC$\underline{H}$), 3.52 (1H maj, br s, NCHC$\underline{H}$), 2.50-2.78 (4H maj + 4H min, m, cy), 2.34 (3H min, s, $COCH_3$), 2.31 (3H maj, s, $COCH_3$); δ_C (126 MHz, $CDCl_3$) 170.1 (C=O), 137.8, 137.3, 135.2, 133.8, 133.5, 133.4, 133.4, 132.8 (ArC quaternary), 129.3, 129.0, 127.5, 127.3, 127.2, 126.8, 126.8, 126.7, 126.6, 126.6, 126.5, 126.4, 126.3, 126.1, 126.1, 125.8 (ArCH), 55.9, 49.9 (NCH), 44.7, 40.5 (NCH_2), 35.7, 34.4 (NCH$\underline{C}$H), 25.3, 25.2, 24.3, 24.2 (cy), 22.1, 21.5 (CO$\underline{C}H_3$); *m/z* (ESI) 300.14 ($[M]^+$Na); [Found: ($[M]^+$H) 300.1359, $C_{19}H_{19}NNaO$ requires 300.1359].

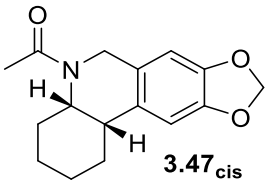
Trans-1-((4bR,10bS)-6,10b,11,12-Tetrahydrobenzo[c]phenanthridin-5(4bH)-yl)ethan-1-one ($\mathbf{3.42_{trans}}$) (1:0.89 mixture of rotamers): Yield 40mg, 51%. ν_{max} (film)/cm^{-1} 2933 (C-H), 1680 (C=O); δ_H ($CDCl_3$, 500 MHz) 7.39 – 7.32 (2H maj + 2H min, m, ArH), 7.30 – 7.24 (4H maj + 4H min, m, ArH), 7.21 – 7.10 (2H maj + 2H min, m, ArH), 5.71 (1H min, d, *J* = 14.5 Hz, NC$\underline{H}_aH_b$), 4.80 (1H min, d, *J* = 10.5 Hz, NCH), 4.63 (1H maj, d, *J* = 15.0 Hz, NC$\underline{H}_aH_b$), 4.34 (1H maj, d, *J* = 10.5 Hz, NCH), 4.25 (1H maj, d, *J* = 14.0 Hz, NC$H_a\underline{H}_b$), 3.67 (1H min, d, *J* = 14.5 Hz, NC$H_a\underline{H}_b$), 3.22 – 3.09 (2H maj + 2H min, m, cy), 2.80 (1H min, br s, NCHC$\underline{H}$), 2.78 – 2.58 (2H maj + 2H min, m, cy + 1H maj, br s, NCHC$\underline{H}$), 2.31 (3H maj, s, $COCH_3$), 2.00 (3H min, s, $COCH_3$); δ_C (126 MHz, $CDCl_3$) 171.8, 171.7 (C=O), 139.4, 139.0, 138.3, 138.2, 137.1, 136.6, 136.0 (ArC quaternary), 129.2, 128.9, 128.3, 127.8, 127.6, 127.1, 126.8, 126.6, 126.1, 126.0, 125.8, 125.2, 124.6, 124.1, 123.8, 123.3 (ArCH), 59.9, 58.3 (NCH), 47.6,

42.0 (NCH_2), 40.6, 39.6 (NCHCH), 26.7, 22.9 (cy), 22.3 ($COCH_3$); *m/z* (ESI) 300.14 ($[M]^+Na$); [Found: ($[M]^+H$) 300.1358, $C_{19}H_{19}NNaO$ requires 300.1359].

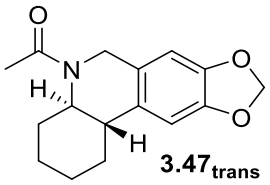
***N*-(2-(1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)benzyl)acetamide (3.43):** Yield 6mg, 8%. δ_H ($CDCl_3$, 500 MHz) 8.03 (1H, dd, *J* = 8.0, 1.0 Hz, ArH), 7.53 (1H, ddd, *J* = 7.5, 1.5 Hz, ArH), 7.36 – 7.26 (5H, m, ArH), 7.18 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 6.11 (1H, s, NH), 4.41 (2H, ddd, *J* = 42.5, 14.0, 5.0 Hz, NCH_2), 4.01 (1H, dd, *J* = 13.0, 4.5 Hz, H^1), 3.22 (1H, ddd, *J* = 17.0, 12.5, 4.5 Hz, H^3), 3.09 (1H, dt, *J* = 16.5, 3.5 Hz, H^3), 2.54 (1H, qd, *J* = 13.0, 4.0 Hz, H^2), 2.41 – 2.32 (1H, m, H^2), 1.90 (3H, s, $COCH_3$); δ_C (126 MHz, $CDCl_3$) 199.4 (C=O), 169.7 (NHC=O), 144.3, 139.1, 136.5 (ArC quaternary), 133.9 (ArCH), 132.5 (ArC quaternary), 130.5, 128.9, 128.6, 128.1, 127.8, 127.6, 126.9 (ArCH), 51.2 (C^1), 42.7 (NCH_2), 30.8 (C^2), 29.8 (C^3), 23.12 ($COCH_3$); *m/z* (ESI) 316.13 ($[M]^+$); [Found: ($[M]^+H$) 316.1307, $C_{19}H_{19}NNaO_2$ requires 316.1308].

Cyclisation of *N*-((6-bromobenzo[1,3]dioxol-5-yl)methyl)-*N*-(cyclohex-1-en-1-yl)acetamide (2.28)

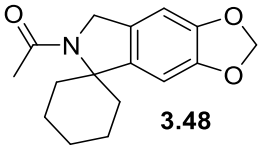
To a solution of *N*-((6-bromobenzo[1,3]dioxol-5-yl)methyl)-*N*-(cyclohex-1-en-1-yl)acetamide (**2.28**) (100mg, $2.84x10^{-1}$mmol) in toluene (10mL) at reflux was added a mixture of Bu_3SnH (0.12mL, $4.26x10^{-1}$mmol) and ABCN (14mg, $5.68x10^{-2}$mmol) in toluene (4mL). After standard work-up, the crude product was obtained as a yellow oil. The mixture was purified by column chromatography (pet ether, then 10:1 to 1:1 pet ether/EtOAc) which led to the isolation of compounds **3.47$_{cis}$**, **3.47$_{trans}$** and **3.48**, present in the crude product in the approximate ratio 45:36:19. Combined yield 40mg, 51%.



3.47$_{cis}$



3.47$_{trans}$



3.48

***Cis*-1-((4aS,11bS)-2,3,4,4a,6,11b-Hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-5(1H)-yl)ethan-1-one (3.47$_{cis}$) (1:0.70 mixture of rotamers)**: Yield 20mg, 25%. ν_{max} (film)/cm^{-1} 2928 (C-H), 1665 (C=O);ν_{max} (film)/cm^{-1}. δ_H ($CDCl_3$, 500 MHz) 6.76 (1Hmaj +1H min, d, *J* = 19.5 Hz, ArH), 6.52 (1H maj +1H min, d, *J* = 21.5 Hz, ArH), 5.94 – 5.79 (2H maj + 2H min, m, O-CH_2-O), 4.86 (1H maj, d, *J* = 17.5 Hz, NC$\underline{H_a}CH_b$), 4.70 (1H min, dt, *J* = 12.0, 4.5 Hz, NCH), 4.46 (1H min, d, *J* = 16.0 Hz, NC$\underline{H_a}CH_b$), 4.37 (1H min, d, *J* = 16.0 Hz, $NCH_aC\underline{H_b}$), 4.16 (1H maj, d, *J* = 17.5 Hz, $NCH_aC\underline{H_b}$), 3.83 (1H maj, dt, *J* = 12.0, 4.5 Hz, NCH), 3.06 (1H maj, br s, NCHC$\underline{H}$), 2.94 (1H min, br s, NCHC$\underline{H}$), 2.41 – 2.33 (1H maj, m, cy), 2.33 – 2.27 (1H min, m, cy), 2.12 (3H maj, s, COC$\underline{H_3}$), 2.08 (3H min, s, COC$\underline{H_3}$), 1.78 – 1.01 (7H maj + 7H min, m, cy); δ_C (126 MHz, $CDCl_3$) 169.3, 169.2 (C=O), 147.2, 146.9, 146.0, 145.9 (ArC quaternary), 129.3, 127.6, 126.3, 125.3 (ArC-O), 106.6, 106.4, 106.0, 106.0 (ArCH), 101.0, 100.9 (OCH_2O), 55.6, 49.8 (NCH), 45.9, 42.6 (NCH_2), 37.1, 36.2 (NCHCH), 28.0, 27.7, 27.0, 25.5, 25.3 (cy), 22.4, 21.7 ($COCH_3$), 19.8, 19.5 (cy); *m/z* (ESI) 296.13 ($[M]^+$Na); [Found: ($[M]^+$Na) 296.1259, $C_{16}H_{19}NO_3Na$ requires 296.1257].

***Trans*-1-((4aR,11bS)-2,3,4,4a,6,11b-Hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-5(1H)-yl)ethan-1-one (3.47$_{trans}$)**: Yield 10mg, 13%. ν_{max} (film)/cm^{-1} 2924(C-H), 1662 (C=O); δ_H ($CDCl_3$, 500 MHz) 6.77 – 6.53 (2H maj + 2H min, m, ArH), 5.86 (2H maj + 2H min, d, *J* = 3.5 Hz, OCH_2O), 5.39 (1H min, d, *J* = 14.0 Hz, NC$\underline{H_a}CH_b$), 4.28 (1H maj, d, *J* = 14.5 Hz, NC$\underline{H_a}CH_b$), 4.12 (1H maj, d, *J* = 14.5 Hz, $NCH_aC\underline{H_b}$), 3.57 (1H min, d, *J* = 14.0 Hz, $NCH_aC\underline{H_b}$), 3.23 (1H maj, t, *J* = 10.0 Hz, NC$\underline{H}$), 2.94 (1H min, m, NC$\underline{H}$), 2.34 (2H maj + 2H min, m, NCHC$\underline{H}$ + *ortho*-cy), 2.07

(3H maj + 3H min, s, COC$\underline{H}_3$), 2.00 – 1.13 (7H maj + 7H min, m, cy); δ_C (126 MHz, $CDCl_3$); *m/z* (ESI) 274.14 ($[M]^+H$); [Found: ($[M]^+H$) 274.1438, $C_{16}H_{20}NO_3$ requires 274.1438]. Insufficient material for carbon NMR.

1-(Spiro[cyclohexane-1,5'-[1,3]dioxolo[4,5-f]isoindol]-6'(7'H)-yl)ethan-1-one (3.48): Yield 10mg, 13%. ν_{max} (film)/cm^{-1} 2930 (C-H), 1670 (C=O); δ_H ($CDCl_3$, 500 MHz) 7.08 (1H, s, ArH), 6.58 (1H, s, ArH), 5.90 (2H, s, OC$\underline{H}_2$O), 4.60 (2H, s, NCH_2), 3.08 – 2.93 (2H, m, cy), 2.05 (3H, s, COC$\underline{H}_3$), 1.76 – 1.41 (8H, m, cy); *m/z* (ESI) 296.13 ($[M]^+Na$); [Found: ($[M]^+Na$) 296.1260, $C_{16}H_{19}NO_3Na$ requires 296.1257]. Insufficient material for carbon NMR.

Cyclisation of *N*-((5-bromobenzo[1,3]dioxol-4-yl)methyl)-*N*-(6,7-dimethoxy-3,4-dihydronaphthalen-1-yl)acetamide (2.29)

To a solution of *N*-((5-bromobenzo[1,3]dioxol-4-yl)methyl)-*N*-(6,7-dimethoxy-3,4-dihydronaphthalen-1-yl)acetamide **(2.29)** (50mg, $1.1x10^{-1}$mmol) in toluene (4mL) at reflux was added a mixture of Bu_3SnH ($4.5x10^{-2}$ mL, $1.6x10^{-1}$mmol) and ABCN (5mg, $2.2x10^{-2}$mmol) in toluene (1.5mL). After standard work-up, the crude product was obtained as a yellow oil containing tin residue (150mg). No cyclisation products were observed in the crude mixture, only 5% of the presumed reduced starting material, which could not be isolated for further analysis.

5.4 Reactions relevant to Chapter Four

5.4.1 Samarium iodide reactions

Attempted cyclisation of 2.8d using SmI_2

To a solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (**2.8d**) (100mg, 3.2 $x10^{-1}$ mmol, 1eq) in THF was added SmI_2 in THF (3.5mL, 0.1M, 3.5 $x10^{-1}$ mmol, 1.1eq), dropwise over several minutes. This solution was stirred at room temperature under nitrogen for 24hrs, after which the SmI_2 was seen to have fully oxidised (colour change from dark blue to yellow). The reaction mixture was washed with NH_4Cl and brine, extracted into EtOAc and dried with $MgSO_4$. The NMR of the crude reaction mixture showed no reaction: only starting material was recovered (96mg, 96%).

Subsequent attempts were made using the same conditions and an additive: 1,3-dimethyl-2-imidazolidinone (0.28mL, 2.56mmol, 8eq), dimethylsulfoxide (0.3mL, 2.56mmol, 8eq) and hexamethylphosphoramide (0.45mL, 2.56mmol, 8eq) were all equally unsuccessful in promoting the reaction under these conditions.

Successful cyclisation of 2.8d using SmI_2

To a solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (**2.8d**) (50mg, 1.5 x 10^{-1} mmol, 1eq) in THF was added HMPA (0.29mL, 1.6 mmol, 10eq) and SmI_2 in THF (8.0mL, 0.1M, 8.0 $x10^{-1}$ mmol, 5eq), dropwise over several minutes. This solution was stirred at room temperature under nitrogen for 24hrs, after which the SmI_2 was seen to have fully oxidised (colour change from dark blue to yellow). The solvent was removed *in vacuo* and the crude reaction mixture analysed by NMR to show the products **3.18a**$_{cis}$, **3.18a**$_{trans}$, **3.19a** and the starting material **2.8d** in the approximate ratio 14:39:14:33. Combined yield 23mg, 67%.

5.4.2 Iron-mediated reactions

To a solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (**2.8d**) (100mg, 3.2 $x10^{-1}$ mmol, 1eq), $Fe(acac)_3$ (1.2mg, 3.2 $x10^{-3}$ mmol, 0.01eq), TMEDA (5µL, 3.2 x 10^{-2} mmol, 0.1eq) in THF (1mL) was added EtMgCl (1.9mL, 0.2M, 3.8 x 10^{-1} mmol, 1.2eq). The solution was heated at reflux until it turned black and then for a further 4 hours. It was then cooled to room temperature, quenched with potassium chloride buffer solution (pH = 2) and extracted with EtOAc. The crude reaction mixture (70mg) was shown by NMR to contain mostly reduced product **2.8a**, with trace amounts of **3.18a$_{cis}$** that was not recoverable by column chromatography.

5.4.3 Indium-mediated reactions

A solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (**2.8d**) (100mg, 3.2 $x10^{-1}$ mmol, 1eq), $InCl_3$ (3mg, 1.5 x 10^{-2} mmol, 0.05eq) and NaOAc (25mg, 3.2 $x10^{-1}$ mmol, 1eq) in DMF was stirred at 140 ^oC for 24 hours. The reaction mixture was then washed with water and extracted with EtOAc, and the solvent was removed under vacuum. The NMR of the crude reaction material showed only starting material.

5.4.4 Cobalt-mediated reactions

A solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (**2.8d**) (150mg, 5.0 $x10^{-1}$ mmol, 1eq), $CoBr_2$ (55mg, 2.5 x 10^{-1} mmol, 0.5eq) and MeMgBr (0.33mL, 3.0M solution in diethyl ether, 1.0 mmol, 2eq) in THF was stirred at room temperature for 24 hours. The mixture was then quenched by careful addition of concentrated HCl, and the solvent was removed under vacuum. The residue was taken up in petroleum ether, washed with sodium bicarbonate solution and dried with $MgSO_4$. The solvent

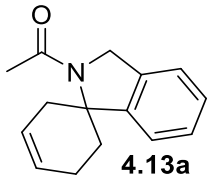
was again removed under vacuum to give the crude product mixture, which was shown by NMR to contain mostly starting material.

5.4.5 Palladium-mediated reactions

5.4.5.1 Preliminary Reactions

Cyclisation of *N*-cyclohex-1-enyl-*N*-2-iodobenzylacetamide (2.8e) using a palladium reagent

A solution of *N*-cyclohex-1-enyl-*N*-2-iodobenzylacetamide **2.8e** (100mg, 2.81×10^{-1}mmol, 1eq), $Pd_2(dba)_3$ (25mg, 2.81×10^{-2}mmol, 0.1eq), $(t\text{-}Bu)_3P$ (13.7μL, 5.64×10^{-2}mmol, 0.2eq) and triethylamine (43μL, 3.1×10^{-1}mmol, 1.1eq) in toluene was stirred at room temperature for 24 hours. The reaction mixture was then poured into saturated LiCl solution and washed with ether. The ether layer was then concentrated under vacuum to give a brown oil. The crude product was purified by column chromatography (9:1 to 2:1 pet ether:EtOAc) to obtain the desired 5-exo cyclised product **4.13a** as a yellow oil (30mg, 47%).



4.13a

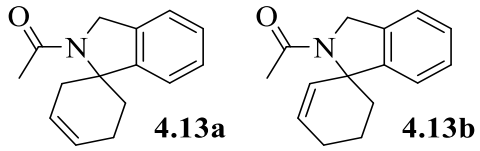
1-(Spiro[cyclohexane-1,1'-isoindolin]-3-en-2'-yl)ethan-1-one (4.13a): ν_{max} (film)/cm^{-1} 2919 (C-H), 1632 (C=O); δ_H ($CDCl_3$, 500 MHz) 7.39 (1H, d, *J* = 7.5 Hz, ArH), 7.35 – 7.18 (3H, m, ArH), 5.92 – 5.76 (2H, m, HC=CH), 4.82 (1H, d, *J* = 14.0 Hz, $NC\underline{H_a}CH_b$), 4.78 (1H, d, *J* = 14.0 Hz, $NCH_aC\underline{H_b}$), 3.94 – 3.76 (1H, m, cy), 3.20 – 3.04 (1H, m, cy), 2.29 (2H, m, cy), 2.17 (3H, s, $COCH_3$), 2.05 (1H, m, cy), 1.50 (1H, m, cy); δ_C (126 MHz, $CDCl_3$) 169.5 (C=O), 146.5 (ArC quaternary), 133.6 (ArC

quaternary), 127.9, 127.6 (ArCH), 126.3, 126.2 (HC=CH), 123.1, 122.0 (ArCH), 68.6 (NC quaternary), 53.7 (NCH_2), 33.3, 28.3 (cy), 25.0 ($COCH_3$), 23.4 (cy); *m/z* (ESI) 250.12 ($[M]^+Na$); [Found: ($[M]^+Na$) 250.1200, $C_{15}H_{17}NONa$ requires 250.1202].

Cyclisation of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide (2.8d) using a palladium reagent

General procedure:

A solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide **2.8d** (1eq), palladium precatalyst (0.1eq), phosphine ligand (0.2eq) and base (1.1eq) in 5mL of solvent was stirred at room temperature or reflux for 24-48 hours. The reaction mixture was then poured into saturated LiCl solution and washed with ether. The ether layer was then concentrated under vacuum to give a brown oil. The crude product was purified by column chromatography (9:1 to 2:1 pet ether:EtOAc) to obtain the desired 5-exo cyclised products **4.13a** and **4.13b** as yellow oils.

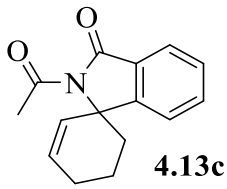


4.13a **4.13b**

1-(Spiro[cyclohex[2]ene-1,1'-isoindoline]-2'-yl)ethanone (4.13b) (1:0.68 mixture of rotamers): ν_{max} (film)/cm^{-1} 2927 (C-H), 1629 (C=O). δ_H ($CDCl_3$, 500 MHz) 7.36-7.16 (4H, m, ArH), 6.06 (1H maj, ddd, *J* = 10.0, 5.0, 2.0 Hz, NCCH=C<u>H</u>), 5.93 (1H min, ddd, *J* = 10.0, 5.0, 2.5 Hz, NCCH=C<u>H</u>), 5.74 – 5.65 (1H maj, m, NCC<u>H</u>=CH), 5.64 – 5.56 (1H min, m, NCC<u>H</u>=CH), 4.96 (1H maj, d, *J* = 16.5 Hz, NC<u>H_a</u>CH_b), 4.86 – 4.77 (2H min, m, NCH_2), 4.74 (1H maj, d, *J* = 16.5 Hz, NCH_aC<u>H_b</u>), 2.76 (1H min, td, *J* = 13.5, 4.0 Hz, NCC<u>H_a</u>CH_b), 2.26 (3H maj, s, $COCH_3$), 2.15 (3H min, s, $COCH_3$), 2.14 – 1.76 (6H maj + 5H min, m, cy); δ_C (126 MHz, $CDCl_3$) 170.1, 168.7 (C=O),

145.7, 145.1 (ArC quaternary), 134.6, 134.3 (ArC quaternary), 131.3, 130.9, 129.5, 128.0, 127.7, 127.5, 127.2, 127.0, 124.1, 123.9, 122.7, 122.3 (ArCH), 68.9, 67.9 (NC quaternary), 53.1, 52.0 (NCH_2), 35.5, 32.0 ($NC\underline{C}H_2$), 24.2 ($COCH_3$), 23.7, 23.6 ($NCCH_2\underline{C}H_2$), 22.5 ($COCH_3$), 19.6, 19.3 ($NCCH{=}CH\underline{C}H_2$); *m/z* (ESI) 250.12 ($[M]^+Na$); [Found: ($[M]^+Na$) 250.1202, $C_{15}H_{17}NONa$ requires 250.1202].

Compound **4.13b** was then observed to decay in air to compound **4.13c**.



4.13c

2'-Acetylspiro[cyclohexane-1,1'-isoindolin]-2-en-3'-one (4.13c): δ_H ($CDCl_3$, 500 MHz) 7.90 (1H, d, *J* = 7.5 Hz, ArH), 7.65 (1H, dd, *J* = 7.5, 1.2 Hz, ArH), 7.55 – 7.47 (2H, m, ArH), 6.07 (1H, ddd, *J* = 10.0, 5.0, 2.5 Hz, NCCH=C$\underline{H}$), 5.40 – 5.34 (1H, m, NCC$\underline{H}$=CH), 2.82 (1H, m, NCC$\underline{H}_a$$CH_b$), 2.67 (3H, s, $COCH_3$), 2.48 – 1.84 (5H, m, cy); δ_C (126 MHz, $CDCl_3$) 170.7, 168.4 (C=O), 151.3 (ArC quaternary, $NCH_2\underline{C}$), 134.0 (ArCH), 130.1 (NCCH=$\underline{C}$H), 128.7 (ArCH), 128.7 (ArC quaternary), 127.7 (NC$\underline{C}$H=CH), 125.0, 123.6 (ArCH), 63.6 (NC quaternary), 31.7 (cy), 27.0 ($CO\underline{C}H_3$), 23.4, 20.0 (cy); *m/z* (ESI) 264.10 ($[M]^+Na$); [Found: ($[M]^+Na$) 264.0990, $C_{15}H_{15}NO_2Na$ requires 264.0995].

5.4.5.2 Palladium screening

All reactions were conducted under nitrogen in a 2-neck 25mL round-bottom flask. A solution of *N*-cyclohex-1-enyl-*N*-2-bromobenzylacetamide **2.8d** (1eq), catalyst (0.1eq), ligand (0.2eq) and base (1.1eq) in toluene was stirred at the given temperature for 24-48 hours. All conditions tested and results thereof are summarised in the following tables.

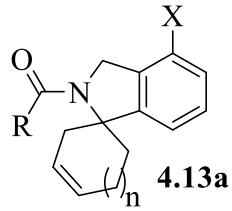
Entry	Catalyst	Ligand	Base	Solvent	Additive	Temp	Time
1	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	Toluene	/	Reflux	24
2	$Pd_2(dba)_3$	PPh_3	NEt_3	Toluene	/	Reflux	24
3	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	NEt_3	Toluene	/	Reflux	24
4	$Pd(OAc)_2$	P(*t*-Bu)$_3$	NEt_3	Toluene	/	Reflux	24
5	$Pd(OAc)_2$	PPh_3	NEt_3	Toluene	/	Reflux	24
6	$Pd(OAc)_2$	P(*o*-Tol)$_3$	NEt_3	Toluene	/	Reflux	24
7	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	Toluene	/	Reflux	24
8	$Pd(PPh_3)_4$	PPh_3	NEt_3	Toluene	/	Reflux	24
9	$Pd(PPh_3)_4$	P(*o*-Tol)$_3$	NEt_3	Toluene	/	Reflux	24
10	$Pd(dba)_2$	P(*t*-Bu)$_3$	NEt_3	Toluene	/	Reflux	24
11	$Pd(dba)_2$	PPh_3	NEt_3	Toluene	/	Reflux	24
12	$Pd(dba)_2$	P(*o*-Tol)$_3$	NEt_3	Toluene	/	Reflux	24
13	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	Toluene	/	RT	48
14	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	THF	/	RT	48
15	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	DMF	/	RT	48
16	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	DMF	/	140	48
17	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	CH_3CN	/	RT	48
18	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	DCE	/	RT	48
19	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	Dioxane	/	RT	48
20	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	NEt_3	DMF	$AgNO_3$[a]	140	48
21	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	/	140	48
22	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	$AgNO_3$[a]	140	48
23	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	DABCO	DMF	/	140	48
24	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	Ag_2CO_3	DMF	/	140	48
25	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	NBu_4Br[a]	140	48
26	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	THF	/	Reflux	48
27	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	CH3CN	/	Reflux	48
28	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	NBu_4Br[b]	140	48
29	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	NBu_4Br[b]	140	48
30	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	NEt_3	DMF	NBu_4Br[c]	140	48
31	$Pd(PPh_3)_4$	PPh_3	NEt_3	DMF	/	140	48

[a]1.1eq; [b]3 eq; [c]10eq

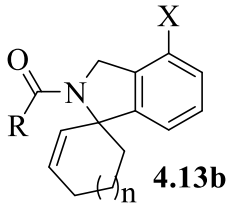
Entry	Results (%)			
	4.13a	**4.13b**	**2.8d**	**Other**
1	22.6	8.4	69.1	
2	2.2	1.9	76.9	19.0
3	17.0	9.4	73.6	
4	9.6	6.6	83.8	
5	3.8	6.5	89.7	
6	2.6	2.4	95.0	
7	29.1	45.3	25.6	
8	1.0	29.6	69.4	
9	0.0	9.0	75.2	15.8
10	2.9	0.0	97.1	
11	2.0	0.0	98.0	
12	8.9	6.6	84.5	
13	0.0	0.0	99.0	1.0
14	0.0	0.0	69.4	30.5
15	11.9	0.0	88.1	
16	28.9	0.0	66.2	4.9
17	0.0	0.0	100	
18	0.0	0.0	100	
19	0.0	0.0	100	
20	0.0	0.0	100	
21	20.6	79.3	0	
22	6.3	13.4	80.3	
23	15.2	72.5	12.3	
24	20.4	62.8	16.8	
25	45.5	41.8	12.7	
26	0.0	0.0	100	
27	0.7	10.1	89.2	
28	41.7	52.9	5.4	
29	42.7	52.1	5.1	
30	38.0	56.3	5.7	
31	4.0	84.5	11.5	

5.4.5.3 Palladium reactions of other compounds

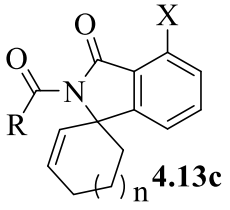
The compounds below were cyclised using the optimised method detailed in entry 31 of the reaction conditions screening table to give the products below. Key diagnostic peaks are listed below for each cyclisation.



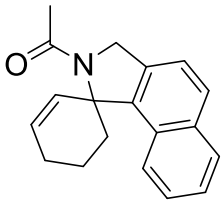
4.13a



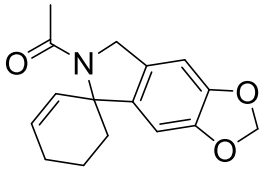
4.13b



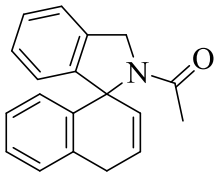
4.13c



4.18b



4.19b



4.20

Compound	**4.13b** (%)	**4.13a** (%)	**SM** (%)	**4.13c** (%)
2.8h	55	20	25	
2.8j	25	tr	69	
2.8k	56	13	31	
2.8m	7	tr	93	
2.8n	64	14	22	
2.8o	100	tr	tr	
2.8t	tr	83	0	17
2.9	100	tr	tr	
2.16b	No reaction			
2.21b	No reaction			
2.27	28	tr	72	
2.28	89	tr	11	
2.29	No reaction			

Cyclisation of 2.8h, Diagnostic peaks: δ_H (300 MHz, $CDCl_3$) 6.14 – 6.03 (1H maj, m, NCCH=C<u>H</u>, 4.13b), 6.01 – 5.90 (1H min, m, NCCH=C<u>H</u>, 4.13b), 5.88 – 5.74 (2H, m, HC=CH, 4.13a), 5.69 (1H maj, d, *J* = 11.5 Hz, NCC<u>H</u>=CH, 4.13b), 5.60 (1H min,

d, *J* = 10.0 Hz, NCC<u>H</u>=CH, 4.13b), 4.98 (1H maj, d, *J* = 5.0 Hz, NC<u>H</u>$_a$CH$_b$, 4.13b), 4.92 (2H min, m, NCH$_2$, 4.13b), 4.81 (1H, m, NC<u>H</u>$_a$CH$_b$, 4.13a), 4.76 (1H, m, NCH$_a$C<u>H</u>$_b$, 4.13a), 4.68 (1H maj, d, *J* = 17.0 Hz, NCH$_a$C<u>H</u>$_b$, 4.13b), 3.87 (1H, m, cy, 4.13a), 3.81 (1H, m, cy, 4.13a), 3.19 – 3.05 (1H, m, cy, 4.13a), 2.81 – 2.70 (1H min, m, NCC<u>H</u>$_a$CH$_b$, 4.13b).

Cyclisation of 2.8j, Diagnostic peaks: δ_H (300 MHz, $CDCl_3$) 6.03 – 5.93 (1H maj, m, NCCH=C<u>H</u>, 4.13b), 5.88 (1H min, dd, *J* = 8.5, 5.5 Hz, NCCH=C<u>H</u>, 4.13b), 5.64 (1H maj, m, NCC<u>H</u>=CH, 4.13b), 5.53 (1H min, m, NCCH=C<u>H</u>, 4.13b), 4.93 (2H, d, *J* = 8.0 Hz, NCH$_2$).

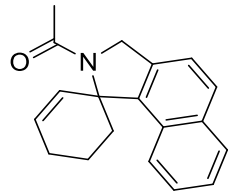
Cyclisation of 2.8k, Diagnostic peaks: δ_H (300 MHz, $CDCl_3$) 5.99 (1H min, ddd, *J* = 7.0, 4.5, 2.0 Hz, NCCH=C<u>H</u>, 4.13b), 5.93 – 5.84 (1H maj, m, NCCH=C<u>H</u>, 4.13b), 5.73 (2H, m, HC=CH, 4.13a), 5.63 (1H min, d, *J* = 9.5 Hz, NCC<u>H</u>=CH, 4.13b), 5.52 (1H maj, d, *J* = 9.5 Hz, NCC<u>H</u>=CH, 4.13b), 4.96 (1H maj, d, *J* = 10.0 Hz, NC<u>H</u>$_a$CH$_b$, 4.13b), 4.90 (1H, d, *J* = 6.5 Hz, NC<u>H</u>$_a$CH$_b$, 4.13a), 4.85 (1H, d, *J* = 6.5 Hz, NCH$_a$C<u>H</u>$_b$, 4.13a), 4.72 (2H min, s, NCH$_2$, 4.13b), 4.59 (1H maj, d, *J* = 10.0 Hz, NCH$_a$C<u>H</u>$_b$, 4.13b), 3.81 (1H, m, cy, 4.13a), 3.13 – 2.99 (1H, m, cy, 4.13a).

Cyclisation of 2.8m, Diagnostic peaks (4.13b only): δ_H (300 MHz, $CDCl_3$) 6.08 – 5.97 (1H min, m, NCCH=C<u>H</u>), 5.93 (1H min + maj, m, NCC<u>H</u>=CH + NCCH=C<u>H</u>), 5.75 (1H maj, d, *J* = 11.0 Hz, NCC<u>H</u>=CH), 5.60 (2H maj, d, *J* = 15.0 Hz, NCH$_2$), 4.87 (1H maj, d, *J* = 11.0 Hz, NC<u>H</u>$_a$CH$_b$), 4.63 (1H min, d, *J* = 11.0 Hz, NCH$_a$C<u>H</u>$_b$).

Cyclisation of 2.8n, Diagnostic peaks: δ_H (300 MHz, $CDCl_3$) 6.02 – 5.92 (1H min, m, NCCH=C<u>H</u>, 4.13b), 5.92 – 5.81 (1H maj, m, NCCH=C<u>H</u>, 4.13b), 5.70 (2H, br s, HC=CH, 4.13a), 5.67 (1H min, d, *J* = 10.0 Hz, NCC<u>H</u>=CH, 4.13b), 5.52 (1H maj, d, *J* = 9.0 Hz, NCC<u>H</u>=CH, 4.13b), 4.90 (1H maj, d, *J* = 10.5 Hz, NC<u>H</u>$_a$CH$_b$, 4.13b), 4.76

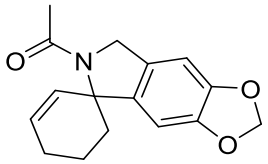
(1H maj, d, *J* = 10.5 Hz, $NCH_aC\underline{H}_b$, 4.13b), 4.70, (2H min, m, NCH_2, 4.13b), 4.64 (2H, m, NCH_2, 4.13a), 3.77 (1H, d, *J* = 16.5 Hz, cy, 4.13a).

Cyclisation of 2.8o, Diagnostic peaks (4.13b only): δ_H (400 MHz, $CDCl_3$) 5.87 – 5.77 (1H maj + 1H min, m, NCH=C<u>H</u>), 5.71 (1H maj + 1H min, d, *J* = 13.0 Hz, NC<u>H</u>=CH), 4.93 (1H min, d, *J* = 16.5 Hz, $NC\underline{H}_aCH_b$), 4.78 (2H maj, s, NCH_2), 4.69 (1H min, d, *J* = 16.5 Hz, $NCH_aC\underline{H}_b$).



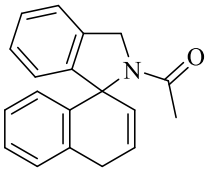
4.18b

Cyclisation of 2.9, Diagnostic peaks (4.18b only): δ_H (300 MHz, $CDCl_3$) 6.32 – 6.23 (1H min, m, NCCH=C<u>H</u>), 6.19 – 6.08 (1H maj, m, NCCH=C<u>H</u>), 5.97 (1H min, d, J = 10.5 Hz, NCC<u>H</u>=CH), 5.73 (1H maj, d, J = 10.0 Hz, NCC<u>H</u>=CH), 5.08 (1H min, d, J = 16.5 Hz, $NC\underline{H}_aCH_b$), 4.87 (2H maj, s, NCH_2), 4.75 (1H min, d, J = 16.5 Hz, $NCH_aC\underline{H}_b$), 2.87 (s, 21H), 2.80 (s, 22H).



4.19b

Cyclisation of 2.28, Diagnostic peaks (4.19b only): δ_H (400 MHz, $CDCl_3$) 6.08 – 6.00 (1H maj, m, NCCH=C<u>H</u>), 5.94 – 5.88 (1H min, m, NCCH=C<u>H</u>), 5.65 (1H min, d, *J* = 10.0 Hz, NCC<u>H</u>=CH), 5.56 (1H maj, d, *J* = 10.2 Hz, NCC<u>H</u>=CH), 4.84 (1H min, d, *J* = 16.0 Hz, $NC\underline{H}_aCH_b$), 4.70 (2H maj, s, NCH_2), 4.63 (1H min, d, *J* = 16.0 Hz, $NCH_aC\underline{H}_b$).



4.20

Cyclisation of 2.27, Diagnostic peaks (4.20 only): δ_H (300 MHz, $CDCl_3$) 6.22 – 6.12 (1H maj + min, m, NCCH=C<u>H</u>), 5.94 (1H maj + min, m, NCC<u>H</u>=CH), 5.16 (1H min, d, *J* = 16.0 Hz, NC<u>H</u>$_a$CH$_b$), 5.06 (2H maj, d, J = 11.0 Hz, NCH_2), 4.96 (1H min, d, *J* = 16.0 Hz, NCH$_a$C<u>H</u>$_b$).

References

1 M. Oki, *Topics in Stereochemistry*, 1983.

2 G. H. Christie and J. Kenner, *J. Chem. Soc., Trans.*, 1922, **121**, 614–620.

3 G. Bringmann and D. Menche, *Acc. Chem. Res.*, 2001, **34**, 615–624.

4 O. Baudoin and F. Guéritte, in *Studies in Natural Products Chemistry*, 2003, vol. 29, pp. 355–417.

5 A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, *J. Am. Chem. Soc.*, 1980, **102**, 7932–7934.

6 S. Akutagawa, *Appl. Catal. A, Gen.*, 1995, 128, 171–207.

7 X. Z. Hidenori Kumobayashi*, Takashi Miura, Noboru Sayo, Takao Saito, *Synlett*, 2001, **Special Is**, 1055–1064.

8 E. Fernández, P. J. Guiry, K. P. T. Connole and J. M. Brown, *J. Org. Chem.*, 2014, **79**, 5391–5400.

9 V. Bhat, S. Wang, B. M. Stoltz and S. C. Virgil, *J. Am. Chem. Soc.*, 2013, **135**.

10 J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev.*, 2015, **44**.

11 D. H. Williams and B. Bardsley, *Angew. Chemie Int. Ed.*, 1999, **38**, 1172–1193.

12 S. Kundu, T. H. Kim, J. H. Yoon, H.-S. Shin, J. Lee, J. H. Jung and H. S. Kim, *Int. J. Oncol.*, 2014, **45**, 2331–2340.

13 Y. S. Park, C. I. Grove, M. González-López, S. Urgaonkar, J. C. Fettinger and J. T. Shaw, *Angew. Chemie - Int. Ed.*, 2011, **50**, 3730–3733.

14 P. D. Davis, G. J. Dougherty, D. C. Blakey, S. M. Galbraith, G. M. Tozer, A. L. Holder, M. A. Naylor, J. Nolan, M. R. L. Stratford, D. J. Chaplin and S. A. Hill, *Cancer Res.*, 2002, **62**, 7247–7253.

15 K. Nicolaou, C. Boddy, S. Bräse and N. Winssinger, *Angew. Chem. Int. Ed. Engl.*, 1999, **38**, 2096–2152.

16 P. Lloyd-Williams and E. Giralt, *Chem. Soc. Rev.*, 2001, **30**, 145–157.

17 D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow and J. L. Katz, *Angew. Chemie - Int. Ed.*, 1998, **37**, 2700–2704.

18 K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando and J. M. Ramanjulu, *Angew. Chemie - Int. Ed.*, 1998, **37**, 2717–2719.

19 K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes and T. Bando, *Angew. Chemie Int. Ed.*, 1999, **38**, 240–244.

20 C. I. Grove, J. C. Fettinger and J. T. Shaw, *Synthesis (Stuttg).*, 2012, **44**, 362–371.

21 X. Liu, Y.-J. Hu, B. Chen, L. Min, X.-S. Peng, J. Zhao, S. Li, H. N. C. Wong and C.-C. Li, *Org. Lett.*, 2017, **19**, 4612–4615.

22 B. Chen, X. Liu, Y.-J. Hu, D.-M. Zhang, L. Deng, J. Lu, L. Min, W.-C. Ye and C.-C. Li, *Chem. Sci.*, 2017, **8**, 4961–4966.

23 R. Adams and H. C. Yuan, *Chem. Rev.*, 1955, **12**, 261–338.

24 G. Bott, L. D. Field and S. Sternhell, *J. Am. Chem. Soc.*, 1980, **102**, 5618–5626.

25 R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345–350.

26 J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857–898.

27 H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa and R. Noyori, *J. Org. Chem.*, 1986, **51**, 629–635.

28 M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.*, 2005, **105**, 1801–1836.

29 R. Noyori, *Chem. Soc. Rev.*, 1989, **18**, 187.

30 S. Akutagawa, *Top. Catal.*, 1998, **4**, 271–274.

31 N. W. Alcock, J. M. Brown and D. I. Hulmes, *Tetrahedron: Asymmetry*, 1993, **4**, 743–756.

32 J. M. Brown, D. Hulmes and T. P. Layzell, *J. Chem. Soc. Chem. Commun*, 1993, **91**, 1673–1674.

33 J. M. Brown, D. I. Hulmes and P. J. Guiry, *Tetrahedron*, 1994, **50**, 4493–4506.

34 Y. Fukuyama and Y. Asakawa, *J. Chem. Soc. Perkin Trans. 1*, 1991, **11**, 2737–2741.

35 A. P. Degnan and A. I. Meyers, *J. Am. Chem. Soc.*, 1999, **121**, 2762–2769.

36 A. I. Meyers, J. J. Willemsen and J. Longmore, *Chem. Commun.*, 1997, **5**, 1573–1574.

37 G. Büchi, D. H. Klaubert, R. C. Shank, S. M. Weinreb, G. N. Wogan, G. Buechi, D. H. Klaubert, R. C. Shank, S. M. Weinreb and G. N. Wogan, *J. Org. Chem.*, 1971, **36**, 1143–1147.

38 G. Bringmann, J. Holenz, R. Weirich, M. Rübenacker, C. Funke, M. R. Boyd, R. J. Gulakowski and G. François, *Tetrahedron*, 1998, **54**, 497–512.

39 T. J. Donohoe, C. R. Jones and L. C. A. Barbosa, *J. Am. Chem. Soc.*, 2011, **133**, 16418–16421.

40 E. Kumarasamy, R. Raghunathan, M. P. Sibi and J. Sivaguru, *Chem. Rev.*, 2015, **115**, 11239–11300.

41 G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563–639.

42 R. Adepu, B. Prasad, M. A. Ashfaq, N. Z. Ehtesham and M. Pal, *RSC Adv.*,

2014, **4**, 49324–49328.

43 J. Clayden and J. H. Pink, *Angew. Chemie Int. Ed.*, 1998, **37**, 1937–1939.

44 P. Bowles, J. Clayden and M. Tomkinson, *Tetrahedron Lett.*, 1995, **36**, 9219–9222.

45 A. Ahmed, R. A. Bragg, J. Clayden, L. W. Lai, C. McCarthy, J. H. Pink, N. Westlund and S. A. Yasin, *Tetrahedron*, 1998, **54**, 13277–13294.

46 J. Clayden, N. Vassiliou and W. S. Knowles, *Org. Biomol. Chem.*, 2006, **4**, 2667.

47 T. Adler, J. Bonjoch, J. Clayden, M. Font-Bardía, M. Pickworth, X. Solans, D. Solé, L. Vallverdú, C. Kashima and J. L. Evenden, *Org. Biomol. Chem.*, 2005, **3**, 3173.

48 J. Clayden, L. Vallverdú and M. Helliwell, *Org. Biomol. Chem.*, 2006, **4**, 2106–2118.

49 J. Clayden, *Synlett*, 1998, **8**, 810–816.

50 J. Clayden, in *Organic Synthesis Set*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2008, pp. 48–52.

51 A. Ates and D. P. Curran, *J. Am. Chem. Soc.*, 2001, **123**, 5130–5131.

52 S. Thayumanavan, P. Beak and D. P. Curran, *Tetrahedron Lett.*, 1996, **37**, 2899–2902.

53 D. P. Curran, C. H.-T. Chen, S. J. Geib and A. B. Lapierre, *Tetrahedron*, 2004, **60**, 4413–4424.

54 D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. Cass, A. L. G. Degani, M. Z. Hernandes and L. C. G. Freitas, *Tetrahedron Asymmetry*, 1997, **8**, 3955–3975.

55 P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson and N. Westlund, *J. Chem. Soc. Perkin Trans. 1*, 1997, **47**, 2607–2616.

56 T. Kawabata, K. Yahiro and K. Fuji, *J. Am. Chem. Soc.*, 1991, **113**, 9694–9696.

57 J. E. Smyth, N. M. Butler, P. A. Keller, G. Bringmann, T. A. M. Gulder, T. A. M. Gulder, M. Breuning, *Nat. Prod. Rep.*, 2015, **32**, 1562–1583.

58 A. Katritzky, I. Alkorta, J. Elguero, C. Roussel, N. Vanthuyne and P. Piras, in *Advances in Heterocyclic Chemistry*, 2012, vol. 105, pp. 1–188.

59 J. Clayden, W. J. Moran, P. J. Edwards and S. R. LaPlante, *Angew. Chem. Int. Ed. Engl.*, 2009, **48**, 6398–401.

60 D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, S. L. Castle, O. Loiseleur, Q. Jin, T. Scripps, N. Torrey, P. Road and L. Jolla, *J. Am. Chem. Soc.*, 1999, **121**, 10004–10011.

61 J. Mandel, X. Pan, E. Ben Hay, S. J. Geib, C. S. Wilcox and D. P. Curran, *J. Org. Chem.*, 2013, **78**, 4083–4089.

62 H. Koide, T. Hata, K. Yoshihara, K. Kamikawa and M. Uemura, *Tetrahedron*, 2004, **60**, 4527–4541.

63 A. Honda, K. M. Waltz, P. J. Carroll and P. J. Walsh, *Chirality*, 2003, **15**, 615–621.

64 D. E. Smith, I. Marquez, M. E. Lokensgard, A. L. Rheingold, D. A. Hecht and J. L. Gustafson, *Angew. Chemie Int. Ed.*, 2015, **54**, 11754–11759.

65 C. Jimeno, R. Rios, P. J. Carroll and P. J. Walsh, *Tetrahedron*, 2004, **60**, 4543–4548.

66 D. B. Guthrie, S. J. Geib and D. P. Curran, *J. Am. Chem. Soc.*, 2011, **133**, 115–22.

67 J. Clayden, M. Oki, A. S. Cooke, M. M. Harris and G. Bringmann, *Chem. Commun.*, 2004, **14**, 127.

68 J. Clayden, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1996, **37**, 5577–5580.

69 A. J. Clark, D. P. Curran, D. J. Fox, F. Ghelfi, C. S. Guy, B. Hay, N. James, J. M. Phillips, F. Roncaglia, P. B. Sellars, P. Wilson and H. Zhang, *J. Org. Chem.*, 2016, **81**, 5547–5565.

70 J. Clayden, L. Vallverdú and M. Helliwell, *Org. Biomol. Chem.*, 2006, **4**, 2106–2118.

71 D. B. Guthrie, K. Damodaran, D. P. Curran, P. Wilson and A. J. Clark, *J. Org. Chem.*, 2009, **74**, 4262–6.

72 A. J. Clark, D. P. Curran, J. V Geden, N. James and P. Wilson, *J. Org. Chem.*, 2011, **76**, 4546–51.

73 M. A. Cuyegkeng and A. Mannschreck, *Chem. Ber.*, 1987, **120**, 803–809.

74 W. H. Pirkle, C. J. Welch and A. J. Zych, *J. Chromatogr. A*, 1993, **648**, 101–109.

75 D. P. Curran, H. Qi, S. J. Geib and N. C. DeMello, *J. Am. Chem. Soc.*, 1994, **116**, 3131–3132.

76 D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. Cass, A. L. G. Degani, M. Z. Hernandes and L. C. G. Freitas, *Tetrahedron Asymmetry*, 1997, **8**, 3955–3975.

77 A. D. Hughes, D. A. Price, O. Shishkin and N. S. Simpkins, *Tetrahedron Lett.*, 1996, **37**, 7607–7610.

78 O. Kitagawa, H. Izawa, T. Taguchi and M. Shiro, *Tetrahedron Lett.*, 1997, **38**, 4447–4450.

79 T. Courant, G. Dagousset and G. Masson, *Synthesis (Stuttg).*, 2015, **47**, 1799–1856.

80 K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599–4657.

81 M.-X. Wang, G. Stork, R. Terrell, J. Szmuszkovicz, G. Stork, H. K.

Landesman, D. W. C. MacMillan, S. Mukherjee, J. W. Yang, *Chem. Commun.*, 2015, **51**, 6039–6049.

82 D. G. Gehring, W. A. Mosher and G. S. Reddy, *J. Org. Chem.*, 1966, **31**, 3436–3437.

83 R. D. Libby, *Advanced Organic Chemistry, Part A: Structure and Mechanism, 4th Edition (Carey, Francis A.; Sundberg, Richard J.)*, 2001, vol. 78.

84 C. Guy, *PhD Thesis, Warwick Univ.*, 2013.

85 B. Giese, B. Kopping, T. Gobel, J. Dickhaut, G. Thoma, K. J. Kulicke and F. Trach, *Org. React. (Hoboken, NJ, United States)*, 1996, **48**, 301-856.

86 A. J. Clark, *Chem. Soc. Rev.*, 2002, **31**, 1–11.

87 O. Tamura, H. Matsukida, A. Toyao, Y. Takeda and H. Ishibashi, *J. Org. Chem.*, 2002, **67**, 5537–5545.

88 C. Chatgilialoglu, *Chem. Rev.*, 1995, **95**, 1229–1251.

89 K. C. Majumdar, P. K. Basu and S. K. Chattopadhyay, *Tetrahedron*, 2007, **63**, 793–826.

90 D. P. Curran, J. Sisko, P. E. Yeske and H. Liu, *Pure Appl. Chem.*, 1993, **65**, 1153–1159.

91 D. P. Curran and D. M. Rakiewicz, *J. Am. Chem. Soc.*, 1985, **107**, 1448–1449.

92 A. N. Abeywickrema, A. L. J. Beckwith and S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072–4078.

93 H. B. Kagan, J. L. Namy and P. Girard, *Tetrahedron*, 1981, **37**, 175–180.

94 G. A. Molander and L. S. Harring, *J. Org. Chem.*, 1990, **55**, 6171–6176.

95 Y. Watanabe, S. Ishikawa, G. Takao and T. Toru, *Tetrahedron Lett.*, 1999, **40**, 3411–3414.

96 A. J. Clark, R. P. Filik, D. M. Haddleton, A. Radigue, C. J. Sanders, G. H. Thomas and M. E. Smith, *J. Org. Chem.*, 1999, **64**, 8954–8957.

97 S. I. Iwamatsu, K. Matsubara and H. Nagashima, *J. Org. Chem.*, 1999, **64**, 9625–9631.

98 H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.*, 1993, **58**, 464–470.

99 A. J. Clark, R. P. Filik and G. H. Thomas, *Tetrahedron Lett.*, 1999, **40**, 4885–4888.

100 A. J. Clark, C. P. Dell, J. M. Ellard, N. A. Hunt and J. P. McDonagh, *Tetrahedron Lett.*, 1999, **40**, 8619–8623.

101 A. J. Clark, G. M. Battle and A. Bridge, *Tetrahedron Lett.*, 2001, **42**, 1999–2001.

102 A. J. Clark, *European J. Org. Chem.*, 2016, **2016**, 2231–2243.

103 A. J. Clark and P. Wilson, *Copper mediated atom transfer radical cyclisations with AIBN*, 2008, vol. 49.

104 A. N. Abeywickrema and A. L. J. Beckwith, *J. Chem. Soc. Chem. Commun.*, 1986, **6**, 464.

105 T. Okitsu, M. Saito, O. Tamura and H. Ishibashi, *Tetrahedron*, 2005, **61**, 9180–9187.

106 D. P. Curran, D. B. Guthrie and S. J. Geib, *J. Am. Chem. Soc.*, 2008, **130**, 8437–45.

107 H. Ishibashi, A. Ishita and O. Tamura, *Tetrahedron Lett.*, 2002, **43**, 473–475.

108 R. F. Heck, *J. Am. Chem. Soc.*, 1968, **90**, 5518–5526.

109 A. De Meijere and F. E. Meyer, *Angew. Chemie Int. Ed.*, 1994, **33**, 2379–2411.

110 M. Shibasaki, E. M. Vogl and T. Ohshima, *Adv. Synth. Catal.*, 2004, **346**, 1533–1552.

111 J. Le Bras and J. Muzart, *Chem. Rev.*, 2011, **111**, 1170–214.

112 A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945–2964.

113 W. A. Herrmann, V. P. . Böhm and C.-P. Reisinger, *J. Organomet. Chem.*, 1999, **576**, 23–41.

114 V. Farina, *Adv. Synth. Catal.*, 2004, **346**, 1553–1582.

115 N. A. Bumagin, P. G. More and I. P. Beletskaya, *J. Organomet. Chem.*, 1989, **371**, 397–401.

116 N. E. Carpenter, D. J. Kucera, L. E. Overman and L. E. O. Nancy E. Carpenter, David J. Kucera, *J. Org. Chem.*, 1989, **54**, 5846–5848.

117 V. H. Rawal, C. Michoud and R. Monestel, *J. Am. Chem. Soc.*, 1993, **115**, 3030–3031.

118 A. Monaco, B. R. Szulc, Z. X. Rao, M. Barniol-Xicota, M. Sehailia, B. M. A. Borges and S. T. Hilton, *Chem. - A Eur. J.*, 2017, **23**, 4750–4755.

119 J.-N. Desrosiers, J. Wen, S. Tcyrulnikov, S. Biswas, B. Qu, L. Hie, D. Kurouski, L. Wu, N. Grinberg, N. Haddad, C. A. Busacca, N. K. Yee, J. J. Song, N. K. Garg, X. Zhang, M. C. Kozlowski and C. H. Senanayake, *Org. Lett.*, 2017, **19**, 3338–3341.

120 G. Satyanarayana and M. E. Maier, *J. Org. Chem.*, 2008, **73**, 5410–5415.

121 J. E. M. N. Klein and R. J. K. Taylor, *European J. Org. Chem.*, 2011, **2011**, 6821–6841.

122 O. Kitagawa, M. Kohriyama and T. Taguchi, *J. Org. Chem.*, 2002, **67**, 8682–8684.

123 A. J. B. Lapierre, S. J. Geib and D. P. Curran, *J. Am. Chem. Soc.*, 2007, **129**, 494–5.

124 D. B. Guthrie and D. P. Curran, *Org. Lett.*, 2009, **11**, 249–51.

125 D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746–2750.

126 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297.

127 S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456–1465.

128 R. B. Boar, M. Robinson, D. H. R. Barton, R. V. Stick, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell and R. V. Stick, *J. Chem. Soc. Perkin I*, 1975, 1237–1241.

129 D. Datta and D. Majumdar, *J. Phys. Org. Chem.*, 1991, **4**, 611–617.

130 H. Ishibashi, N. Nakamura, T. Sato, M. Takeuchi and M. Ikeda, *Tetrahedron Lett.*, 1991, **32**, 1725–1728.

131 H. Ishibashi, M. Higuchi, M. Ohba and M. Ikeda, *Effect of Temperature of 5-Endo- and 4-Exo-Trig Radical Cyclizations of N-Vinylic α-Halo Amides*, 1998, vol. 39.

132 A. F. Parsons and D. A. J. Williams, *Tetrahedron*, 2000, **56**, 7217–7228.

133 L. J. Johnston, J. C. Scaiano and K. U. Ingold, *J. Am, Chem. Soc*, 1984, **106**, 4877–4881.

134 N. Ahmad, S. Gupta, M. M. Husain, K. M. Heiskanen and H. Mukhtar, *Clin. Cancer Res.*, 2000, **6**, 1524–8.

135 B. J. R. Pitts and L. R. Meyerson, *Drug Dev. Res.*, 1981, **1**, 43–49.

136 Z. Qu, X. Zou, X. Zhang, J. Sheng, Y. Wang, J. Wang, C. Wang and Y. Ji, *Mol. Med. Rep.*, 2015, **13**, 1336–44.

137 Z.-X. Ma, J. B. Feltenberger and R. P. Hsung, *Org. Lett.*, 2012, **14**, 2742–2745.

138 H. Ishibashi, K. Ohata, M. Niihara, T. Sato, M. Ikeda, *J. Chem. Soc. Perkin Trans. 1*, 2000, **31**, 547–553.

139 H. Ishibashi, I. Kato, Y. Takeda, M. Kogure and O. Tamura, *Chem. Commun.*, 2000, 1527–1528.

140 T. Taniguchi, D. Yonei, M. Sasaki, O. Tamura and H. Ishibashi, *Tetrahedron*, 2008, **64**, 2634–2641.

141 H. Ishibashi, H. Kawanami and M. Ikeda, *J. Chem. Soc. Perkin Trans. 1*, 1997, **33**, 2291–2295.

142 H. Ishibashi, H. Kawanami and M. Ikeda, *J. Chem. Soc. Perkin Trans. 1*, 1997, **7**, 817–822.

143 S. Takano, M. Suzuki, A. Kijima and K. Ogasawara, *Tetrahedron Lett.*, 1990, **31**, 2315–2318.

144 A. G. Schultz, M. A. Holoboski and M. S. Smyth, *J. Am. Chem. Soc.*, 1996, **118**, 6210–6219.

145 A. G. Schultz, P. R. Guzzo and D. M. Nowak, *J. Org. Chem.*, 1995, **60**, 8044–8050.

146 A. G. Schultz, M. A. Holoboski and M. S. Smyth, *J. Am. Chem. Soc.*, 1993, **115**, 7904–7905.

147 J. H. Rigby and M. Qabar, *J. Am. Chem. Soc.*, 1991, **113**, 8975–8976.

148 J. R. Fuchs and R. L. Funk, *Org. Lett.*, 2001, **3**, 3349–3351.

149 I. Jabin and P. Netchitalo, *Tetrahedron Lett.*, 2001, **42**, 7823–7827.

150 H. Ishibashi, A. Ishita and O. Tamura, *Tetrahedron Lett.*, 2002, **43**, 473–475.

151 T. Taniguchi, A. Ishita, M. Uchiyama, O. Tamura, O. Muraoka, G. Tanabe and H. Ishibashi, *J. Org. Chem.*, 2005, **70**, 1922–1925.

152 J. Fidalgo, L. Castedo and D. Domínguez, *Tetrahedron Lett.*, 1993, **34**, 7317–7318.

153 G. Rodríguez, M. M. Cid, C. Saá, L. Castedo and D. Domínguez, *J. Org. Chem.*, 1996, **61**, 2780–2782.

154 W. T. Eckenhoff and T. Pintauer, *Catal. Rev.*, 2010, **52**, 1–59.

155 A. I. Meyers and G. Milot, *J. Am. Chem. Soc.*, 1993, **115**, 6652–6660.

156 A. J. Clark, *Personal communication*, 2017.

157 S. A. Glover and J. Warkentin, *J. Org. Chem.*, 1993, **58**, 2115–2121.

158 H. L. Gordon, S. Freeman and T. Hudlicky, *Synlett*, 2005, **2005**, 2911–2914.

159 C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237–1286.

160 C. Chatgilialoglu, K. U. Ingold and J. C. Scaiano, *J. Am. Chem. Soc.*, 1981, **103**, 7739–7742.

161 J. Hynes, L. E. Overman, T. Nasser and P. V Rucker, *Tetrahedron Lett.*, 1998, **39**, 4647–4650.

162 I. Yalavac, S. E. Lyons, M. R. Webb and D. J. Procter, *Chem. Commun.*, 2014, **50**, 12863–12866.

163 A. Rivkin, F. González-López de Turiso, T. Nagashima and D. P. Curran, *J. Org. Chem.*, 2004, **69**, 3719–25.

164 J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.*, 1987, **16**, 1485–1486.

165 I. Bauer and H.-J. Knölker, *Chem. Rev.*, 2015, **115**, 3170–387.

166 M. N. Zhao, L. Yu, R. R. Hui, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *ACS Catal.*, 2016, **6**, 3473–3477.

167 K. Adams, A. K. Ball, J. Birkett, L. Brown, B. Chappell, D. M. Gill, L. K. Tony, N. J. Patmore, C. R. Rice, J. Ryan, P. Raubo and J. B. Sweeney, *Nat Chem*, 2017, **9**, 396–401.

168 A. J. Clark, D. I. Davies, K. Jones and C. Millbanks, *J. Chem. Soc. Commun.*, 1994, **6**, 41–42.

169 A. Ashimori and L. E. Overman, *J. Org. Chem.*, 1992, **57**, 4571–4572.

170 L. Liu, Y. Liu, B. Ling and S. Bi, *J. Organomet. Chem.*, 2017, **827**, 56–66.

171 J. P. Stambuli, S. R. Stauffer, K. H. Shaughnessy and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 2677–8.

172 Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297–299.

173 L. Ripa and A. Hallberg, *J. Org. Chem.*, 1997, **62**, 595–602.

174 P. Liu, Y. M. Pan, K. Hu, X. C. Huang, Y. Liang and H. S. Wang, *Tetrahedron*, 2013, **69**, 7925–7930.

175 L. E. Overman and D. A. Watson, *J. Org. Chem.*, 2006, **71**, 2587–2599.

176 D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard and T. Skrydstrup, *J. Am. Chem. Soc.*, 2010, **132**, 7998–8009.

177 K. Olofsson, *PhD Thesis, Uppsala Univ.*, 2001.

178 M. Lautens and Y. Q. Fang, *Org. Lett.*, 2003, **5**, 3679–3682.

179 R. Grigg, V. Sridharan, P. Stevenson and S. Sukirthalingam, *Tetrahedron*, 1989, **45**, 3557–3568.

180 S. E. Denmark and M. E. Schnute, *J. Org. Chem.*, 1995, **60**, 1013–1019.

181 S. Laschat, F. Narjes and L. E. Overman, *Tetrahedron*, 1994, **5**, 347–358.

182 N. J. Whitcombe, K. Kuok, M. Hii, S. E. Gibson, K. K. (Mimi) Hii and S. E. Gibson, *Tetrahedron*, 2001, **57**, 7449–7476.

183 A. J. Clark, C. P. Dell and J. P. McDonagh, *Comptes Rendus l'Académie des Sci. - Ser. IIC - Chem.*, 2001, **4**, 575–579.

184 A. J. Clark, J. V Geden, S. Thom and P. Wilson, *J. Org. Chem.*, 2007, **72**, 5923–6.

185 A. J. Clark, G. M. Battle, A. M. Heming, D. M. Haddleton and A. Bridge, *Tetrahedron Lett.*, 2001, **42**, 2003–2005.

186 N. A. Zhukovskaya and E. A. Dikusar, *Russ. J. Org. Chem.*, 2010, **46**, 180–185.

187 G. E. Hawkes, K. Herwig and J. D. Roberts, .

188 A. van den Hoogenband, J. H. M. Lange, W. I. Iwema-Bakker, J. A. J. den Hartog, J. van Schaik, R. W. Feenstra and J. W. Terpstra, *Tetrahedron Lett.*, 2006, **47**, 4361–4364.