Enecarbamates as Platforms for the Synthesis of Diverse Polycyclic Scaffolds

Alexandra Lucy Joyce Hindle

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Modular Synthesis of Bicyclic Twisted Amides and Anilines, Hindle A., Baj K., Iggo J. A., Cox D. J., Pask C. M., Nelson A., Marsden S.P., *Chem. Comm.* 2023, **59**, 6239–6242.

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Abstract

The efficient and continued exploration of novel chemical space is vital for the discovery of new drugs, with the construction of sp^3-rich scaffolds being of particular interest. This thesis describes the elaboration of a common intermediate, *via* a toolkit of techniques, to access structurally diverse, novel, and highly three-dimensional polycyclic scaffolds, based on pharmaceutically valuable *N*-heterocyclic cores.

Chapter one discusses the importance of properties and structure at several stages in the drug discovery process, including those for leads and fragments. Common motifs are highlighted and associated modern synthetic approaches discussed.

Chapter two describes the delivery of a library of enecarbamate and hemiaminal ether-based building blocks through a unified approach. A toolkit of α- and β-functionalisation methods are applied for their elaboration.

Chapter three describes the development and use of the β-functionalisation toolkit for enecarbamates, through the photocatalysed construction of spirocyclic systems. Herein, five exemplary spirocyclic structures are accessed based on two scaffolds.

Chapter four evaluates the versatility of the photoredox toolkit *via* its application in the synthesis of ten bicyclic amides and five bicyclic anilines, from enecarbamates, through a modular approach. The resulting structural distortion regarding *N* lone pair and π-system overlap is assessed, *via* their physical properties, including measured nonaqueous pK_aH. The subsequent impact on reactivity and bioactivity is evaluated.

Chapter five discusses the use of enecarbamates in annulative technologies for the preparation of a series of fused motifs including two bicyclic lactams, seven oxetanes and nine cyclic aminals. A fully diastereoselective, photochemical synthesis of oxetanes is described and cyclic aminals have been highlighted as structures bearing a potential novel warhead.

Chapters six and seven present the thesis conclusion and all associated experimental details, including full characterisation of synthesised compounds.

List of abbreviations

δ	chemical shift
δ_{obs}	observed chemical shift
δ_{H}	fully protonated chemical shift
δ_{L}	fully deprotonated chemical shift
λ	wavelength
ν	frequency
Σ_{angles}	sum of angles
τ	twist angle
χ_{N}	pyramidalisation at nitrogen
χ_{C}	pyramidalisation at carbon
$\omega_{1\text{-}4}$	torsional angles
Ac	acetyl
APS	ammonium persulfate
Ar	aryl
ATCC	American Type Culture Collection
BLA	biological license application
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br	broad
Bt	benzotriazole
Bu	butyl
Bz	benzoyl
b.p.	boiling point
Cbz	carboxybenzyl
CLND	chemiluminescent nitrogen detection
*c*logP	logarithm of the partition coefficient (fragment-based prediction)

CLSI	Clinical and Laboratory Standards Institute
CSI	chemical shift index
CSTR	continuous stirred tank reactor
COSY	correlation spectroscopy
CuAAc	copper-catalysed azide-alkyne cycloaddition
CySH	cyclohexane thiol
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEL	DNA encoded library
DEPT	distortionless enhancement through polarisation transfer
DFT	density functional theory
DIPA	diisopropylamine
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
dr	diastereomeric ratio
DTT	dithiothreitol
EDA	ethylenediamine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
e.g.	*exempli gratia*

EI	electron impact
ESI	electrospray ionisation
eq	equivalents
er	enantiomeric ratio
Et	ethyl
FBDD	fragment-based drug discovery
FDA	US Food and Drug Administration
Fsp^3	fraction of sp^3 hybridised carbons
GSK	GlaxoSmithKline
GVK BIO	GVK Biosciences
HA	heavy atom count
hERG	the human Ether-à-go-go-Related Gene
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilazane
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HTS	high-throughput screening
IR	infrared
ISB	Iso Sensitest Broth
J	coupling constant
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LED	light-emitting diode
LHMDS	lithium bis(trimethylsilyl)amide
LLE	ligand-lipophilicity efficiency
logD	logarithm of the distribution coefficient

logP	logarithm of the partition coefficient
logS	logarithm of the solubility
LOS	lead-oriented synthesis
m	meta
Me	methyl
MDDR	MDL drug data report database
MHB-II	Mueller-Hinton Broth
MIC	minimum inhibitory concentration
MMP-9	matrix metallopeptidase 9
mw	molecular weight
Ms	methanesulfonyl
m.p.	melting point
n	primary
NBS	*N*-bromosuccinimide
nd	not determined
NME	new molecular entity
NMR	nuclear magnetic resonance
No.	number
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NPR1/NPR2	normalised principal moments of inertia
o	*ortho*
OD	optical density
p	*para*
p	pentet
PBF	Poisson Boltzmann Finite
PBS	phosphate-buffered saline
Ph	phenyl

PG	protecting group
Piv	pivaloyl
pK_a	logarithm of the acid dissociation constant
PMI	principal moments of inertia
POC	propargyloxycarbonyl
Ppm	parts per million
Pr	propyl
PTH	*N*-phenyl phenothiazine
PySSPy	2,2'-dipyridyldisulfide
q	quartet
R_f	retention factor
RO5	rule of five
rt	room temperature
s	singlet
SBDD	structure-based drug design
SCX	strong cation exchange
SDS	sodium dodecyl sulfate
SDS-PAGE	sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SET	single electron transfer
SLB	sample loading buffer
S_N	nucleophilic substitution
SRI	strategic reagent initiative
t	triplet
t	*tert* (tertiary-)
TBTA	tris((1-benzyl-4-triazolyl)methyl)amine
TCEP	tris(2-carboxyethyl)phosphine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl

TFAA	trifluoroacetic anhydride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TEMED	tetramethylethylenediamine
TMS	trimethylsilyl
tol	tolyl
TPPO	triphenylphosphine oxide
TPSA	total polar surface area
TRIP	triisopropylbenzene
Ts	*p*-toluenesulfonyl
TSA	*p*-toluenesulfonic acid
UV	ultraviolet
VT	variable temperature

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1 Chapter 1: Introduction

1.1 Challenges facing the pharmaceutical industry

The development of medicines has played a crucial role in increasing average life expectancy, which has risen from approximately 45 to 77 over the last 100 years.[1] The 1990's, also known as a golden era, saw a peak in the success of the pharmaceutical industry where several blockbuster drugs were brought to market (e.g. Lipitor).[2,3] Figure 1.1 presents the number of drugs approved by the FDA annually since 1993 and illustrates a peak in the mid to late 1990s.[4] In 1996, the number of new molecular entities (NMEs) and biologics license applications (BLAs) introduced by the FDA was at its highest at 53 and these figures were not surpassed until recent years.[5,3,6] In 2018, a record breaking 59 novel drugs were approved and in 2019 this remained high at 48.[6,4] Even with the recently improved number of drug molecules entering the market, the pharmaceutical industry is currently facing significant challenges including low approval rates, rising research and development costs and diminishing pipelines amongst others.[1,3]

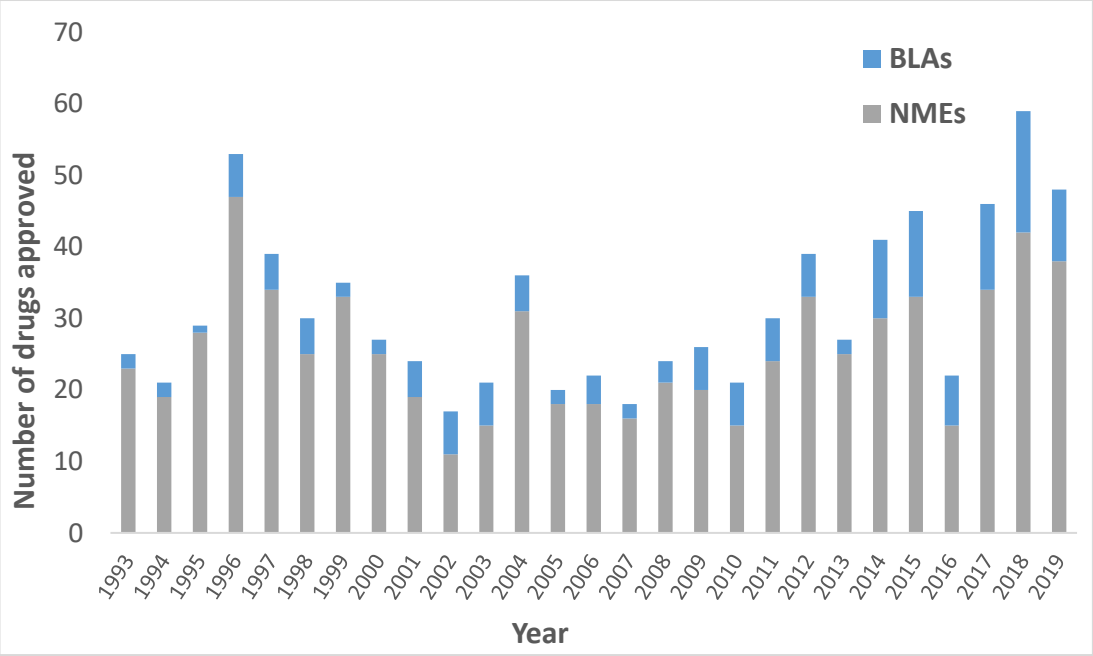


Figure 1.1: The number of new molecular entities (NMEs) and biological license applications (BLAs) approved each year by the FDA, since 1993, adapted from Mullard.[4]

Rising research and development costs are a challenge for the pharmaceutical industry. The industry has the highest expenditure in terms of research and development compared to all other industries, for example, in the US pharmaceutical industry, the research and development spending constituted 17% of global sales.[3] Another challenge concerns low approval rates of new drug molecules, which were reported to be at their lowest between 2005 and 2010.[3] Factors contributing to this may include a diminishment in product pipelines with many pharmaceutical companies only focusing on drug molecules with a high market size. Between the years of 2009 and 2014, the expiration of patents was at its worse (209 billion dollars loss from revenues), contributing to a diminishment in sales.[3] Potentially the most significant factor contributing to low approval rates is a substantial increase in attrition rate. Between 1991 and 2000, the average success rate from first-in-man to registration was 11% (based on ten leading pharmaceutical companies). This was even lower for specific therapeutic areas, for instance, a 5% success rate was reported for oncology-related drug candidates. In 1991, significant attrition was deemed to be due, in part, to inappropriate pharmacokinetic properties, such as bioavailability, and this was seen to improve in 2000, with the development of additional screening methods relating to pharmacokinetic properties.[1] Around 30% of attrition in 2000 was linked to toxicity and safety-related properties.[3,7] Between 2008 and 2010 the most significant reasons for attrition were reported as lack of efficacy, strategy-related reasons and safety issues.[3]

A study conducted in 2008 reported a correlation between low total polar surface area (TPSA) and adverse toxicity-related outcomes, presumably due to the distribution properties of these compounds. Blood brain barrier penetration (predicted using *in silico* methods) was also used as a measure of membrane permeability and was also shown to correlate with the frequency of adverse toxicological outcomes, however further information was not provided. Compounds with a high *c*logP were also associated with adverse effects. Overall, it was concluded that compounds displaying a high *c*logP (>3) and a low TPSA (<75 $Å^2$) were more likely (by a factor of 2.5) to result in adverse outcomes.[8] The selection of optimal drug

candidates, which demonstrate good pharmacokinetic and pharmacodynamic properties as well as low toxicity, is therefore paramount to ensure that attrition rates will diminish in the future.

1.2 Molecular properties and structural features in drug discovery

The synthesis and development of drug candidates with suitable physicochemical properties is extremely important in ensuring a decrease in attrition rates. Therefore, the relationship between structure and properties has been investigated and subsequent models have been proposed. The most well-known of these was introduced by Lipinski and is known as the 'rule of five' which relates to orally bioavailable drug molecules and is summarised in table 1.1. This rule predicts that if a compound has more than 10 H-bond acceptors, 5 H-bond donors, a molecular weight of over 500 Da and a larger logP than 5, then it is more likely to exhibit lower permeation or absorption.[9]

Table 1.1: An overview of Lipinski's 'rule of five'.

Property	Value in which lower permeation/absorption is likely
Molecular weight	>500 Da
LogP or MLogP[a]	>5 or 4.15
H-bond acceptors	>10
H-bond donors	>5

[a]MLogP = calculated LogP using the rule-based Moriguchi computational method.[9]

A study was also conducted that investigated the impact of compounds containing aromatic rings on several development parameters, including lipophilicity and aqueous solubility, using a large database of compounds from the GSK corporate collection. Table 1.2 presents the number of candidates in each stage of the GSK drug development pipeline and the average aromatic ring count per molecule for each stage. A decreasing trend in mean aromatic ring count was observed further along the drug development pipeline.[10] This suggests that aromatic ring count may affect

the likelihood of a drug candidate reaching the market. A related study was carried out by Lovering *et al*, in which the fraction of sp^3 hybridised carbon atoms (Fsp^3) for compounds at different stages in the drug development process within the GVK BIO database were analysed. A complementary trend was reported to that relating to aromatic ring count, where Fsp^3 was shown to increase with clinical progression.[11] These findings therefore highlight that saturation and the number of sp^3 carbon atoms are key factors determining the success of drug molecules in the drug development process.

Table 1.2: The number of aromatic rings present in GSK's drug molecules during each stage of the drug development pipeline, adapted from Ritchie *et al*.[10]

Stage of drug development pipeline	**Number of molecules**	**Mean number of aromatic rings per molecule**
Preclinical candidate selection	50	3.3
First time in human	68	2.9
Phase 1	35	2.5
Phase 2	53	2.7
Proof-of-concept	96	2.3

Ritchie and co-workers additionally reported that an increase in the number of aromatic rings correlated with less desirable molecular properties. Increasing aromatic ring count resulted in adverse effects in terms of limiting solubility by increasing *c*logP.[10] A summary of these trends is presented in table 1.3. Comparatively, Fsp^3 was shown to increase with logS and decrease with increasing melting point.[11] Furthermore, it was reported that increasing aromatic ring count also led to an increase in serum albumin binding (a crude measure of the free fraction of a drug), P450 inhibition (mechanisms which can cause pharmacokinetic drug-drug interactions) and was linked with hERG activity (hERG channel inhibition which can cause cardiotoxicity).[10]

Table 1.3: A summary of the impact of aromatic ring count on various physicochemical parameters of compounds in the GSK pipeline, adapted from Ritchie *et al*.[10]

Aromatic ring count of compounds in the GSK pipeline	**Mean aqueous CLND solubility of compounds in the GSK pipeline (μg mL^{-1})**	**Mean *c*logP of compounds in the GSK pipeline**
1	100	1.9
2	79	2.9
3	57	3.7
4	36	4.4
5	28	5.1

An increase in saturation can also lead to enhanced 3-dimensionality, and this geometry of the central scaffold has been suggested to influence the overall shape-space coverage. A study reported a link between overall shape-space coverage and biological activity, through the assessment of collections of known bioactive compounds (e.g., MDDR - MDL drug data report database).[12] Principal moments of inertia plots (PMI) are frequently used to assess the 3D diversity of compound libraries and are generated by analysing each molecule's lowest energy conformation.[13] Molecules are assessed on their 'rod-like', 'disk-like' and 'sphere-like' nature and then normalised to provide PMI ratios (NPR1 and NPR2) which can then be plotted in 2D to construct a triangular plot. Existing fragment libraries, and their respective PMI plots, generally demonstrate low 3-dimensionality, such as those representing commercial fragment space, with most fragments lying on or close to the rod-disk-like axis. Figure 1.2 showcases an exemplar PMI plot representing the foundation library of approximately 170 compounds, selected by Morley *et al,* with interesting scaffolds highlighted (**1**-**3**). Although the selected fragments cover most of the PMI triangle in this case, a preference for those qualifying as 'flat' was still observed (NPR1 + NPR2 < 1.1 for 70% of fragments). Therefore, efforts to synthesise more 3D-like scaffolds are vital to the success of fragment-based drug discovery.[13]

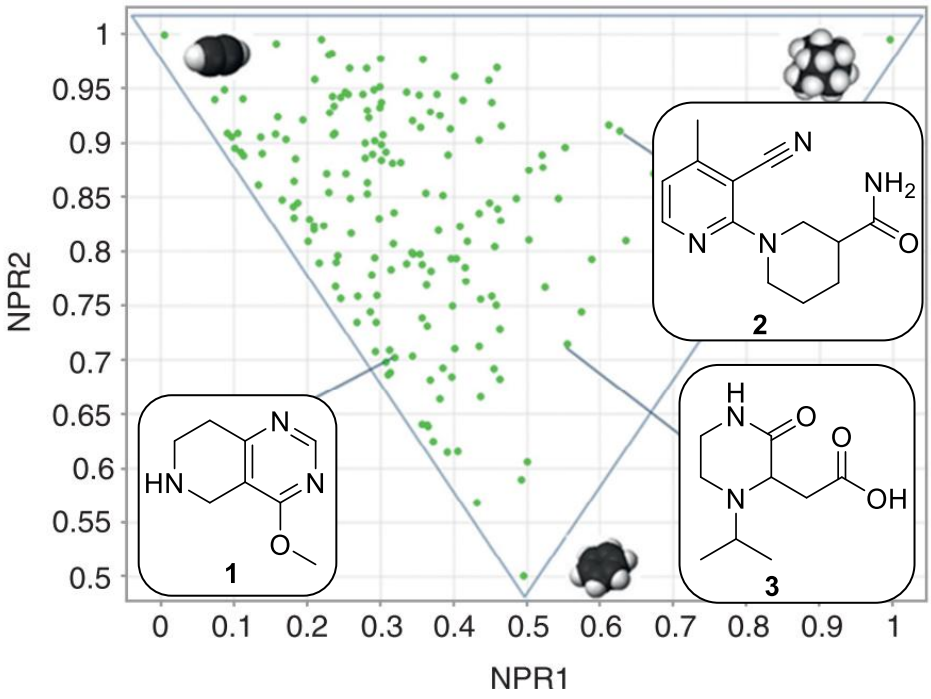


Figure 1.2: An exemplar PMI plot and associated structures, depicting the foundation library of approximately 170 compounds as reported by Morley *et al*.[13]

1.3 Saturated *N*-heterocyclic motifs in drug discovery

Saturated nitrogen heterocycles are prevalent subunits of many pharmaceutically relevant compounds due to being highly sp^3-rich in nature and exhibiting desirable biological activity. It has been shown that more than 85% of biologically active compounds are heterocyclic and almost 60% of small-molecule drugs contain a *N*-heterocycle. Furthermore, these cores are frequently present in natural products including vitamins, hormones, and antibiotics.[14,15] Within drug molecules and bioactive compounds, these cores are often highly functionalised, and comprise complex and polycyclic ring systems. Spirocyclic systems amongst other three-dimensional polycyclic structures are also often present, as illustrated by exemplar drug molecules **4**-**8**, bearing spiro, bridged and fused systems, presented in figure 1.3.[16,17,18,19] Methods that allow rapid access to these types of diverse small cyclic amine cores are therefore invaluable.

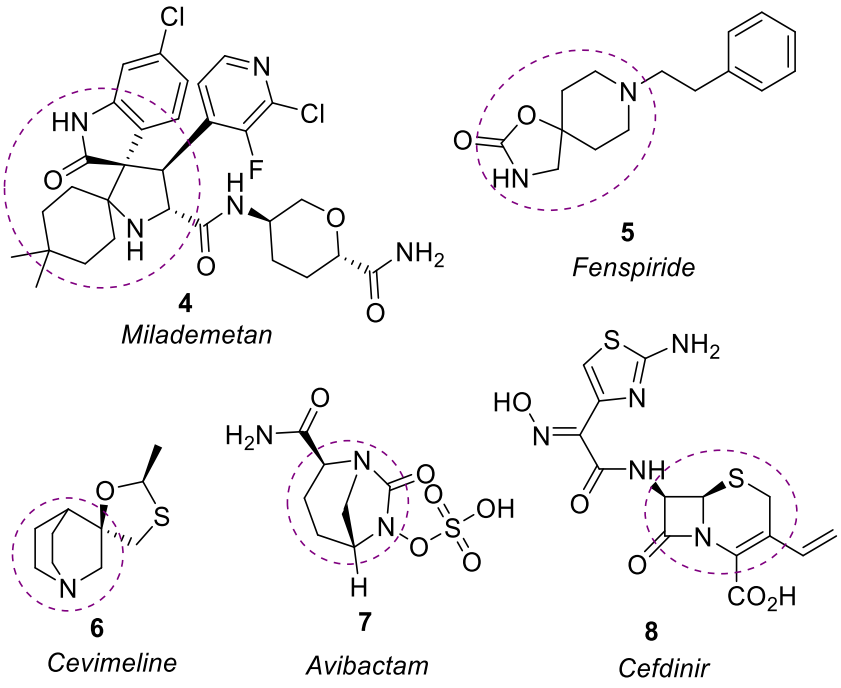


Figure 1.3: Examples of drug candidates showcasing polycyclic *N*-heterocyclic cores consisting of those which are spirocyclic, bridged and fused ring systems, as highlighted.[16,17,18,19]

The introduction of highly three-dimensional polycyclic motifs and therefore enhanced Fsp^3 can result in desirable improvements in terms of physicochemical properties, especially relating to lipophilicity and solubility.[18] In 2008, a peak in the number of medicinal chemistry publications featuring 'spiro' as the key word was observed, coinciding with Lovering's[11] 'escape from flatland' review that suggested a trend between high Fsp^3 and clinical candidate success.[18] For example, Degorce *et al* demonstrated this by comparing and contrasting the resulting physicochemical properties when exchanging a morpholine motif with its analogous spirocyclic azaspiroheptane (figure 1.4). Spirocyclic azaspiroheptane **10** exhibited a higher basicity and lower lipophilicity than the non-spirocyclic morpholine-containing analogue **9**. These differences resulted in an improved ligand-lipophilicity efficiency (LLE).

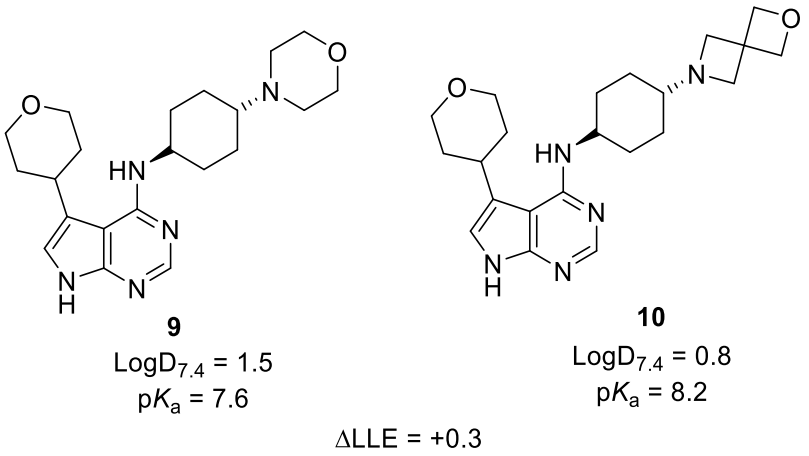


Figure 1.4: A comparison of the physicochemical properties of the morpholine and azaspiroheptane motifs as reported by Degorce *et al*.[20]

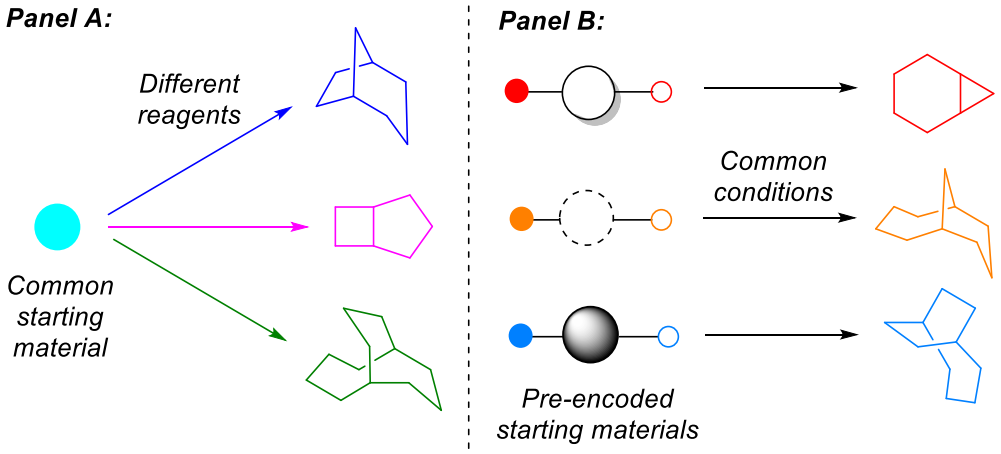
1.4 Methods for drug screening and discovery

Traditional drug discovery screening methods include high throughput screening (HTS), fragment-based drug discovery (FBDD), structure-based drug design (SBDD) and DNA-encoded library screening (DEL).[21] HTS plays a significant role in the discovery of new drug molecules and focuses on screening large databases of random compounds. SBDD concerns *in silico* screening of compound collections and involves the target protein 3D structure. FBDD utilises smaller libraries of compounds with low molecular weights (<200 Da) that are screened at higher concentrations. In more recent years, DEL approaches have also been employed, which allow rapid and efficient screening of very large libraries through the conjugation of small molecule compounds to DNA tags.[21,22] These traditional screening methods can be accelerated *via* the inclusion of diversity and lead oriented syntheses (DOS/LOS) as described below:

1.4.1 Diversity oriented synthesis (DOS)

Diversity oriented synthesis (DOS) aims to enable the efficient synthesis of a range of structurally diverse and complex molecular scaffolds, facilitating chemical space

exploration.[23] Perhaps the simplest, most frequently employed approach for the introduction of diversity is the synthesis of a complex building block that is then divided and used to conduct reactions in parallel with different reactants so that different functionalities can be incorporated (scheme 1.1, Panel A). [23,24,25] Stereochemistry can also be manipulated to create diversity, and each synthesised stereoisomer of a building block will therefore explore chemical space in a unique way.[23,25] A more complex but effective approach requires branching points; at which a building block is divided up and carried through different reactions, or a series of reactions, to attain products which are diverse in terms of functionalities and skeletal arrangements.[23,26] Finally, substrate-based approaches can also be employed, in which applying common conditions to pre-encoded starting materials can result in skeletal diversity (scheme 1.1, Panel B).[25]



Scheme 1.1: A summary of key DOS approaches adapted from Galloway *et al.*[25] Panel A: the reagent-based approach towards scaffold diversity through the employment of a common starting substrate and different reagents or conditions. Panel B: The substrate-based approach towards scaffold diversity where common conditions are applied to pre-encoded starting substrates, resulting in distinct molecular skeletons.

1.4.2 Lead oriented synthesis (LOS)

Lead-oriented synthesis (LOS) focuses on the development of molecules that are suitable to be used in the drug discovery process and therefore demonstrate 'lead-like' molecular properties. Figure 1.5 illustrates this lead-like chemical space in comparison with fragment space, optimal drug-like space and the Lipinski rule of five

(Ro5) limits.[9,27] The process of lead optimisation from a lead-like compound to a drug molecule often results in an increase in molecular weight and *c*logP as modifications are required to enhance potency and to deliver appropriate properties. Therefore, by designing compounds that lie in this lead-like chemical space, the desired molecular properties after lead-optimisation should be achievable.[27]

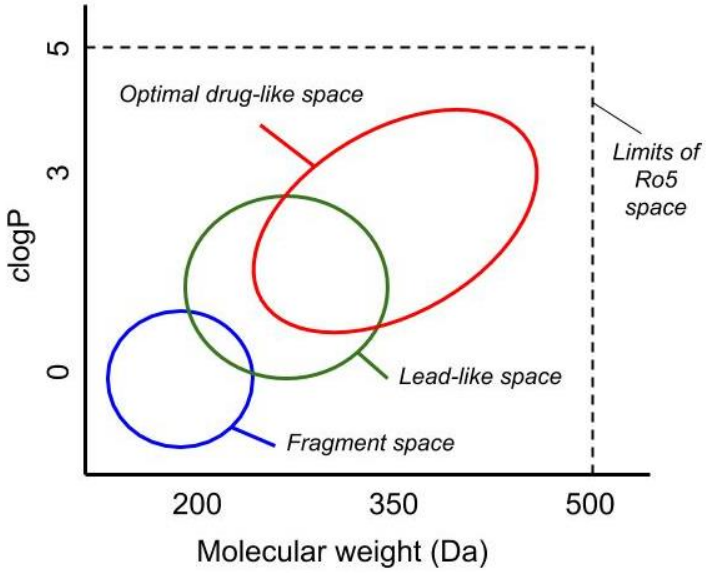
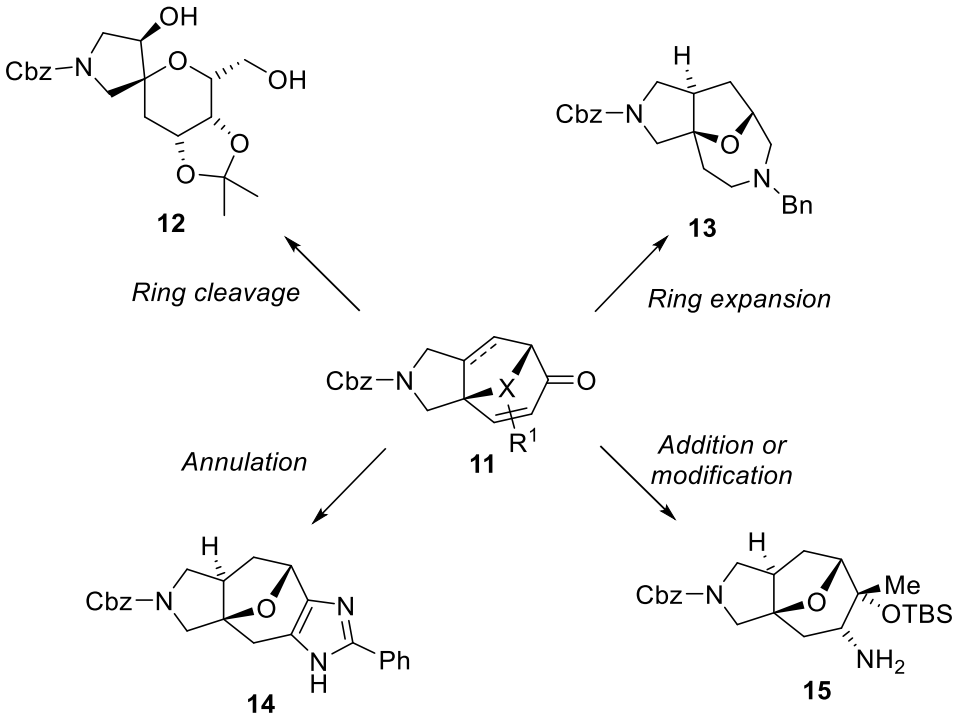


Figure 1.5: An illustration of fragment, lead-like and optimal drug-like space in terms of *c*logP and molecular weight, adapted from Churcher *et al*.[27]

There are several important requirements that lead-oriented syntheses should meet. These include the ability to efficiently deliver diverse, lead-like structures, using affordable reagents and array-compatible conditions. A range of polar functional groups should be tolerated and molecules with residual reactive centres should not be produced. Finally, logP drift tendencies should not be exhibited; a feature where an array's profile can shift to favour more lipophilic compounds, caused by the failure of more polar compounds, either due to the chemical or purification methods used.[27]

An example of a LOS approach was described by Foley *et al*, in which a 'top-down' strategy for the diverse synthesis of complex natural product-like compounds was employed.[28] This type of approach requires a complex scaffold which can be broken down in a variety of ways to efficiently prepare a range of diverse structures. Scheme

1.2 presents an overview of this strategy, in which a library of 26 sp^3-rich compounds that occupy lead-like chemical space was produced. General scaffolds **11** were constructed *via* intramolecular [5 + 2] cyclisation reactions and subsequently converted into natural product-like structures **12**-**15**, using various chemistries. This toolkit of reactions included ring cleavage, ring expansion, annulation and addition or modification methods, which enabled a diverse range of structurally unique scaffolds to be accessed. 'Bottom-up' approaches have also been devised which differ by employing small building blocks exhibiting numerous reaction handles. These can then be built up into structurally complex scaffolds.[29]



Scheme 1.2: An overview of a 'top-down' LOS strategy employed for the synthesis of a diverse range of lead-like scaffolds, adapted from Marsden and Nelson *et al*.[28]

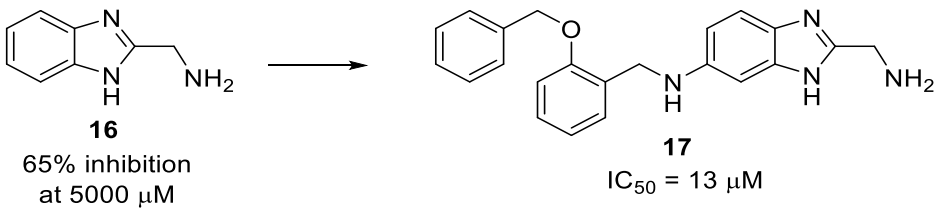
1.4.3 Fragment-based drug discovery (FBDD)

High throughput screening (HTS) approaches utilise and screen large libraries of compounds that are structurally complex and exhibit similar sizes to drug molecules. In more recent years, efforts have turned towards alternative screening methods as HTS often leads to low hit rates as well as limiting further optimisation of potential

hits. This is due to the screened compounds already displaying molecular complexity and occupying drug-like chemical space.[30]

Fragment based drug discovery (FBDD) instead employs small molecules that are termed as fragments. These are compounds that exhibit approximately 20 or fewer heavy atoms, therefore reducing the total possible number of molecules compared with other screening techniques, making the process more manageable. This means that chemical space can be more efficiently explored and hit rates are therefore often higher.[13,30] The comparatively low molecular weight of fragments to those seen in typical HTS hits means that successful fragments can be easily modified to enhance potency whilst still displaying desirable molecular weight and drug-like properties and maintaining ligand efficiency.[30] The small and simple nature of fragments when compared to lead-like compounds also means that binding affinities during screening, are much lower, and therefore require screening techniques of much higher sensitivity.[13]

The advancement of fragment hits to drugs usually occurs *via* three main methods: fragment growing, linking, and merging. Fragment growing is generally more successful when neighbouring binding sites on the protein are present, whereas fragment merging or linking is more challenging as it requires multiple binding sites near one another. An example of a drug molecule discovered by FBDD is presented in scheme 1.3. The (aminomethyl)benzimidazole core **16** was identified as a weak inhibitor of gelatinase B (MMP-9). Chemical elaboration led to the development of functionalised (aminomethyl)benzimidazole **17** which demonstrated a >100-fold increase in potency than the original fragment.[31,32]



Scheme 1.3: An example of initial fragment hit **16**, followed by elaboration to provide **17**, demonstrating a significant increase in potency.

1.5 The synthetic toolkit for small molecule discovery

PMI plots have been able to illustrate the bias towards fragments that exist on the disk-rod axis and therefore are flatter than desired (see figure 1.2). This can be explained in part by the limited synthetic toolkit employed in organic synthesis over recent decades where limited uptake of newly developed synthetic methods, except for Suzuki-Miyaura and Buchwald-Hartwig couplings, has been observed.[33,34,35,36] Figure 1.6 presents the 20 most employed reactions in 2014, clearly showcasing a strong bias towards certain reaction types, in particular; amide bond formation reactions and aromatic substitutions (S_NAr).[35]

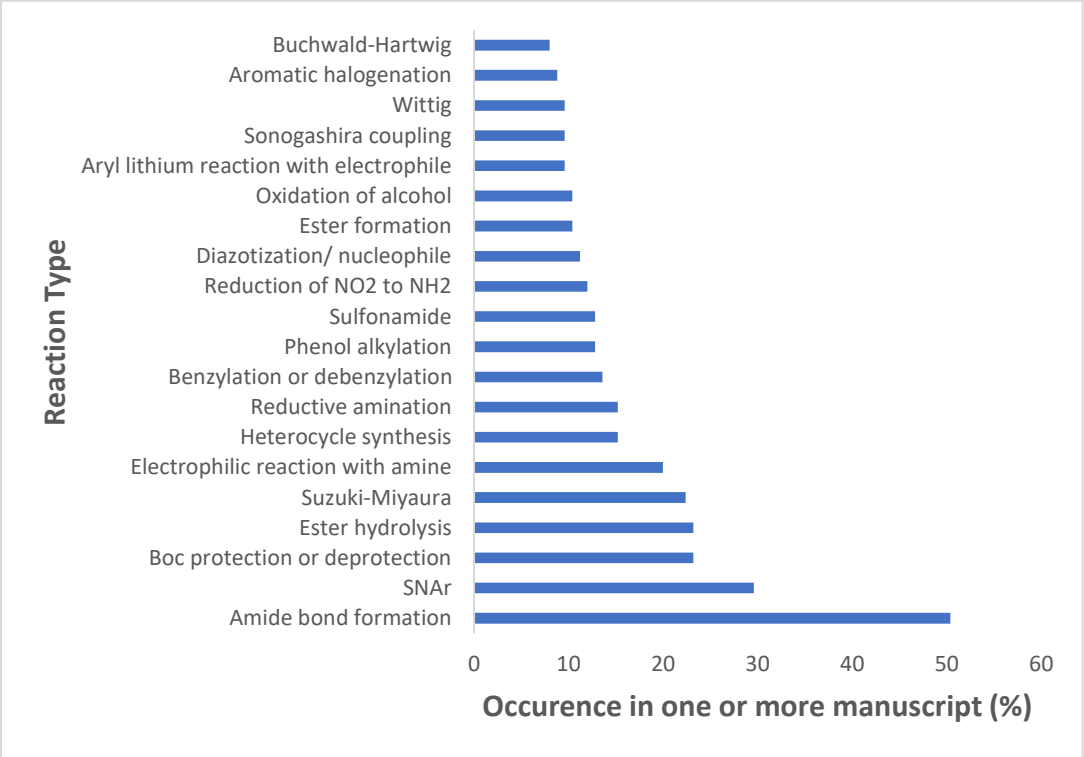


Figure 1.6: The frequency in which the 20 most employed reactions appear in at least 1 out of 125 manuscripts, adapted from Brown *et al*.[35]

Reasons for this bias have been linked to the preference for a narrow range of desirable and convenient experimental conditions, concerning reaction duration, solvent, temperature, and purification technique to enable adaptation to high-throughput platforms. Other factors include the functional group tolerance of reagents as well as time and productivity pressures within the industry.[37] In addition

to a limited range of reactions being employed in drug discovery, the preference for chemistry that favours the production of specific regioisomeric products has also been highlighted.[38]

The reliance on certain reaction types could explain the presence of fewer, less diverse molecular scaffolds. If fragment libraries were to contain compounds arising from a range of chemistries, then this may contribute to increased shape diversity. Böstrom and co-workers have suggested that the expansion of available building block collections would allow for the scope of popular reactions to be fully exploited.[34] Since 2009, AstraZeneca have focused on developing a collection of novel building blocks, including those which exhibit high Fsp^3 character, to address this through a 'strategic reagent initiative' (SRI). As a result, by 2015, SRI reagents had been employed in the generation of three candidate drugs as well as many shortlist candidates.[39]

1.6 Project aims and objectives

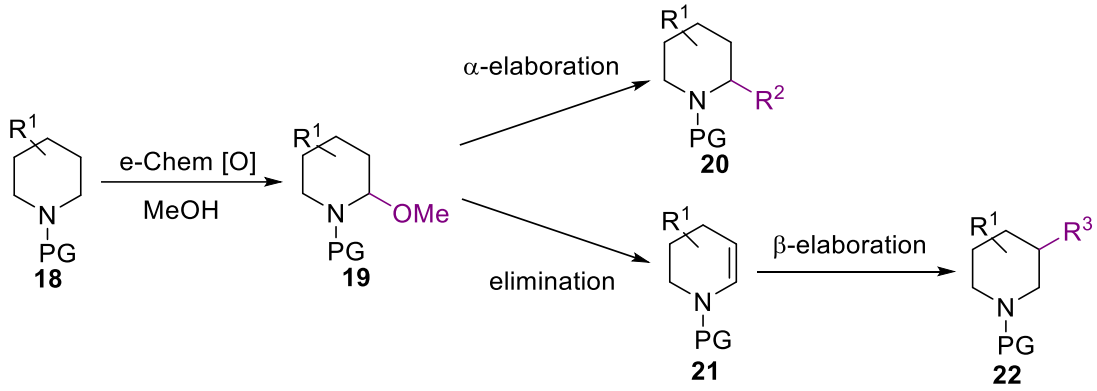
The overall project aim is the development of synthetic strategies for the construction of diverse, highly three-dimensional, and valuable polycyclic scaffolds, providing an efficient means of chemical space exploration. To achieve this, these strategies will share common key intermediates accessed from simple and readily-available precursors. We plan that the subsequent application of a toolkit of elaboration methodologies, mostly employing photoredox catalysis, will allow the generation of a library of diverse and lead-like structures. From these aims, four main project objectives can be identified as discussed below:

Objective one: Synthesis of an enecarbamate and hemiaminal ether-based building block library:

The first objective concerns the preparation of a library of hemiaminal ether and enecarbamate-based building blocks as illustrated in scheme 1.4. It is proposed that these will be accessed directly from their corresponding simple and affordable saturated amines, therefore providing a highly desirable route towards building blocks of varied ring sizes and substitution patterns. This synthetic approach comprises of a key anodic (electrochemical) oxidation step, which has been well established in the literature,[40] providing significant value *via* the activation of a CH site and subsequent installation of a reactive handle for further elaboration.

Objective two: Development of a synthetic toolkit of α- and β-functionalisation strategies:

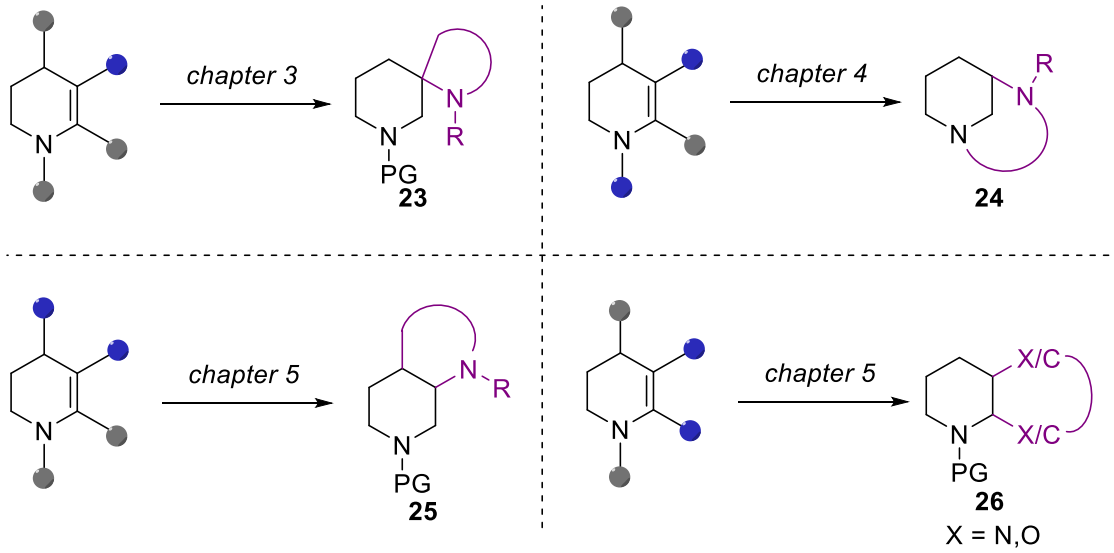
With a library of enecarbamate and hemiaminal ether building blocks in hand, a toolkit of α- and β-elaboration methodologies will be developed based mostly on previous chemistries from our group (scheme 1.4).[41,42] These methodologies should demonstrate good yields and a broad functional group tolerance including various substrate ring sizes and substitution patterns. We propose that this will provide a unified and efficient strategy for the library generation of decorated scaffolds.



Scheme 1.4: The proposed synthesis of a building block library of hemiaminal ethers **19** and enecarbamates **21** from simple and affordable precursors **18**. The development of a toolkit of α- and β-functionalisation strategies can then take place to afford decorated scaffolds **20** and **22**.

Objective three: Synthesis of novel and 3D-polyclic scaffold libraries:

The developed toolkit of β-elaboration strategies for enecarbamates, can then be implemented in the construction of complex and sp^3-rich polycyclic scaffolds. We envisage the preparation of four diverse key scaffolds as summarised in scheme 1.5. Chapters three, four and five will discuss the synthesis of spirocyclic, bridged and fused scaffolds **23**, **24** and **25** *via* sequential application of β-functionalisation and cyclisation. Chapter five will also report annulative strategies facilitating direct and simultaneous elaboration of multiple vectors, efficiently introducing complexity and the construction of complementary fused scaffolds **26**. The modular nature of this synthetic approach means that variation in both the original and appended rings can be easily and efficiently achieved, generating the delivery of a library of diverse and potentially lead-like compounds.



Scheme 1.5; The proposed modular application of β-elaboration methods of enecarbamates (objective two) towards the construction of novel, sp^3-rich and diverse polycyclic scaffolds (objective three).

Objective 4: Assessment of scaffold properties and evaluation of biological activity:

The last objective is to analyse interesting physical and biological properties of the prepared scaffold libraries. Related bicyclic and bridged ring systems to **24** often demonstrate unusual perturbation of nitrogen lone pair and π-system overlap, and

therefore deviated reactivity. This will be probed *via* analysis of the scaffolds' physical properties including pK_aH measurements. Finally, the application of aminal-bearing scaffolds **26** in chemical proteomics will be explored, and associated biological value assessed. More specifically, their use as potential novel warheads, resulting from suspected electrophilic and covalent reactivity, will be investigated.

2 Chapter 2: Synthesis of enecarbamates and their functionalisation

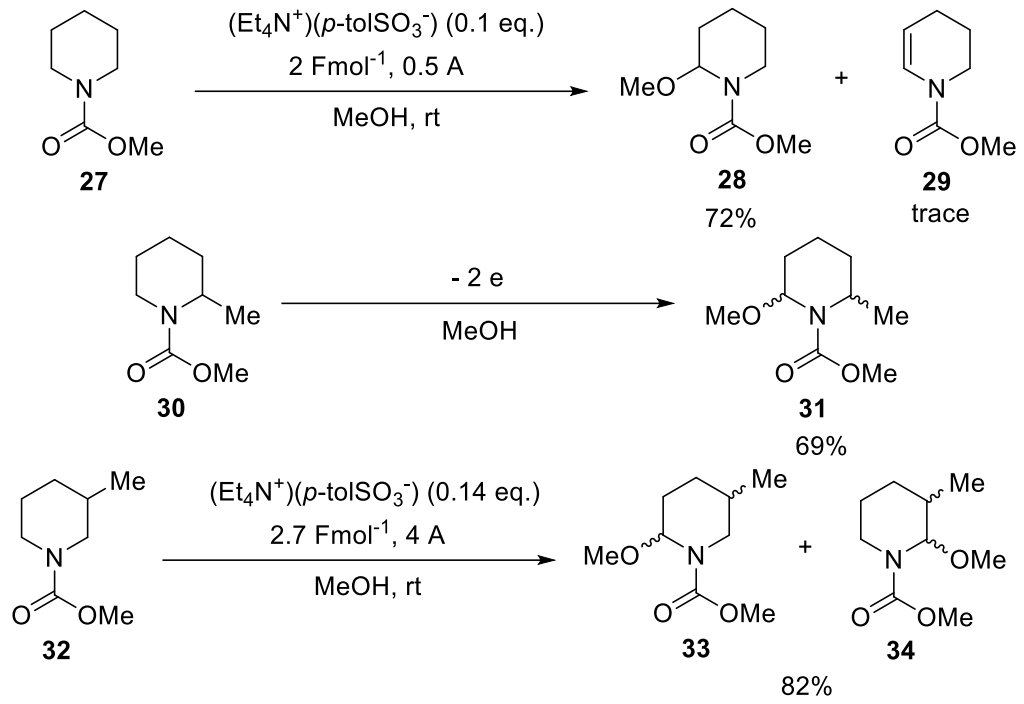
2.1 Background

2.1.1 Electrochemical anodic oxidation

Electrochemical anodic oxidation is a valuable tool used for the oxidation of simple acyclic and cyclic amides and carbamates. The installation of an α-OMe group to *N* allows facile elaboration of the products and is an effective C-H functionalisation method, advantageous to alternative strategies where preinstallation of a reactive handle is required. It is therefore applicable to simple and affordable *N*-containing saturated heterocycles as a mode of efficiently adding molecular complexity.

The first electrochemical anodic oxidation of methyl *N*-alkyl cyclic and acyclic substituted carbamates, was carried out by Shono,[40] employing an electrolyte in methanol at rt to yield the α-methoxylated carbamates, conducted using an electrolysis cell that was fitted with two carbon electrodes. Scheme 2.1 presents an example, where the anodic oxidation of *N*-carbomethoxypiperidine **27** in methanol at a constant current of 0.5 A gave the α-methoxy product **28** in a high yield of 72% after a Faraday conversion of 2 F mol^{-1} had passed. In some cases, enecarbamate-type products were isolated as by-products (e.g., **29**).[40] Efforts have also been made to investigate whether other *N*-functionalities can be tolerated in this methodology, for example, the successful tolerance of cyclic and acyclic *N*-Ac amines and

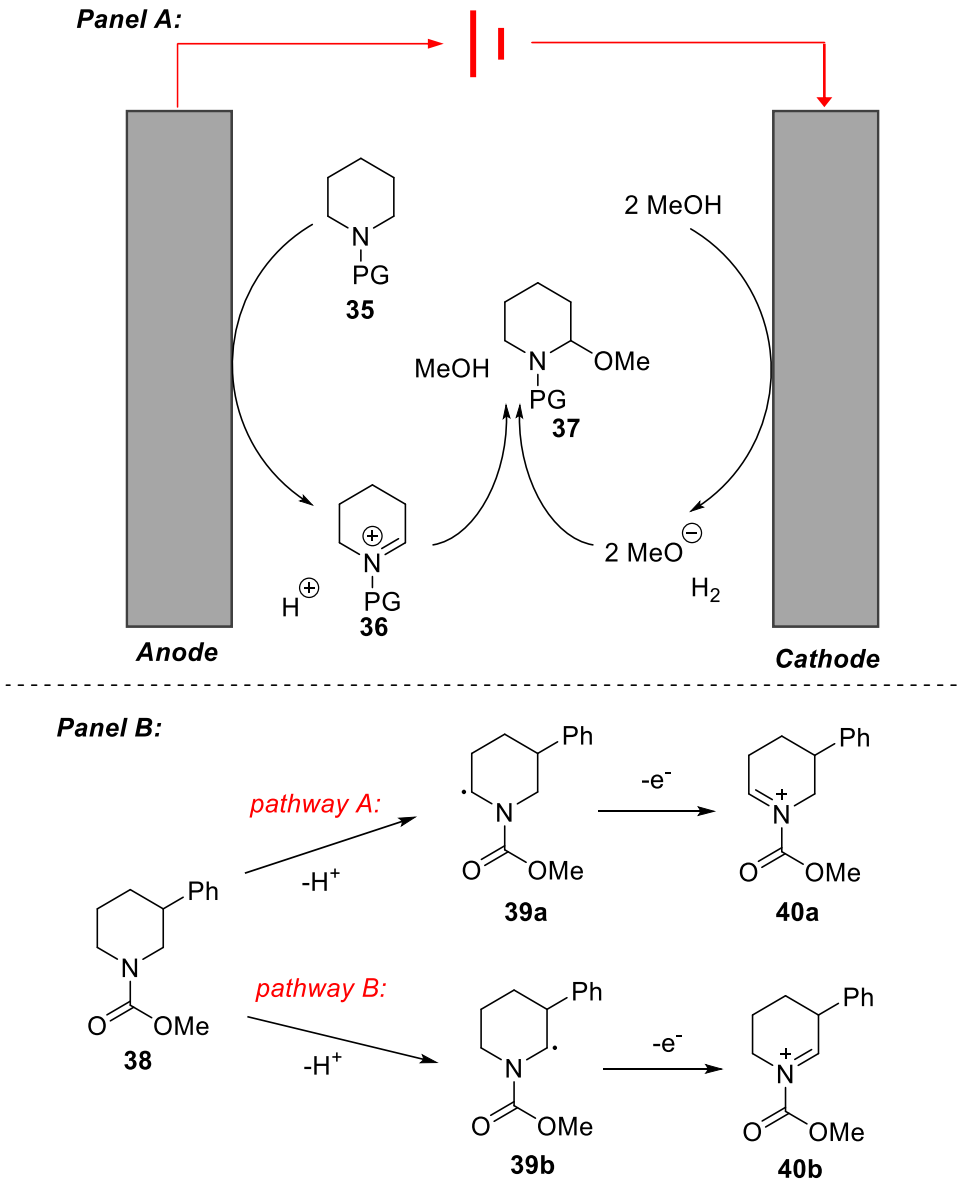
sulfonamides.[43,44,45,46] Shono has additionally investigated the use of unsymmetrical α-substituted substrates. For example, oxidation of 2-methyl-*N*-carbomethoxypiperidine **30** gave the less substituted α-methoxy product **31**, as a single regioisomer, in a good yield (69%, scheme 2.1).[47] Shono and Libindi *et al* have also investigated the oxidation of 2-substituted *N*-functionalised pyrrolidines and piperidines which were shown to proceed with full regioselectivity in high yields. Previous work carried out in our group also observed the preferential formation of the less-substituted 2,n-aminoacetals.[43,48,41] Anodic oxidation of 3-substituted *N*-carbomethoxypiperidines was also performed and resulted in regioisomeric mixtures, favouring the formation of the less-substituted isomer. For example, 3-methyl *N*-carbomethoxypiperidine **32** led to the formation of α-methoxylated products **33** and **34**, where conversion to the corresponding enecarbamates resulted in a 64:36 mixture of regioisomers in a 96% yield (**33** and **34** were isolated in an 82% yield, ratio unspecified).[43] Related work has also been carried out within our research group showcasing similar regioselectivity (2:1) for a 3-methylated analogue of carbamate **32**, after conversion to their respective enecarbamates, whereas those bearing alternative 3-substituents (e.g., Ph, CO_2Me) produced only single regioisomeric products (see scheme 2.3).[41]



Scheme 2.1: Examples of electrochemical oxidation reactions performed in the literature employing cyclic carbamates.[40,47,43]

Scheme 2.2 presents an overview of the anodic oxidation mechanism within an undivided cell setup (panel A). This schematic is also applicable to the use of the IKA Electrasyn setup, an example of a commercialised undivided cell often employed in modern accounts of anodic oxidation, including those published within our group[41] (see section 2.2.2 for experimental details), for its ease of use and high reproducibility.[49] Initial oxidation of carbamates or amides **35** takes place at the anode, liberating a proton *in situ* and generating a radical cation at *N*. Then, deprotonation affords the neutral radical and a second oxidation gives acyliminium ion **36**. This can then be trapped with methanol producing the hemiaminal ether product **37**.[49,50] Trindade *et al*,[41] within our research group, have recently sought to rationalise the regioselective outcome, observed for 3-substituted systems, discussed previously, using DFT calculations. Two proposed mechanistic pathways for the formation of each regioisomer are presented in scheme 2.2, panel B. Following formation of the radical cation at *N*, proton loss affords α-amino radicals **39a/b**

generated *via* either pathway A or B, prior to further oxidation to the corresponding acyliminium ions **40a/b**.

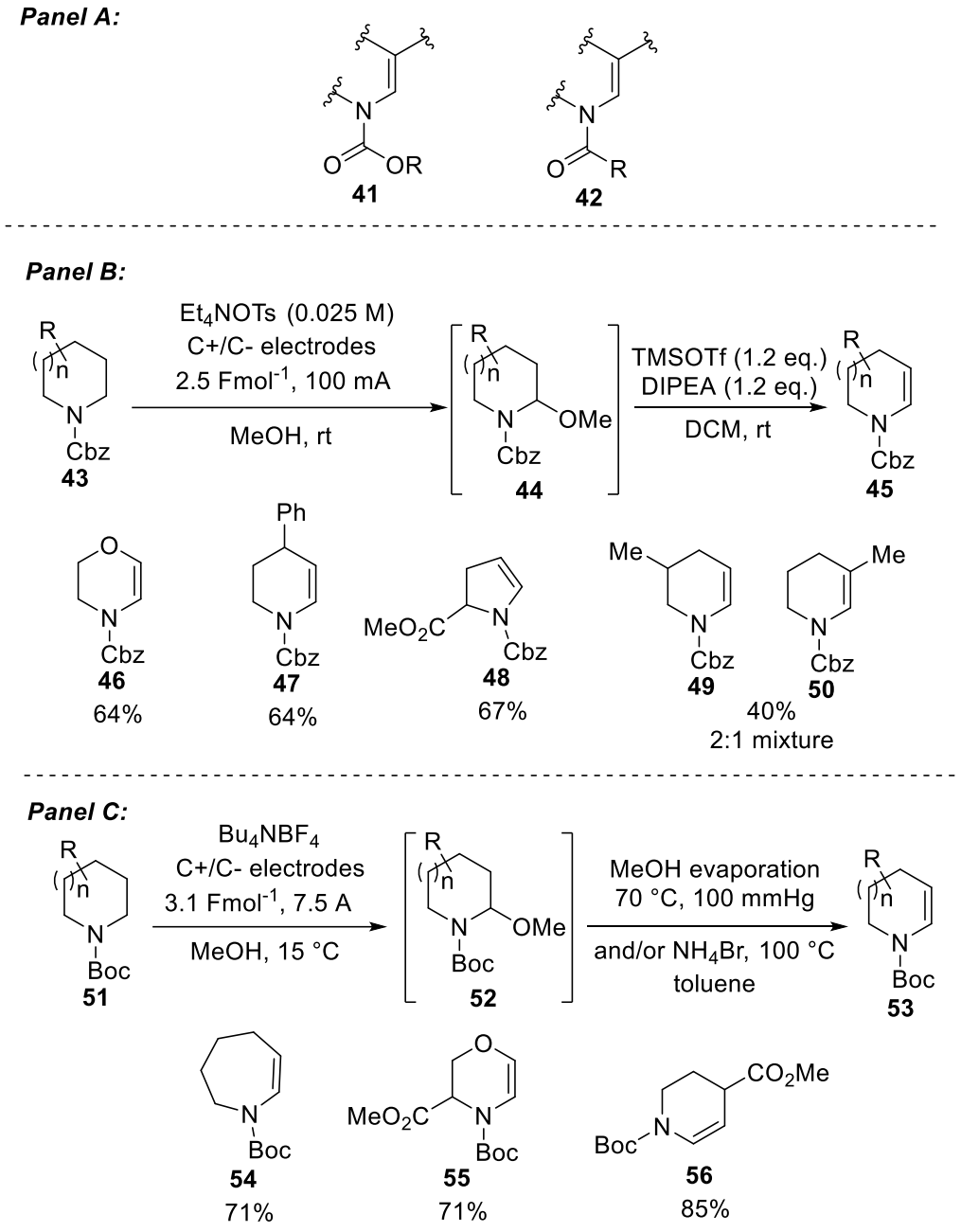


Scheme 2.2: A schematic of the electrochemical oxidation mechanism taking place in an undivided cell setup (panel A) and mechanistic rationale for the formation of regioisomeric products (panel B).[49,41]

2.1.2 Synthesis of enecarbamates from hemiaminal ethers

Hemiaminal ethers, accessed *via* anodic oxidation can easily undergo Lewis acid-mediated α-substitution chemistry as explored significantly within the literature[51,52] (*vide infra*), or alternatively converted to their respective enecarbamate and enamides (exemplar enecarbamate and enamide structures **41** and **42** are provided in scheme 2.3, panel A). The latter allows instead for elaboration through both the β- and γ-vectors, though methods for these are limited in the literature despite the development of a toolkit of sp^2 C-H functionalisation methodologies.[53]

Work carried out in our group by Trindade *et al*[41] has focused on a one-pot direct conversion from saturated cyclic carbamates to their respective enecarbamates *via* the formation of the hemiaminal ether intermediates discussed previously. Treating intermediate hemiaminal ethers **44** with TMSOTf and DIPEA in DCM at rt readily afforded the corresponding enecarbamates **45** in mostly high yields (scheme 2.3, panel B). A broad scope of *N*-Cbz heterocyclic amines including a range of ring sizes could be tolerated including the presence of β-heteroatoms and appended functionalities such as arenes and esters (e.g., **46** ,**47** and **48**). 2-, 3- and 4-Substituted substrates could also be tolerated with usually good regioselectivity, where applicable, as discussed previously (e.g., **47**, **48**, **49** and **50**). Tereshchenko *et al*[54] also reported a similar strategy, where following electrolysis, intermediate hemiaminal ethers **51** underwent elimination either by solvent evaporation at 70 °C and 100 mmHg and/or by treatment with NH_4Br in toluene at 100 °C (scheme 2.3, panel C). This allowed the preparation of *N*-Boc enecarbamates **53** varying in ring size, ester, and heteroatom inclusion (e.g., **54**, **55** and **56**) and tolerated carbamates bearing 2- and 4-substituents (e.g., **55** and **56**). Some examples of methods for the synthesis of enecarbamates from alternative starting substrates have also been reported in the literature including those employing lactams[55,56] (*vide infra*) in addition to a recent account of their direct preparation from the corresponding saturated cyclic carbamates *via* organic photoredox catalysis.[57]



Scheme 2.3: General exemplar structures of enecarbamates and enamides (panel A). Synthesis of enecarbamates from their corresponding hemiaminal ether intermediates as reported by Trindade *et al*[41] (panel B) and Tereshchenko *et al*[54] (panel C), with exemplar enecarbamate products provided to illustrate the reaction scopes. Yields are reported over two steps.

2.2 Synthesis and functionalisation of enecarbamates

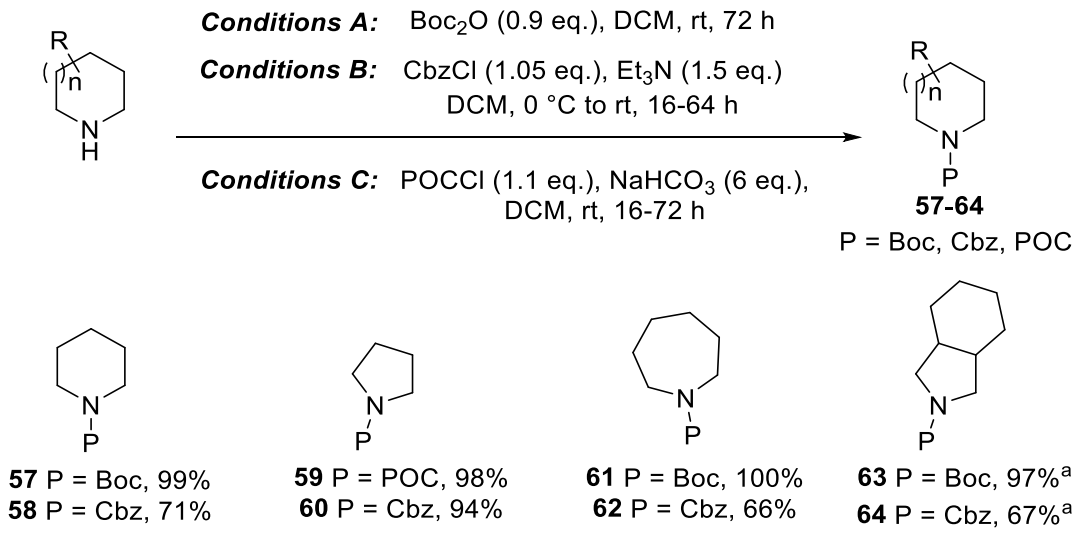
2.2.1 Introduction

We decided to employ Shono's[40] electrochemical oxidation methodology as the pivotal step in the synthesis of enecarbamates due to its ability to transform otherwise unreactive simple and affordable saturated carbamates into valuable building blocks. Following this with Brønsted acid-mediated elimination methodology[54] would easily allow the preparation of a library of enecarbamates (*N*-Cbz and *N*-Boc) suitable for further elaboration. Cyclic enecarbamates would be focused on due to the importance of highly 3D, saturated *N*-containing heterocycles in pharmaceutical compounds and so it was planned that a library of enecarbamates based on a variety of ring sizes and functionalised ring systems would be prepared. A toolkit of functionalisation methodologies would then be employed for enecarbamate decoration and construction of novel and valuable 3D scaffolds.

2.2.2 Synthesis of enecarbamates *via* electrochemical anodic oxidation

Initially, *N*-functionalisation of the desired saturated cyclic amines was required and it was decided that this would be carried out with predominantly Cbz and Boc groups. This was due to their convenient means of installation and removal, as well as use in related scaffolds prepared previously in the group.[42,41] The inclusion of a POC (propargyloxycarbonyl) protecting group was also decided for the delivery of products that could be employed in potential biological labelling experiments at a later stage. Scheme 2.4 presents an overview of the preparation of *N*-Boc, *N*-Cbz and *N*-POC carbamates **57**-**64** using a series of known literature procedures. Boc protection was achieved easily using Boc_2O in DCM at rt and Cbz protection using CbzCl and Et_3N in DCM at 0 °C to rt.[58,59] For bicyclic systems **63** and **64**, the corresponding starting amine was only available as the HCl salt and so conditions were modified to enable desalting by employing an excess of Et_3N in each case. POC protection was similarly achieved, using POCCl and $NaHCO_3$ in DCM at rt.[60] Success

of the reactions was determined by agreement of spectroscopic data with that reported in the literature for previously synthesised carbamates.[61,62,63,64,65,66]

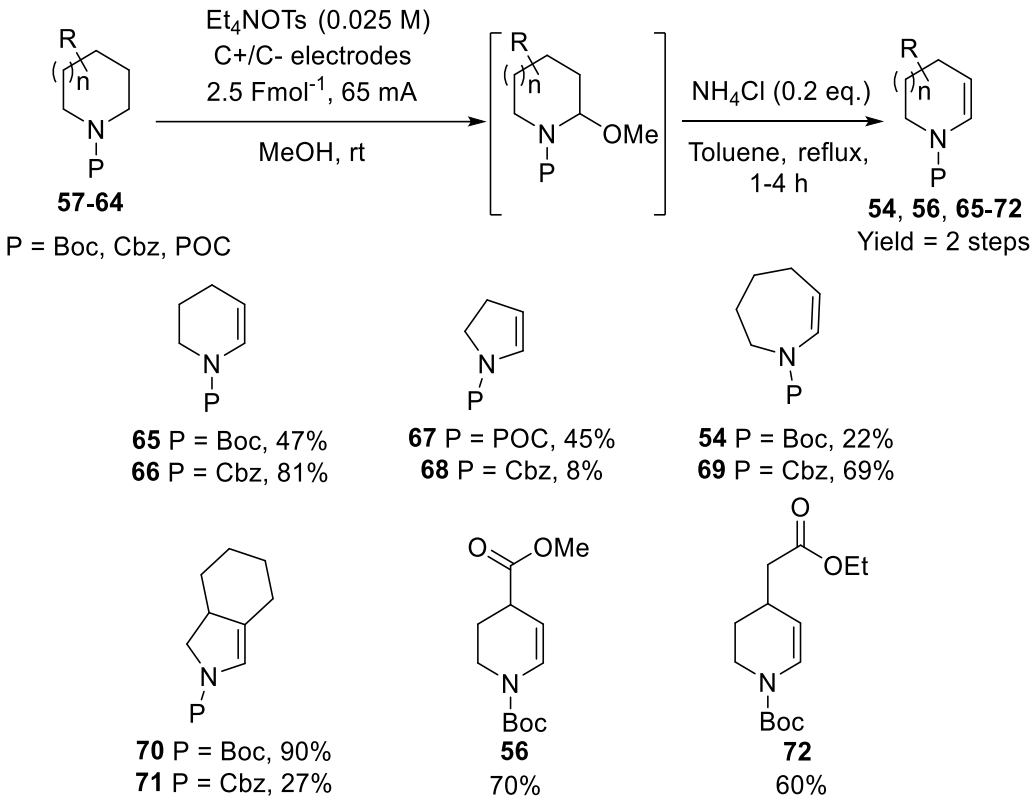


Scheme 2.4: Synthesis of *N*-Boc, *N*-POC and *N*-Cbz protected cyclic amines **57**-**64**. [a]Starting amine was purchased as the HCl salt and therefore conditions were modified. Modified conditions A: Boc_2O (1.2 eq.), Et_3N (2 eq.), DCM, rt, 72h. Modified conditions B: CbzCl (1.05 eq.), Et_3N (2.3 eq), 0 °C to rt, 16 h.

With cyclic carbamates **57**-**64** in hand, the analogous enecarbamates **54**, **56**, and **65**-**72** were prepared as summarised in scheme 2.5. For each example, the intermediate hemiaminal ethers were accessed *via* Shono anodic oxidation previously described and carried out in the group.[41] This was performed *via* treatment of the saturated carbamates with electrolyte Et_4NOTs in MeOH in a 10 or 20 mL Electrasyn-compatible vial (setup described in figure 2.1). The vial was then fitted to the Electrasyn 2.0 with a pair of graphite electrodes immersed in the solution. A constant current of 65 mA and excess of electrons (2.5 $Fmol^{-1}$) was then passed through the solution, whilst stirring, affording the crude hemiaminal ethers upon solvent removal. These were then immediately subjected to the elimination conditions, comprising of treatment with a Brønsted acid (NH_4Cl) in toluene at reflux until completion was determined by TLC (1-4 h).[54] Removal of the solvent and purification by column chromatography afforded the desired enecarbamates **54**, **56**, and **65**-**72** in mostly good yields. All carbamate protecting groups (*N*-Boc, *N*-Cbz, *N*-POC) were tolerated as well as varying ring sizes (scheme 2.5). An unusually low yield was observed for 5-ring *N*-Cbz

enecarbamate **68**, which was suspected to be due to product degradation, possibly by further oxidation to the *N*-Cbz pyrrole, although this was not observed for *N*-POC enecarbamate **67**. Furthermore ester-containing enecarbamates **56** and **72** could also be accessed in high yields (70% and 60%), presenting examples bearing additional points for functionalisation. Successful synthesis of each enecarbamate was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis and agreement with literature data for applicable compounds.[54,42,41,41] Diagnostic signals for the installation of the new alkene were easily identifiable as rotameric pairs of broad doublets at around δ_H 7.0–6.5 (2-H) and 5.0–4.5 (3-H).

These different elimination conditions, compared to those previously reported by our group (TMSOTf and DIPEA in DCM at rt, see scheme 2.3), were chosen since they were found to work with a wider range of substrates and be easier to perform practically.[41] Six and seven-membered *N*-Cbz enecarbamates **66** and **69** were successfully prepared using both sets of conditions; however, six-membered *N*-Boc enecarbamate **65** could only be accessed under the Brønsted acid-based conditions, presumably due to the sensitivity of the Boc group towards TMSOTf.



Scheme 2.5: Synthesis of enecarbamates **54**, **56**, and **65**-**72** *via* a one-pot sequential electrochemical anodic oxidation and elimination.

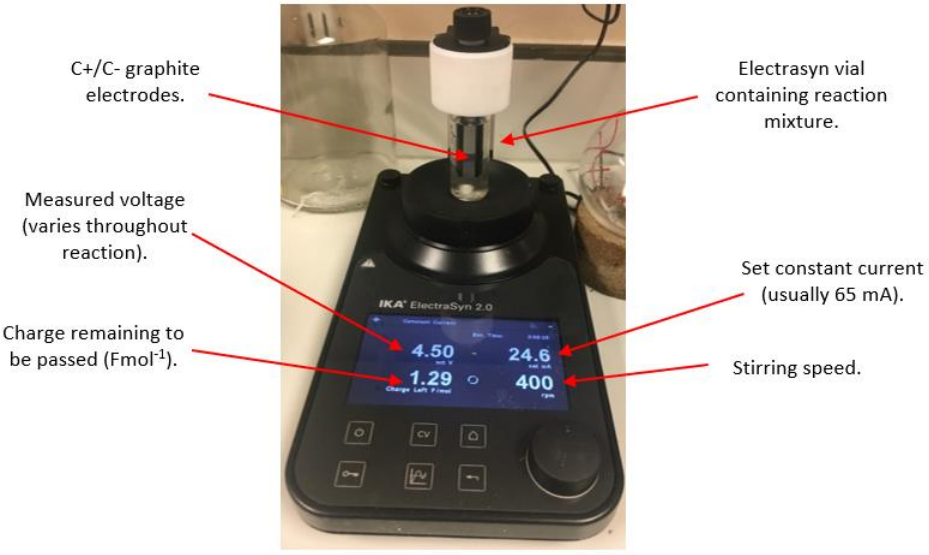
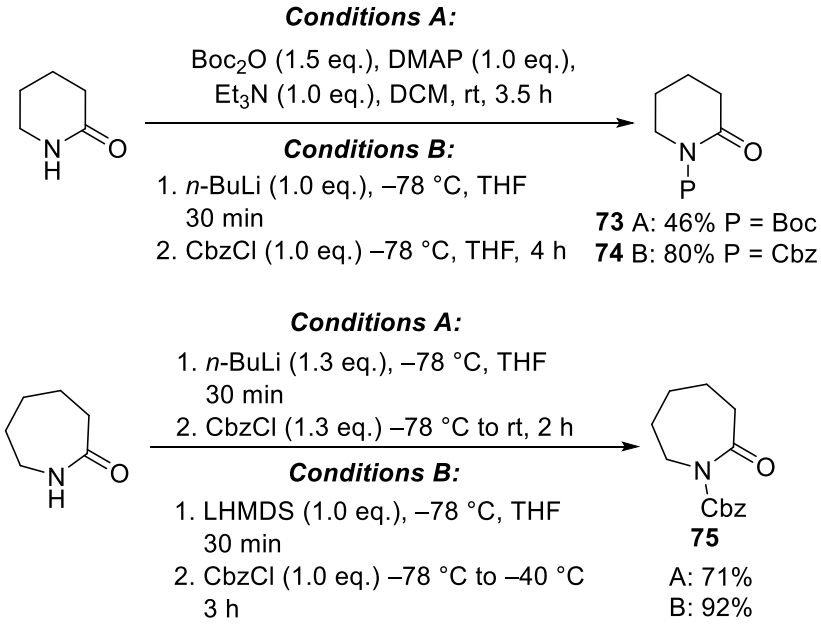


Figure 2.1: An annotated photograph illustrating the setup of the Electrasyn 2.0 kit employed for the anodic oxidation of cyclic saturated carbamates.

2.2.3 Complementary methods for the synthesis of enecarbamates

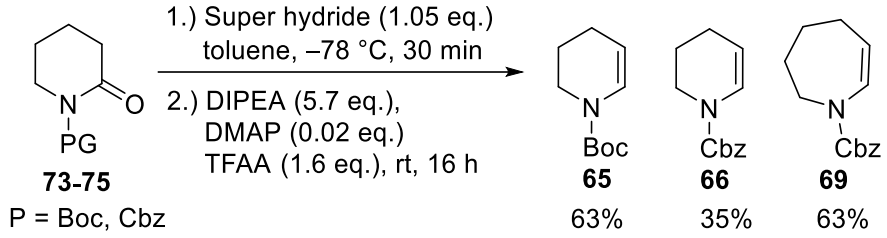
Enecarbamates can also be accessed from complementary methods described by Mudryk *et al*[55] and Sharma *et al*,[56] by subjecting protected saturated lactams to a reduction and elimination/dehydration-based sequence. As a comparison, we planned to synthesise several examples previously prepared *via* the electrochemical-based approach. To begin with, starting lactams were protected at *N* with Boc or Cbz as summarised in scheme 2.6. *N*-Boc lactam **73** was accessed *via* treatment with Boc_2O, Et_3N and DMAP according to a literature procedure.[67] *N*-Cbz 6-membered lactam **74** was prepared *via* deprotonation with *n*-BuLi and subsequent trapping with CbzCl at –78 °C in THF.[68] *N*-Cbz 7-membered lactam **75** was also synthesised *via* lithiation-trapping methodology in a good yield of 71%, however it was found that by employing LHMDS as an alternative base, an even higher yield of 92% could be achieved (scheme 2.6).[69,70] In all cases, reaction success was confirmed *via* the agreement of spectroscopic data with those reported in the literature.



Scheme 2.6: The *N*-protection of lactams **73**-**75**.

With *N*-Boc and *N*-Cbz lactams **73**-**75** in hand, we carried out the reduction and elimination procedure (scheme 2.7). Treatment of each *N*-protected lactam with

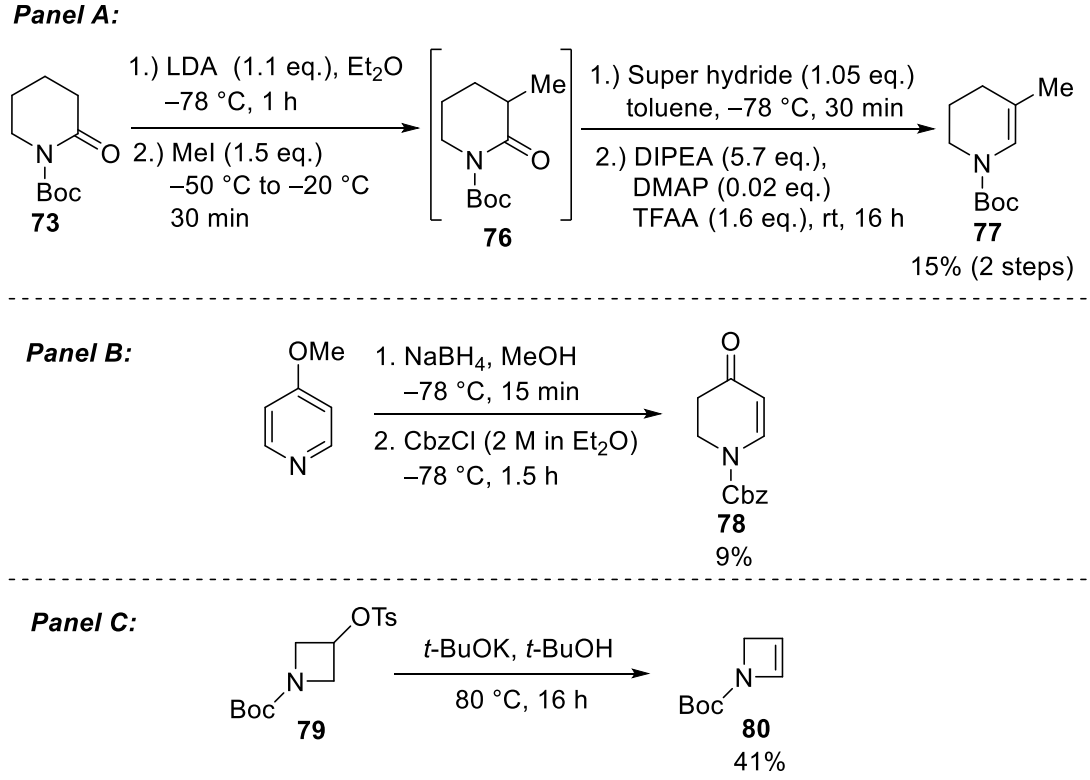
Super hydride© at –78 °C in THF for 30 mins followed by the subsequent, sequential addition of DIPEA, DMAP and TFAA afforded the corresponding enecarbamates **65**, **66** and **69** in moderate to good yields of 35-63%. This chemistry allows the use of complementary starting materials, as well as avoiding the necessity of specialist equipment such as the Electrasyn and offering a simple means of scale-up. Conversely however, the use of pyrophoric and hazardous reagents is required under inert and cryogenic conditions.



Scheme 2.7: The synthesis of enecarbamates **65**, **66** and **69** from their corresponding *N*-protected lactams.

We additionally identified several desirable enecarbamate substrates requiring the use of alterative preparative procedures, summarised in scheme 2.8. 3-Me *N*-Boc six-membered enecarbamate **77** was highlighted as an interesting substrate due its inclusion of a trisubstituted alkene; however, this could not be easily accessed *via* the electrochemical-based approach due to the predominant formation of the regioisomeric enecarbamate (see sections 2.1.1 and 2.1.2). Instead, a modification of this reduction and elimination-based approach, was employed as described in the literature (scheme 2.8, Panel A).[55,56] *N*-Boc δ-valerolactam **73** was treated with LDA at –78 °C for 1 h followed by trapping with MeI at –50 °C with warming to –20 °C to yield methylated intermediate **76**. Performing the usual reduction and elimination conditions then yielded 3-Me *N*-Boc enecarbamate **77**. As an alternative six-membered enecarbamate exhibiting modulated electronic properties, Cbz-dihydropyridone **78** was also synthesised. Treatment of 4-methoxypyridine with $NaBH_4$ and subsequent slow addition of CbzCl according to a literature procedure delivered 4-keto enecarbamate in 9% (scheme 2.8, panel B).[71] Azetidine-based *N*-Boc

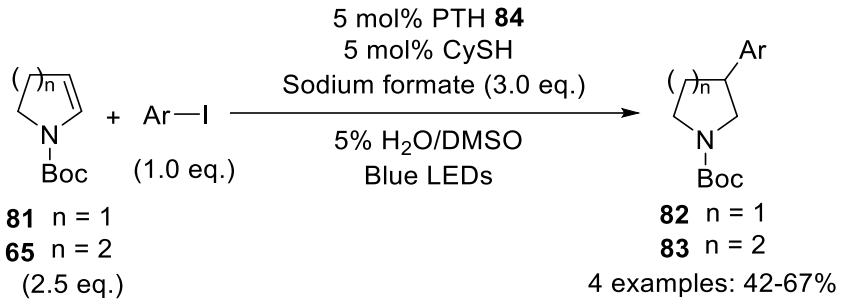
enecarbamate **80** was also prepared as a potentially highly reactive substrate again as per literature conditions (scheme 2.8, panel C).[72] Treatment of tosylate **79**, prepared by Mr Harrison Johnson-Evans, with *t*-BuOK and *t*-BuOH at 80 °C afforded 4-membered enecarbamate **80** in 41% yield. In all cases, spectroscopic data matched those reported in the literature.



Scheme 2.8: Enecarbamate systems **77**, **78** and **80** prepared using alternative methodologies.

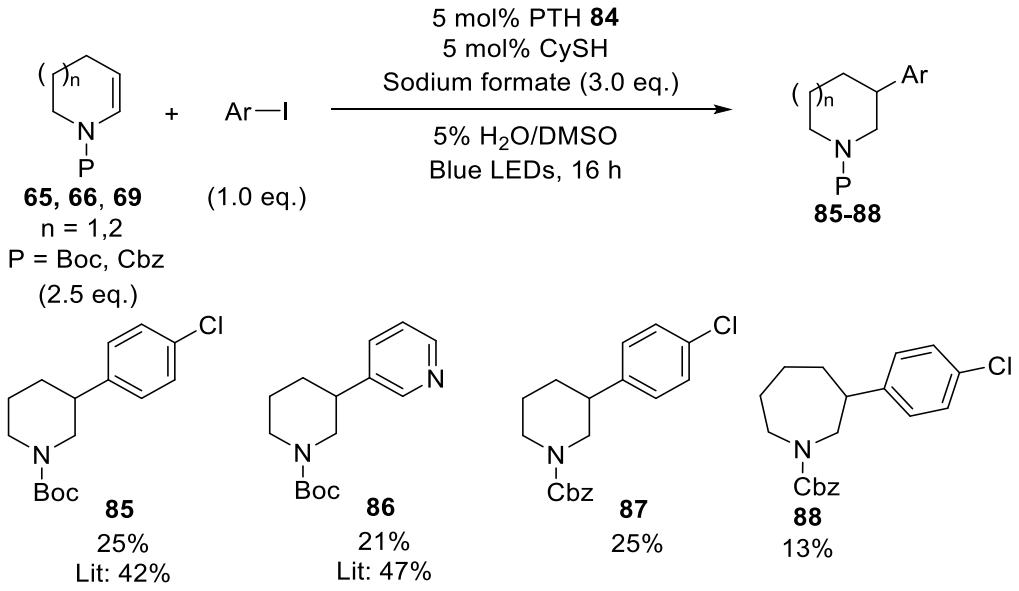
2.2.4 β-Arylation of enecarbamates

Jui and co-workers recently reported a procedure for the β-selective hydroarylation of vinyl amine derivatives and demonstrated its applicability to cyclic enecarbamates.[73] Four cyclic β-arylated products, based on scaffolds **82** and **83**, were reported employing enecarbamates **81** and **65** and two aryl iodides in yields of 42-67% (scheme 2.9). This is the only report of the β-arylation of cyclic enecarbamates to date in the literature and so we planned to harness this chemistry as an exemplar approach for the development of unique and valuable β-functionalised building blocks *via* enecarbamate elaboration.



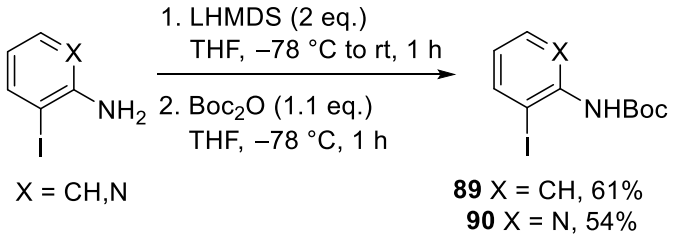
Scheme 2.9: A summary of the β-arylation reactions performed on cyclic enecarbamates by Jui.[73]

We began by repeating some of the literature coupling reactions using *N*-Boc enecarbamate **65**.[73] Treatment of enecarbamate **65** and 1-chloro-4-iodobenzene with PTH **84**, cyclohexanethiol, and sodium formate in H_2O/DMSO under blue light irradiation for 16 h provided the corresponding β-arylated product **85** in a 25% yield, slightly lower than that reported in the literature (42%, scheme 2.10). The analogous reaction with 3-iodopyridine afforded the β-arylated product **86** in a 21% yield, again lower than that reported in the literature (47%). All spectroscopic data for β-arylated carbamates **85** and **86** was consistent to those reported in the literature.[74,73] The reaction of *N*-Cbz enecarbamate **66** and 1-chloro-4-iodobenzene gave the novel β-arylated product **87** in a similar yield to the analogous reactions (25%). To expand the enecarbamate scope, 7-membered enecarbamate **69** was employed, due to the underrepresentation of β-functionalised scaffolds containing this motif in the literature. The reaction of enecarbamate **69** with 1-chloro-4-iodobenzene, provided the desired product **88** in a 13% yield.



Scheme 2.10: The photoredox-mediated coupling reactions of enecarbamates **65**, **66** and **69** with aryl halides to give β-functionalised piperidines **85**-**88**.

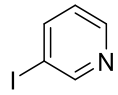
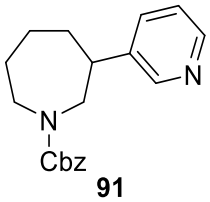
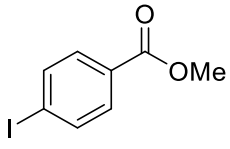
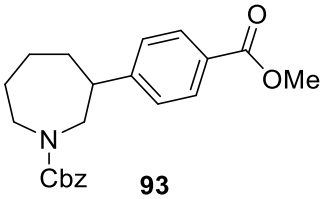
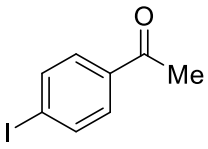
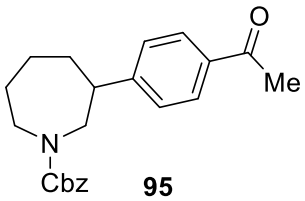
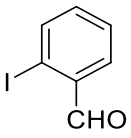
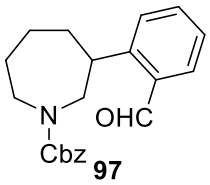
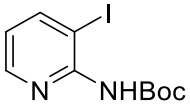
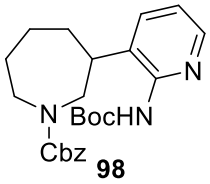
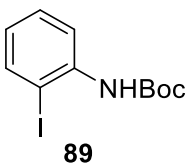
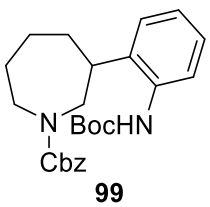
Due to the consistently low yields observed, we turned our attention towards the optimisation of the reaction. Unfortunately, after a series of experimental modifications (see Appendix 9.1 for full optimisation details), we were not able to improve the reaction yield significantly for 7-membered enecarbamate **69**. Using our modified conditions (see Appendix 9.1, entry 13) we then planned to explore the scope of the aryl iodide. *N*-Boc aniline **89** and *N*-Boc amino pyridine **90** were prepared as non-commercially available aryl halide examples from their respective primary amines (scheme 2.11).[75]



Scheme 2.11: The preparation of non-commercially available *N*-Boc aryl halides **89** and **90**.

A series of aryl iodides were then investigated with limited success (table 2.1). Reaction of enecarbamate **69** with 3-iodopyridine gave the desired product **91** in a good yield of 23% (entry 1), however unfortunately all other aryl iodides **89**, **90**, **92**, **94** and **96** provided no isolable desirable products **93**, **95** and **97-99**. The formation of a reduced aryl iodide species was however observed (90% isolated yield) for the reaction with aminopyridine **90** suggesting formation of the aryl radical (entry 5). This suspected occurrence of alternative reaction pathways was confirmed *via* optimisation work (see appendix section 9.1), through observation of the consumption of starting enecarbamate **69** under the reaction conditions without aryl iodide.

Table 2.1: The aryl iodide scope of the β-arylation methodology with 7-membered enecarbamate **69**.

Entry	Aryl iodide	Product	Isolated yield (%)
1		 **91**	23
2	 **92**	 **93**	0
3	 **94**	 **95**	0
4	 **96**	 **97**	0
5	 **90**	 **98**	0 (desired product) 90 (reduced aryl iodide species)
6	 **89**	 **99**	0

2.2.5 Summary of results

A library of cyclic enecarbamate building blocks have been prepared *via* an efficient two-step electrochemical anodic oxidation and elimination-based approach. Enecarbamates of varied ring sizes and functionalities were accessed from simple and affordable starting saturated amines. We have additionally evaluated an alternative synthesis of enecarbamates from their corresponding lactams as a complementary route. We have then performed preliminary work regarding the functionalisation of enecarbamates in which several novel and valuable β-arylated scaffolds have been successfully prepared. Due to the occurrence of unknown competing reaction pathways, we concluded that the complex nature of this reaction would cause difficulty regarding further optimisation required to attain good yields.

2.3 Synthesis and functionalisation of hemiaminal ethers

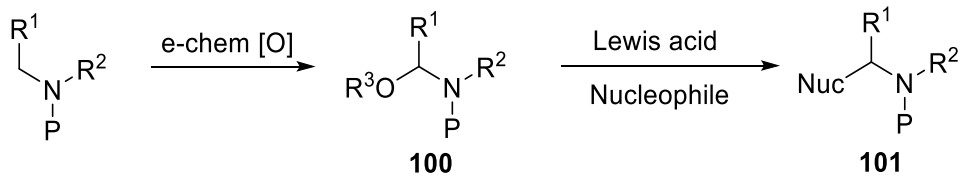
2.3.1 Introduction

As indicated in section 2.1.1, it is possible to isolate and purify the intermediate hemiaminal ether from electrochemical oxidation of carbamate-protected saturated cyclic amines without direct conversion to the enecarbamate, therefore opening potential alternative functionalisation avenues. Significant work within the literature has focused on using these species to install a variety of functionalities at the α-position. We have carried out significant efforts regarding the investigation of these methodologies, however due to discovered limitations of this work, only a summary of the most successful results will be presented in this chapter.

2.3.2 Background

α-Functionalisation methodologies of hemiaminal ethers **100** typically employ a Lewis acid to regenerate the *N*-acyliminium ion followed by trapping with the desired nucleophile, to deliver α-substituted carbamates **101**, as described in scheme

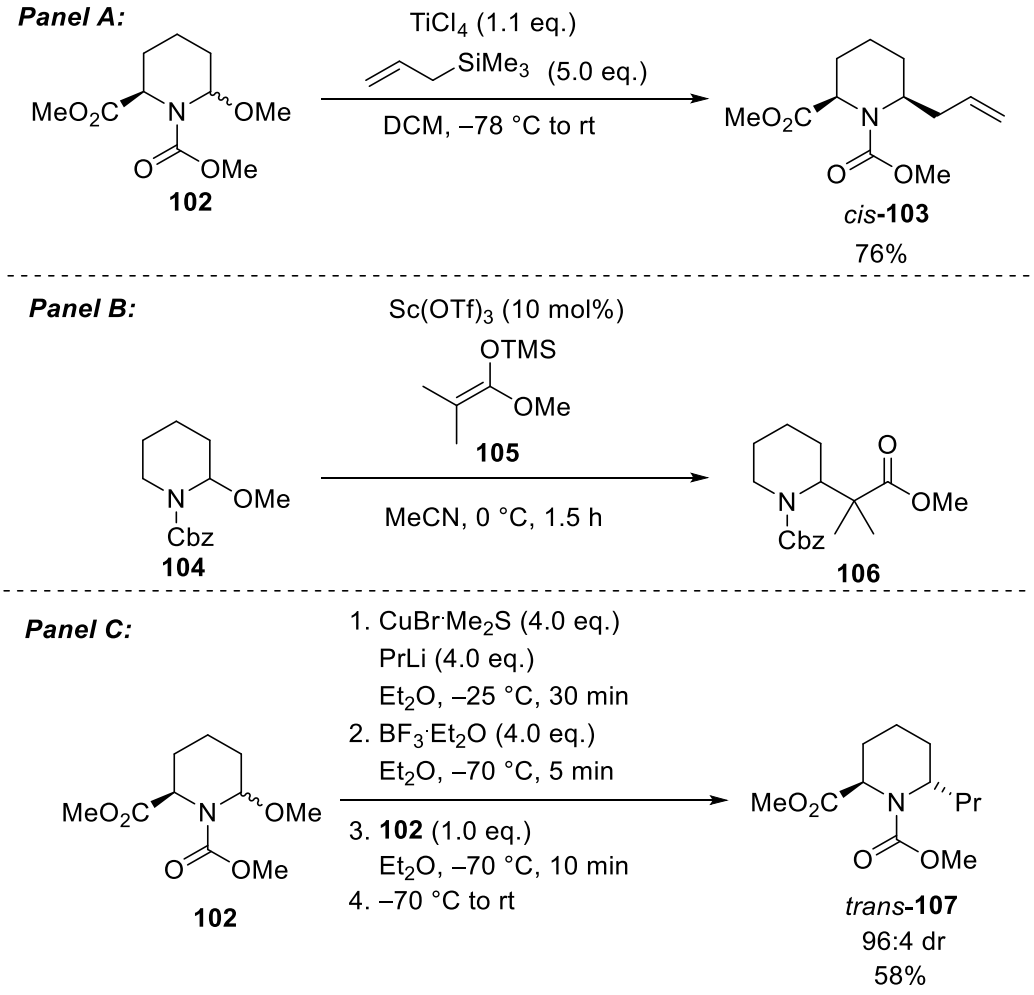
2.12.[51,52] Many studies have been carried out and a large range of methodologies have been reported for the installation of various functional handles including allyl,[76] aldehyde,[77,78] ester,[76,79,80] cyano,[81] aliphatic[82,83] and aromatic groups.[84,85,86] A concise selection of these reactions will be reviewed in this section.



Scheme 2.12: The synthesis of α-substituted carbamates **101** *via* sequential electrochemical oxidation and Lewis acid-mediated substitution methodologies.

α-Allyl functionalities have frequently been installed using a Lewis acid and allyltrimethylsilane. For example, David *et al* has shown that treatment of α-methoxy carbamate **102** with allyltrimethylsilane and $TiCl_4$ gave α-allyl product *cis*-**103** in a 76% yield (scheme 2.13, panel A).[76] The synthesis of β-amino acid esters from the coupling with silyl ketene acetals is also commonly reported in the literature. Shono functionalised acyclic α-methoxy carbamates to generate the corresponding β-amino acid esters in high yields using this method.[79] Okitsu and co-workers expanded this work by employing substituted carbamates and optimising this methodology. Treatment of α-methoxy piperidine **104** with scandium triflate, followed by silyl enol ether **105** gave the desired ester **106** in 93% yield (scheme 2.13, panel B).[80] Alkyllithiums have been employed, usually as organocopper reagents with the addition of a Lewis acid (e.g., BF_3) to enable the installation of both aromatic and aliphatic groups. Ludwig and Wistrand installed aliphatic functionalities onto *N*-COR and *N*-CO_2R α-methoxy-substituted piperidines and pyrrolidines to yield the corresponding products *via* this approach.[82] They then went on to explore these reactions on 2-substituted piperidine and pyrrolidine systems.[83] The reaction of α-methoxy carbamate **102** with propylcopper and boron trifluoride diethyl etherate produced a 96:4 mixture of *trans* and *cis*-diastereomeric products **107** (*trans*-isomer isolated in a 58% yield, scheme 2.13, panel C). This was a reversed selectivity to that

observed with π-nucleophiles and the same trends were also observed with the related pyrrolidine systems. The authors explain this reversed selectivity by proposing a model for the transition state where the copper species can coordinate to both the carbonyl oxygen and the *N*-acyl iminium double bond. Axial attack on this iminium ion can then take place to yield the *trans* isomer.

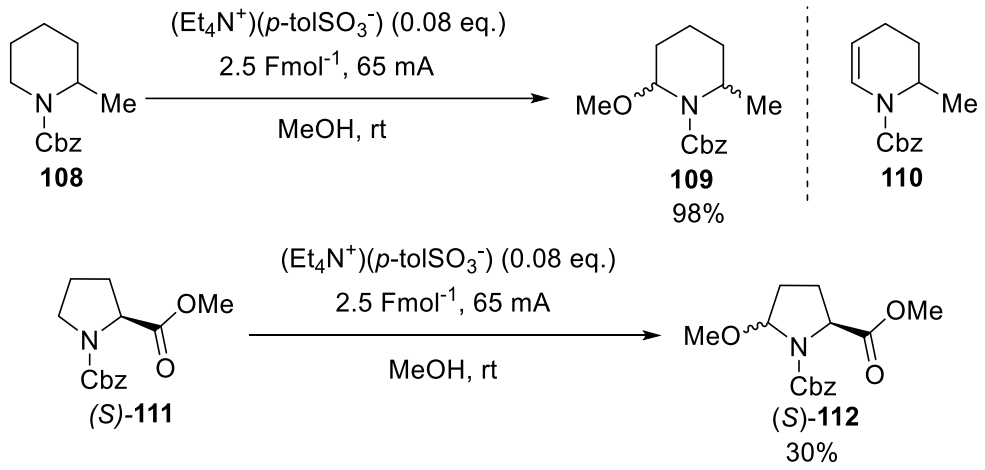


Scheme 2.13: A summary of literature methods for the direct α-functionalisation of hemiaminal ethers.

2.3.3 Synthesis of hemiaminal ethers

To begin with, electrochemical oxidation of 2-substituted carbamates **108** and *(S)*-**111** was carried out. Oxidation of *N*-Cbz 2-methyl-piperidine **108** under the standard conditions of 65 mA and 2.5 $Fmol^{-1}$ in methanol gave the desired product **109** as an

undetermined mixture of diastereomers and rotamers in a high yield (98%, scheme 2.14). Upon purification by column chromatography, conversion to enecarbamate **110** was observed and therefore hemiaminal ether **109** was used without purification. A comparison of the ^{1}H NMR spectrum with that of the major diastereomer reported in the literature demonstrated that all of the key signals were present.[87] Electrochemical oxidation of 2-susbtituted pyrrolidine *(S)*-**111** gave desired hemiaminal *(S)*-**112**, in a 30% yield obtained as an undetermined mixture of diastereomers and rotamers (scheme 2.14). Unfortunately, efforts to employ 3-substituted cyclic carbamates within the electrochemical oxidation chemistry were less successful due to the poorer regioselectivity and therefore complex mixtures of isomers produced.

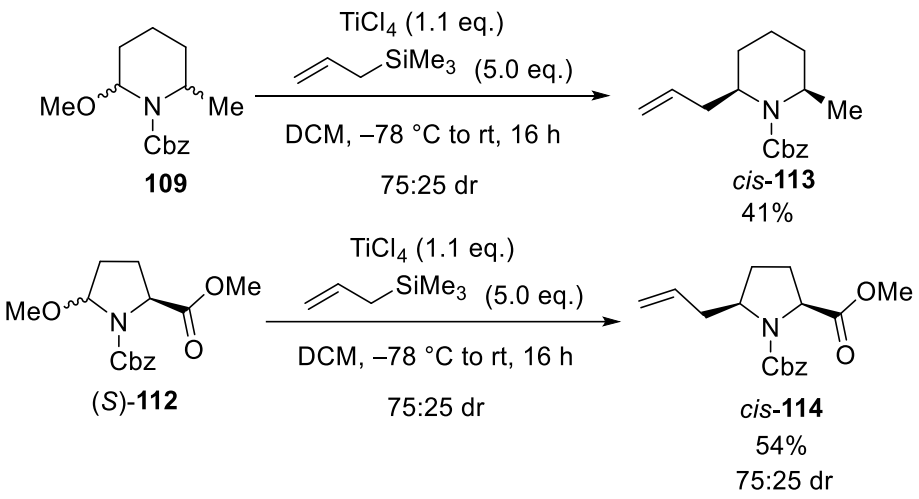


Scheme 2.14: The synthesis of hemiaminal ethers **109** and *(S)*-**112** *via* electrochemical anodic oxidation.

2.3.4 Lewis acid-mediated substitution reactions of hemiaminal ethers

Once the desired hemiaminals had been synthesised, Lewis acid-mediated substitution reactions could then be carried out. We began with the installation of an allyl group.[76] Treatment of hemiaminal ether **109** with $TiCl_4$ and then allyltrimethylsilane resulted in a 75:25 mixture of diastereomeric products *cis*-**113** and *trans*-**113** (scheme 2.15). A single diastereomeric product *cis*-**113** was isolated after purification by column chromatography in a 41% yield. *Trans*-**113** was not

isolated presumably due to degradation. Treatment of 2-substituted pyrrolidine (*S*)-**112** under the same conditions was also successful, leading to a 75:25 mixture of *cis* and *trans* diastereomeric products being obtained, with the major *cis* diastereomer depicted in scheme 2.15. After purification, an inseparable 75:25 mixture of *cis*-**114** and *trans*-**114** was isolated in a 54% yield.



Scheme 2.15: The preparation of α-allyl functionalised carbamates *cis*-**113** and *cis/trans*-**114** from their corresponding hemiaminal ether precursors **109** and *(S)*-**112**.

The stereochemistry of *cis*-**113** was assigned by comparison with the ^{1}H NMR spectrum reported in the literature, and by analysis of the NOESY NMR spectrum presented in figure 2.2. A positive nOe interaction was observed between the methyl and allyl CH_2 signals indicating the *cis* conformation. It has been suggested that the high *cis* stereoselectivity arises from chair-like conformation **115**, where the methyl group is in a pseudoaxial position to minimise unfavourable $A^{1,3}$ interactions with the Cbz group.[88] Then a stereoelectronically-preferred axial-attack on the *N*-acyliminium ion would occur to yield the *cis* stereoisomer *cis*-**113**. The stereochemistry of the 5-ring based α-allyl carbamate *cis*-**114** was assigned based on comparison with a literature ^{1}H NMR spectrum.[89] The high *cis* selectivity in this reaction is comparable with similar reactions performed in the literature.[90,91]

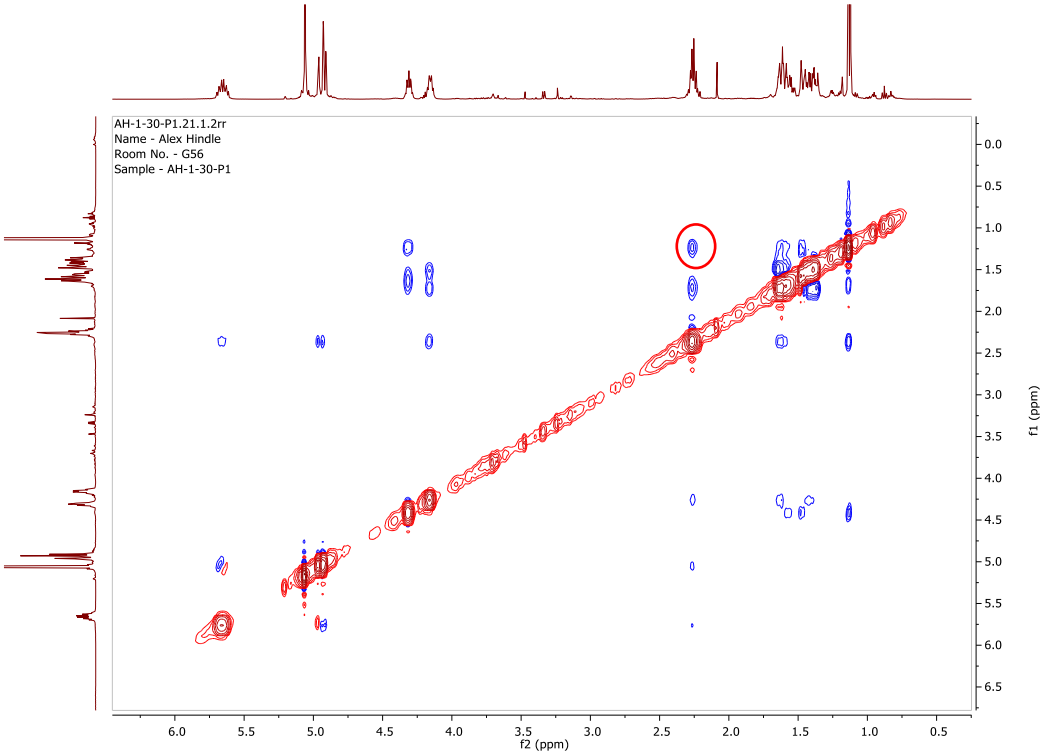
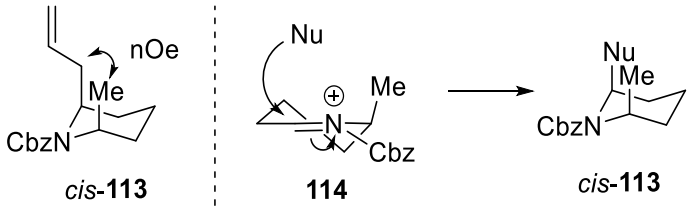
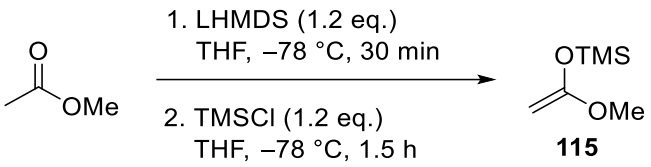


Figure 2.2: The NOESY NMR spectrum of *cis*-**113** used to determine the stereochemistry, where the interaction between the methyl and allyl CH_2 signals is highlighted with a red circle.



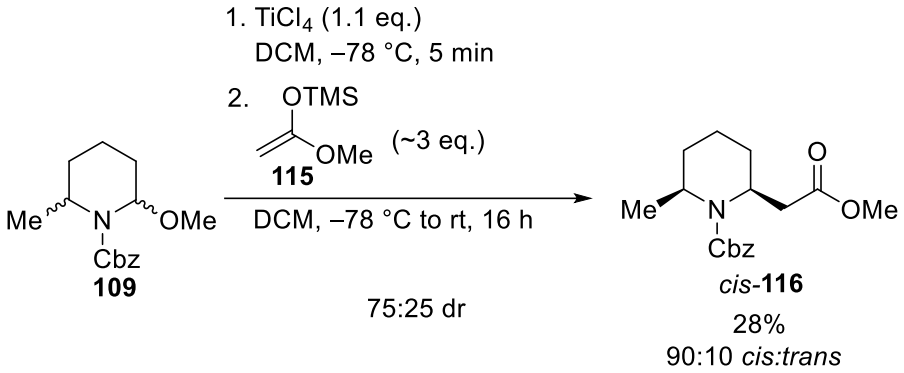
Scheme 2.16: Stereochemical rationale for the favourable formation of *cis*-**113**.

Our attention was then turned to the installation of ester functionalities. To do this, the synthesis of the appropriate silyl ketene acetal was required. Treatment of methyl acetate with LHMDS at –78 °C in THF for 30 mins followed by trapping with TMSCl at –78 °C for 1.5 h gave impure silyl ketene acetal **115** according to a literature procedure (scheme 2.17).[92] Purification by vacuum distillation at room temperature using a receiver flask cooled to –78 °C was unsuccessful, yielding impure silyl ketene acetal **115**. Key signals were however observed in the ^{1}H and ^{13}C NMR spectra which agreed with those reported in the literature.



Scheme 2.17: The synthesis of silyl ketene acetal **115**.

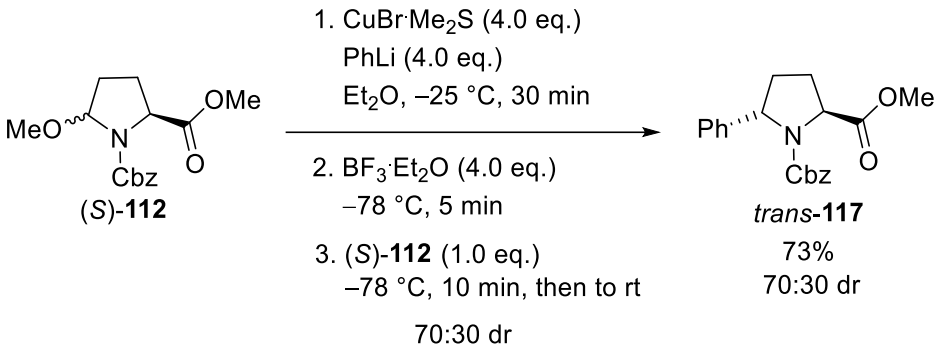
Using an approach adapted from the literature, carbamate **109** was treated with $TiCl_4$ at –78 °C in DCM for 5 min.[79] Impure TMS silyl ketene acetal **115** was then added in excess and the mixture allowed to warm to room temperature in the Dewar for 16 h, resulting in a 75:25 mixture of *cis* and *trans* diastereomeric products (scheme 2.18). An inseparable 90:10 mixture of novel esters *cis*-**116** and *trans*-**116** were then isolated after column chromatography in a yield of 28%. The stereochemistry was assigned in a similar way to *cis*-**113**, with the analogous positive nOe being observed between the methyl and ester CH_2 environments.



Scheme 2.18: The synthesis of ester-functionalised piperidine *cis/trans*-**116** prepared from the corresponding hemiaminal precursor **109** and silyl ketene acetal **115**.

In an attempt to install aromatic functionalities, a final procedure was employed.[83] Treatment of hemiaminal ether *(S)*-**112** with $CuBr{\cdot}Me_2S$, PhLi and $BF_3{\cdot}Et_2O$ in Et_2O at –25 ° to –78 °C to rt afforded a 70:30 mixture of diastereomeric α-aryl-substituted pyrrolidines *trans*-**117** and *cis*-**117**. After purification a 70:30 mixture of diastereomeric pyrrolidines *trans*-**117** and *cis*-**117** were isolated in a 73% yield (scheme 2.19). Spectroscopic data for *cis*-**117** were consistent with those reported in

the literature, however no data was reported for *trans*-**117**.[93] This reversed stereoselectivity, from that of allylation, is comparable with the outcome of some related reactions performed in the literature, which have employed alkyl and alkenyl copper-reagents.[94,95,96]



Scheme 2.19: The synthesis of Ph-functionalised carbamates *trans*-**117** and *cis*-**117** using an organocopper-mediated approach.

2.3.5 Summary of results

We have successfully been able to install α-methoxy substituents onto 5- and 6-membered cyclic carbamates. This has shown to be regioselective for the 2-substituted systems and less so for those with 3-substituents. We have then been able to further functionalise at the α-position to install allyl, ester and aromatic containing groups.

2.4 Chapter summary

This chapter has described the successful synthesis of a series of hemiaminal ethers and their corresponding enecarbamates *via* an efficient one-pot approach employing electrochemical anodic oxidation as the pivotal transformational setup. Some preliminary β-functionalised novel scaffolds have been accessed in low yields, whereas progress regarding α-functionalisation efforts of hemiaminal ethers has been limited due to the modest regioselectivity observed for the oxidation of substituted hemiaminal ethers. Chapters 3-5 will therefore explore alternative

avenues for the β-elaboration of enecarbamates and their subsequent construction into valuable and complex 3D-polycyclic scaffolds.

3 Chapter 3: Enecarbamates as platforms for the synthesis of spirocyclic bicycles

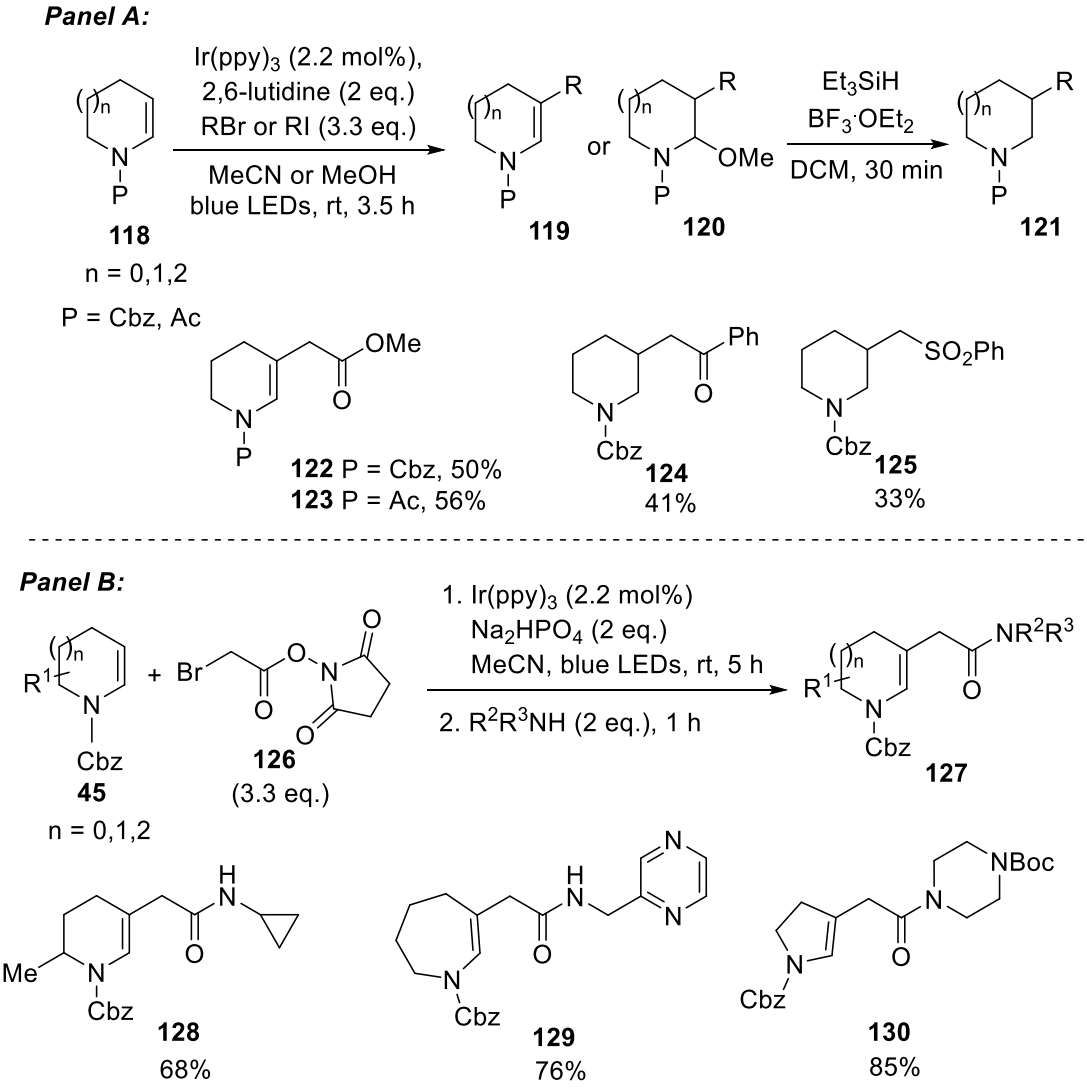
3.1 Background - Ir-catalysed photochemical approaches for the β-functionalisation of enecarbamates

Metal-catalysed approaches for the elaboration of enecarbamates and enamides are prevalent within the literature,[97,98] however those that describe photocatalytic-mediated techniques are much more limited, and few accounts exist including those reported by our research group.[41,42,57,99] These are complementary to the photocatalysed β-hydroarylation described in chapter 2[73] and mostly facilitate the incorporation of amines and construction of new C-C bonds. A selection of key photocatalytic methods employed within this chapter will be reviewed in this section.

3.1.1 β-Alkylation of enecarbamates

Previous work published in our group has reported the use of photocatalysed β-alkylation chemistry for the direct elaboration of enecarbamates.[41] Scheme 3.1 presents a summary of this work where panel A describes the incorporation of ester, ketone and sulfone-functionalised alkyl groups (**122**-**125**) *via* treatment with $Ir(ppy)_3$, 2,6-lutidine and the required alkyl halide under blue LED irradiation. Tuning of the reaction solvent (MeCN or MeOH) enabled selective formation of either enecarbamate **119** or hemiaminal ether **120**. Applying subsequent reductive conditions (Et_3SiH and $BF_3{\cdot}OEt_2$) to the prepared hemiaminal ethers delivered the analogous saturated carbamates **121**, therefore providing a tailorable route to both

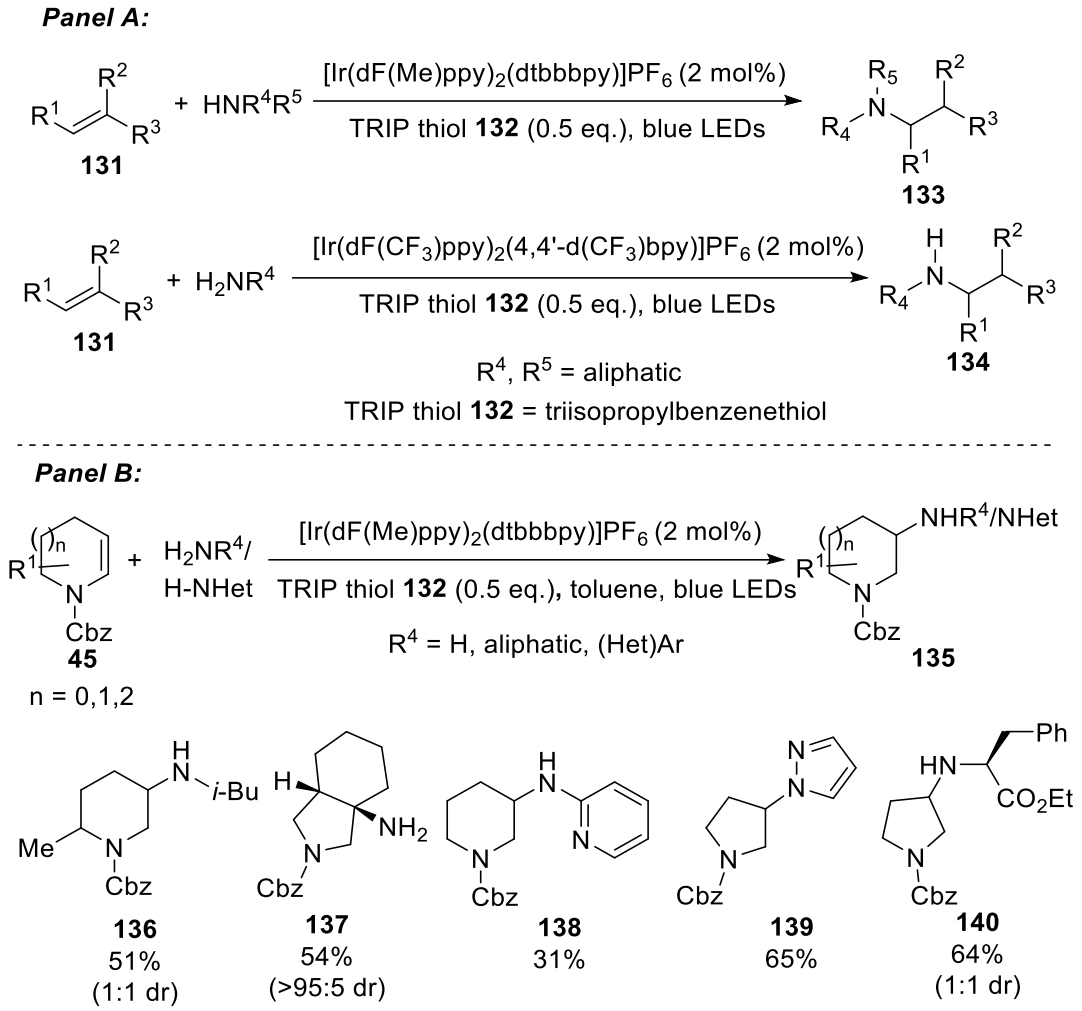
saturated and unsaturated products. The approach was also modified for the installation of amide-functionalised alkyl groups which could not be coupled directly (scheme 3.1, panel B). In this case, treatment with $Ir(ppy)_3$, Na_2HPO_4, and succinimide-containing alkyl halide **126** under blue LED irradiation in MeCN afforded intermediate succinimidyl activated esters which were then reacted with the desired amine to yield amides **127**. Once again, reductive conditions could be employed to access the analogous saturated products. Both reactions were able to tolerate a variety of ring sizes and preinstalled substituents (**128**-**130**), as well as enabling access to both secondary and tertiary amide containing products.



Scheme 3.1: The preparation of β-alkylated enecarbamates and carbamates as described by Trindade *et al*.[41]

3.1.2 β-Hydroamination of enecarbamates

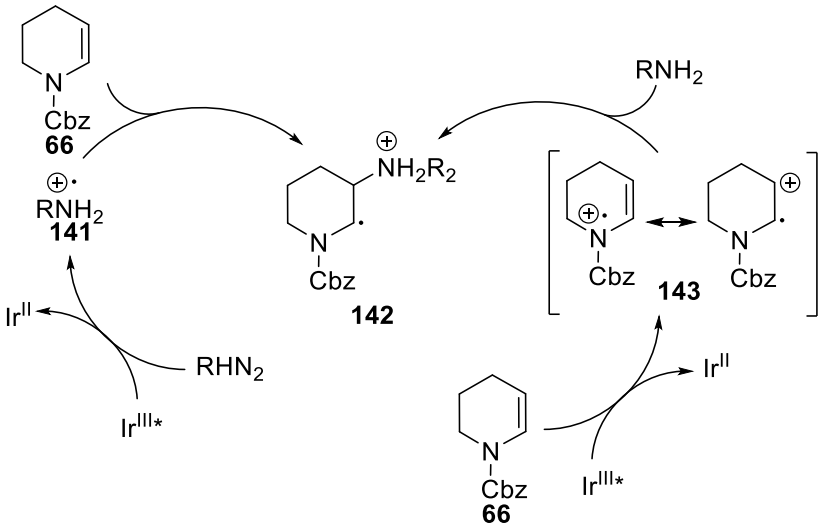
Regioselective photocatalysed intermolecular hydroaminative couplings of alkenes have been a focus of recent years. Knowles has pioneered the field by reporting the direct intermolecular photocatalysed hydroaminative couplings of secondary alkyl amines with a range of alkenes **131** (scheme 3.2, panel A).[100] Treatment of the desired alkene **131** and secondary amine with cocatalyst 'TRIP thiol' **132** under the irradiation of blue LEDs, afforded acyclic tertiary amines **133**. By employing an alternative Ir-based catalyst, Knowles has also been able to achieve the hydroamination of primary alkyl amines, producing secondary amine products **134** (scheme 3.2, panel A).[101] In recent years, our group has applied and extended Knowles' hydroamination methodology to incorporate enecarbamates **45** to deliver a range of β-aminated *N*-Cbz carbamates **135** (scheme 3.2).[42] Ammonia, primary and secondary amines (e.g., **136** and **137**) as well as aromatic and heteroaromatic functionalities could be tolerated (e.g., **138** and **139**), in generally good to high yields. Furthermore, a range of ring sizes and preinstalled substituents were tolerated as indicated by exemplar β-aminated products **136**, **137** and **138**. Amino esters could also be employed (e.g., **140**) allowing the preparation of β-functionalised scaffolds with avenues for further elaboration (*vide infra*).



Scheme 3.2: The synthesis of secondary and tertiary amines from their respective alkenes as described by Knowles *et al* (panel A)[100,101] and the hydroamination as a method for enecarbamate β-amination as reported by our group (panel B).[42]

A possible mechanism was also proposed for the hydroamination of enecarbamates (scheme 3.3).[100,101,42] Knowles originally suggested the formation of primary and secondary aminium radicals (e.g., **141**), *via* reductive quenching with the iridium photocatalyst. These could then react with the alkene (e.g., **66**), generating the corresponding α-carbon-centred radical species (e.g., **142**), which would subsequently undergo hydrogen atom abstraction from the cocatalyst.[100,101] A potential alternative mechanism was instead suggested by Knowles[100] and Francis *et al*[42] regarding the hydroamination of enecarbamates with primary amines (scheme 3.3). In this case, reductive quenching of the photocatalyst by enecarbamate **66**

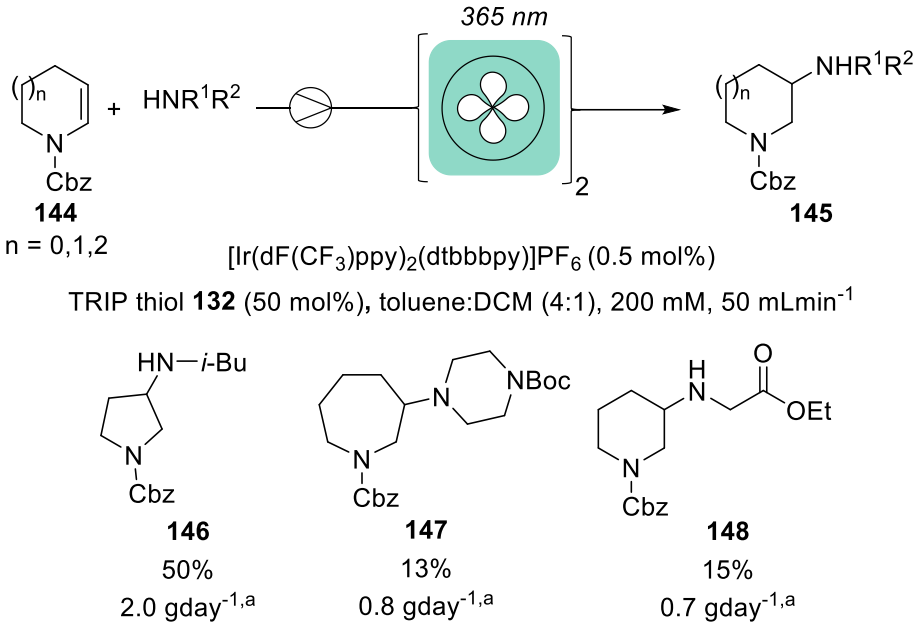
would provide the analogous radical cationic intermediate **143** which would form the same α-carbon-centred radical species **142** upon amine trapping. This alternative mechanistic pathway was proposed due to the use of iridium photocatalyst ($[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$), and its associated inability to serve as a sufficiently strong oxidant to form aminium radicals **141** from primary amines (and likely ammonia). Furthermore, Stern-Volmer quenching studies were able to identify enecarbamate **66** as better quenching agent than primary amines (*iso*-butylamine).[42]



Scheme 3.3: Proposed enecarbamate hydroaminative mechanistic pathways for the generation of α-carbon-centred radical species **142**.[100,101,42]

Frequent limitations associated with these types of photocatalytic processes include reproducibility and poor scalability. Therefore, efforts to carry out these transformations using continuous flow have received increasing attention in the literature as a means of addressing these concerns.[102,103] Work within our group has focused on utilising the newly developed photochemical module for the CSTR fReactor platform for the scale up of the hydroamination of enecarbamates amongst other processes.[104] Mixing enecarbamates **144** and primary or secondary amines with an iridium catalyst and cocatalyst **132** in a mixed solvent system (4:1 toluene:DCM, 200 mM) provided a sufficiently homogeneous solution which was then irradiated in flow at 365 nm using two fReactor modules, at 50 $mLmin^{-1}$ (scheme

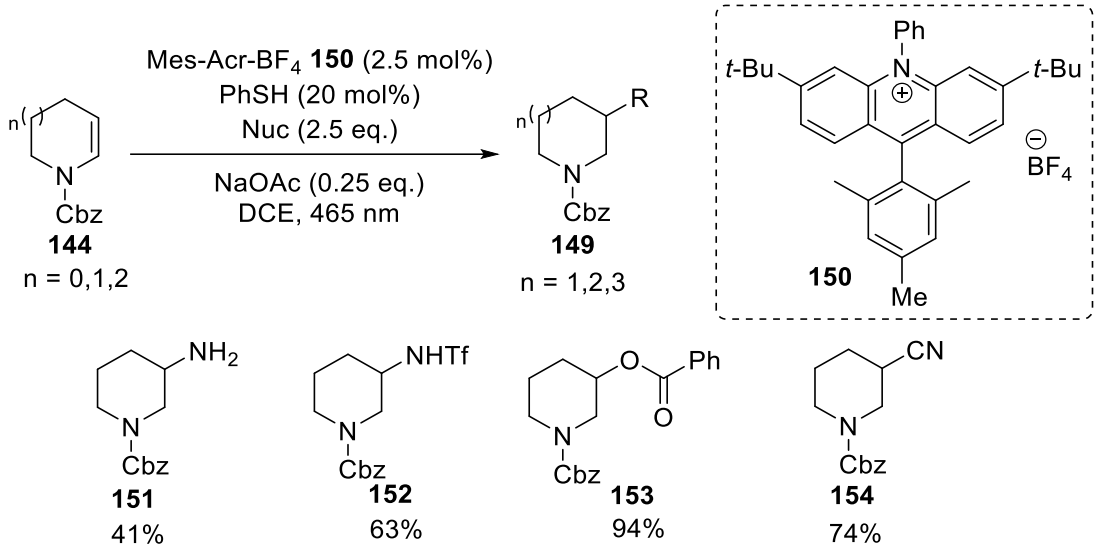
3.4). This yielded β-aminated carbamates **145**, of varying ring sizes and functionalities (e.g., **146**-**148**), in productivities of up to 2 gday^{-1}.



Scheme 3.4: The photocatalysed hydroamination of enecarbamates in flow using the fReactor platform as reported by Francis *et al*.[104] [a]day = 24 h.

3.1.3 Other β-functionalisations of enecarbamates

Recently, Nicewicz and coworkers[57] have developed alternative β-functionalisation methodology of enecarbamates employing acridinium-based catalyst **150** to deliver a range of β-functionalised *N*-heterocycles **149** in good to high yields (scheme 3.5). In this case, treatment of enecarbamates **144** with acridinium-based catalyst **150**, thiophenol, sodium acetate and the desired nucleophile yielded the desired functionalised products **149**. The methodology demonstrated a broad scope allowing the installation of amines (**151**), sulfonamides (**152**), esters (**153**) and nitriles (**154**) amongst others.

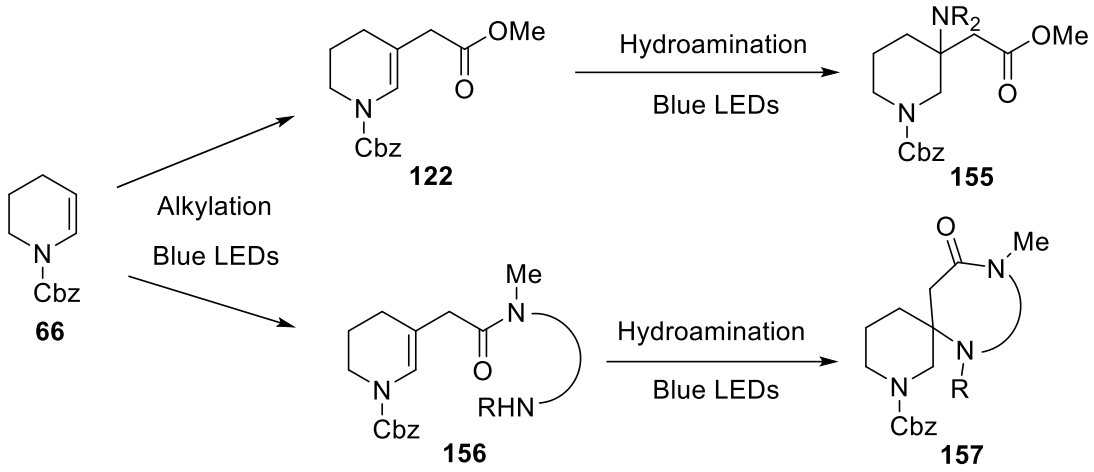


Scheme 3.5: An overview of the scope of the Mes-Acr-BF_4 **150** catalysed hydroamination methodology as developed by Nicewicz and coworkers.[57]

3.2 Synthesis of [6,7] and [6,8] spirocyclic motifs from enecarbamates

3.2.1 Introduction

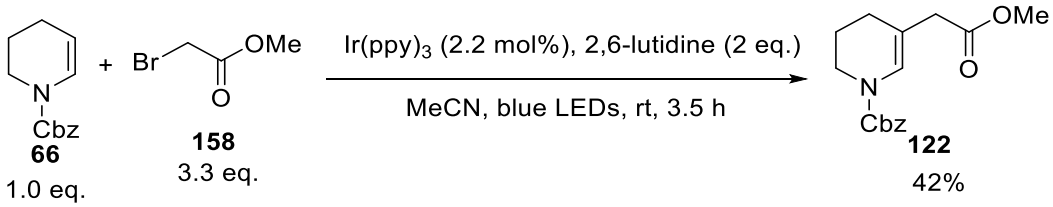
This section describes a photocatalysed approach towards a series of highly valuable β,β-difunctionalised spirocyclic scaffolds of medicinal relevance, utilising the library of enecarbamates previously prepared as well as methodologies previously developed within the group.[42,41] We proposed that by sequentially combining the photocatalysed alkylation and hydroamination β-functionalisation methodologies, high-value and high-complexity compounds containing quaternary centres and spirocyclic motifs **155** and **157** could be accessed in a simple and efficient two-step procedure (scheme 3.6).



Scheme 3.6: An overview of the two-step β-functionalisation strategies proposed to construct quaternary and spirocyclic motifs **155** and **157**.

3.2.2 Synthesis of esters *via* photochemically mediated β-alkylation chemistry

We began by repeating the synthesis of ester **122**, using the photochemically-catalysed alkylation chemistry (see section 3.1.1).[41] Treatment of enecarbamate **66** (30 mg scale) with methyl bromoacetate **158** and $Ir(ppy)_3$ under the irradiation of blue LEDs for 3.5 h, gave ester **122** in a 42% yield (scheme 3.7).



Scheme 3.7: Photochemically catalysed synthesis of ester **122**.

To use ester **122** as a handle for further β-functionalisation, we set about the scale up of this methodology. A 16-fold scale up could be achieved by simultaneous scale out and scale up of reaction vessels, whilst maintaining a moderate yield of 36%. Further attempted scale up resulted in a significant decrease in yield and was limited due to the necessary access to specialist equipment (e.g., blue LEDs). To address these scalability implications, we turned our attention to performing its synthesis in

flow, using the fReactor platform (see section 3.1.2).[104] Initially, test runs were performed in batch using the fReactors to find the appropriate residence time, (table 3.1, entries 1-5). 60 min was selected as the optimum residence time due to it resulting in the highest product yield (50%) whilst also showing high conversion of starting material (85%). Decreased catalyst loadings using this residence time were also investigated, however this resulted in poorer product yields (table 3.1, entries 6 and 7).

Table 3.1: The use of the fReactor platform in batch for reaction residence time optimisation.

Entry	Duration (min)	Catalyst loading (mol%)	Conversion of SM (%)[a]	Yield of product (%)[a]
1	30	2.2	80	45
2	60	2.2	85	50
3	90	2.2	95	45
4	120	2.2	95	40
5	180	2.2	90	35
6	60	1.1	95	35
7	60	0.55	95	25

[a]Yields and conversions determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard added following completion of the reaction.

The reaction was then performed in flow, using a residence time of 60 min. Aliquots were collected at 1 h intervals and the ratio of product to starting enecarbamate recorded (table 3.2). Unfortunately, the consumption of starting enecarbamate was

much lower than that observed when using the fReactors for batch synthesis. These results demonstrate the potential for scale up of the photochemically-catalysed β-alkylation methodology, however further optimisation would be required to deliver suitable conversions.

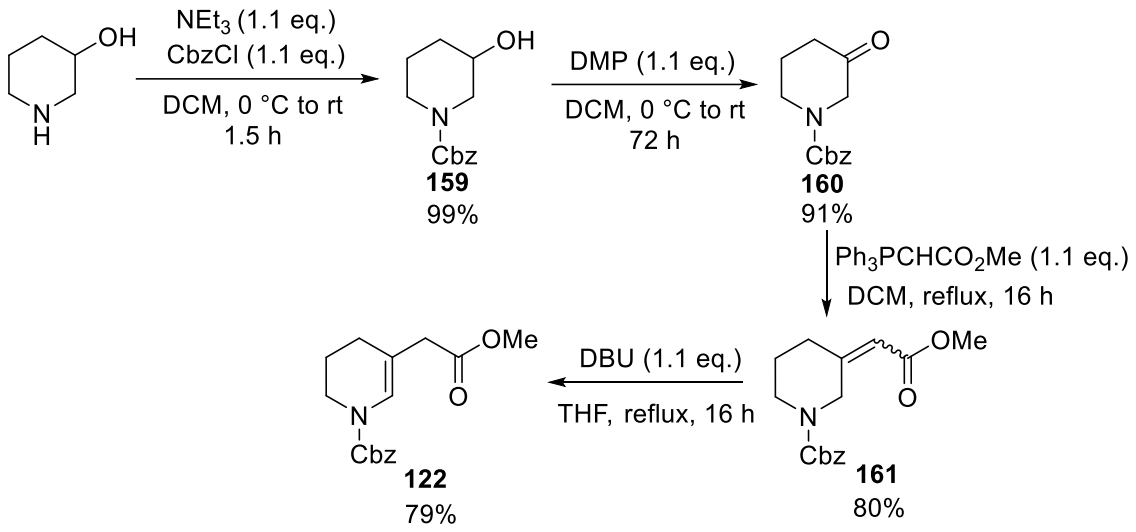
Table 3.2: Results of the synthesis of ester **122** as performed in flow using the fReactor platform.

Entry	Duration before collection (h)	Ratio product: starting enecarbamate[a]
1	1	25:75
2	2	40:60
3	3	40:60
4	4	40:60

[a]Ratios determined by ^{1}H NMR spectroscopic analysis.

3.2.3 Synthesis of esters *via* alternative methodologies

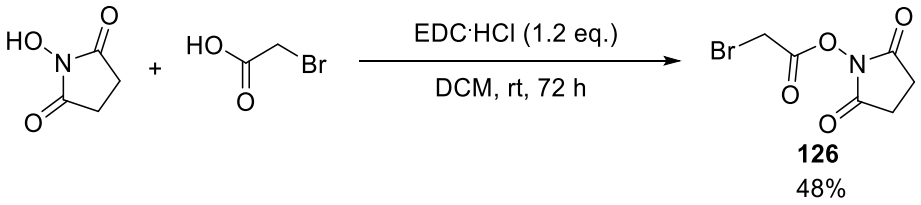
Due to the complexity and expense involved when performing the photochemically-catalysed alkylation methodology on a large scale, we also explored an alternative but complementary synthesis of ester **122** as described in scheme 3.8. This comprised of an initial Cbz protection of 3-hydroxypiperidine in a high yield (99%),[105] followed by DMP oxidation[106] to the corresponding ketone **160** in a 91% yield. This was followed by treatment with Ph_3PCHCO_2Me to provide alkene **161** in an 80% yield and subsequent alkene isomerisation using DBU afforded ester **122** in a high yield (79%).[107] Using this route, we were able to efficiently prepare ester **122** on large scale (up to 14 g) from an inexpensive, commercially available starting compound.



Scheme 3.8: The alternative non-photochemical synthetic route towards ester **122**.

3.2.4 Synthesis of amides *via* photochemically mediated β-alkylation chemistry

We then turned our attention to the preparation of amide-containing heterocycles using the photocatalysed-alkylation chemistry (see scheme 3.1). Initially, succinimidyl bromide **126** was synthesised from *N*-hydroxysuccinimide, in 48% yield (scheme 3.9).

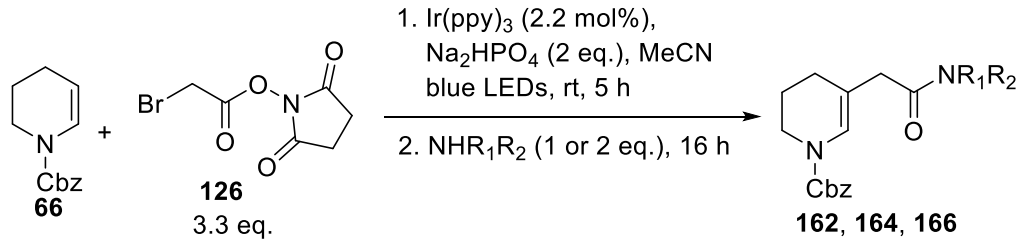


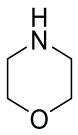
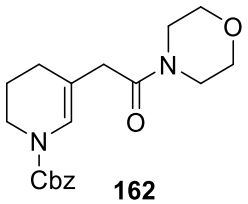
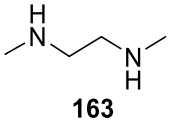
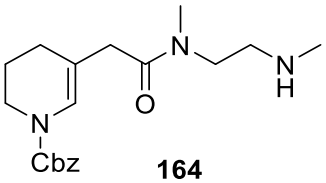
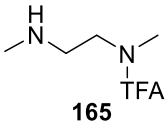
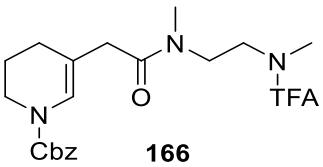
Scheme 3.9: Synthesis of succinimidyl bromide **126**.

Succinimidyl bromide **126** and enecarbamate **66** were then reacted under the photocatalytic conditions, followed by trapping with a range of amines as indicated in table 3.3, to produce corresponding amides **162**. Initially, we began with morpholine (entry 1) producing amide **162** in a yield of 19%. We then employed 1,n-diamines for the preparation of amides containing a tethered amine to facilitate the construction of spirocyclic motifs (see scheme 3.6). Commercially available,

symmetrical diamine **163** (entry 2) gave impure amine **164** in an approximate yield of 27%. Purification was attempted *via* column chromatography, SCX chromatography and acid-base extraction, however pure amine **164** could not be obtained due to the presence of numerous by-products. To combat this, *N*-TFA-monoprotected amine **165** was prepared (*vide infra*) as an alternative to diamine **163**. Reaction with *N*-TFA amine **165** provided amide **166** in an approximate yield of 31%, however purification was again unsuccessful (entry 3).

Table 3.3: Amides **162**, **164** and **166** as prepared using the photocatalysed-alkylation chemistry developed in the group.[41]

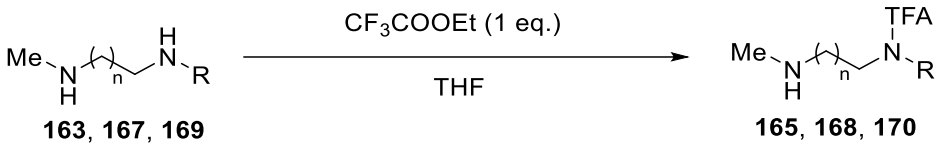


Entry	Amine	Product	Isolated yield (%)
1		 **162**	19%
2	 **163**	 **164**	~27% (impure)
3	 **165**	 **166**	~31% (impure)

3.2.5 Synthesis of amides *via* alternative methodologies

As amine **164** proved challenging to prepare using the photocatalysed-mediated alkylation methodology, we again sought an alternative synthesis. Treatment of diamine **163** with ethyl trifluoroacetate, as per a literature method,[108] selectively delivered *N*-TFA amine **165** in a high yield (table 3.4, entry 1). Two other *N*-TFA amines **168** and **170** were also prepared using related procedures[108,109] (table 3.4, entries 2 and 3), in high yields (100% and 94%) and selectivities.

Table 3.4: The selective syntheses of *N*-TFA protected amines **165**, **168** and **170**.

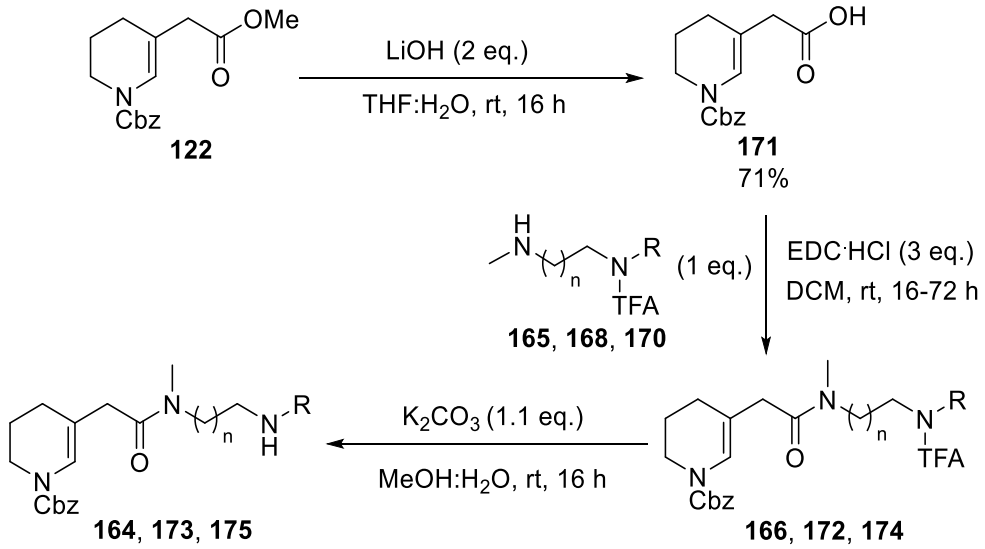


163, **167**, **169** → **165**, **168**, **170**

Entry	Amine	R	n	Temperature (°C)	Duration	Product	Isolated yield (%)
1	**163**	Me	1	0 °C to rt	16 h	**165**	94%
2	**167**	H	1	0 °C	10 min	**168**	100%
3	**169**	Me	2	0 °C to rt	1.5 h	**170**	94% (9:1 *mono*:*bis*)

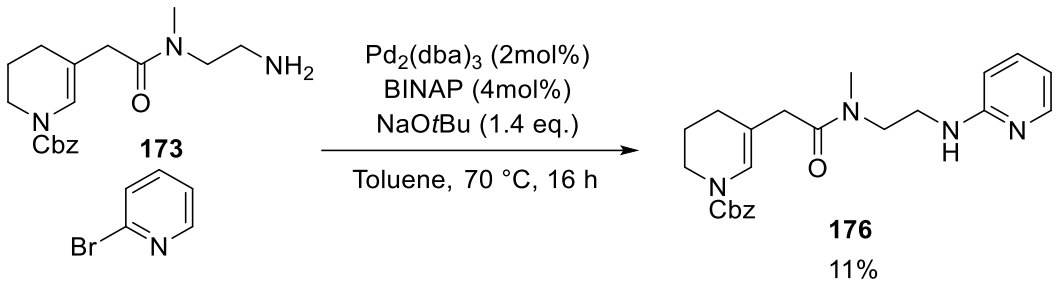
Using methyl ester **122**, prepared from the photochemically-catalysed alkylation methodology (see section 3.2.2) as a starting point, we attempted the direct amidation to deliver *N*-TFA amine **166**, however this was unsuccessful. Instead, carboxylic acid **171** was prepared *via* hydrolysis with LiOH and subsequent acidification to pH 5 with citric acid (table 3.5). Amides **166**, **172** and **174** were then prepared *via* the amide coupling of carboxylic acid **171** with amines **165**, **168** and **170** and EDC·HCl in moderate to good yields (36-78%), followed by TFA deprotection to give the amines **164**, **173** and **175** in good yields (55-83%, table 3.5, entries 1-3).[110]

Table 3.5: The synthesis of spirocyclic amine precursors **164**, **173** and **175** from ester **122**.



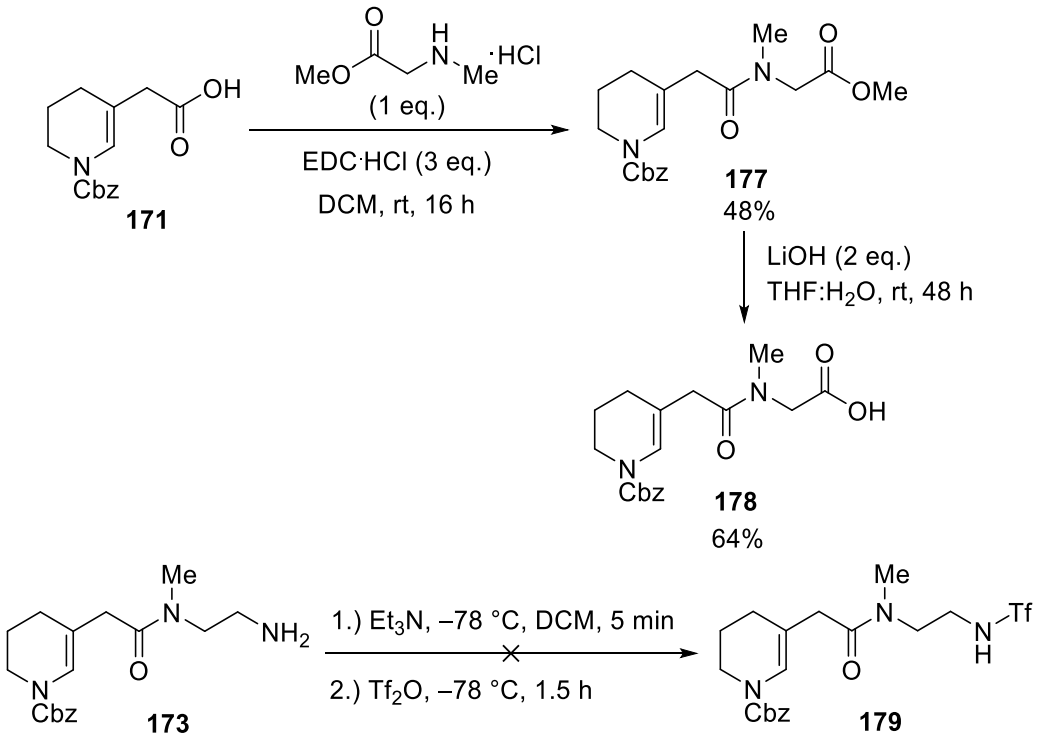
Entry	R	n	*N*-TFA product	Amide coupling isolated yield (%)	NH product	TFA deprotection isolated yield (%)
1	Me	1	**166**	47%	**164**	78%
2	H	1	**172**	78%	**173**	55%
3	Me	2	**174**	36%	**175**	83%

We then investigated whether NH amine **173** could be used as a handle to enable the construction of alternative spirocyclisation precursors. Incorporating aminopyridine functionalities into these cyclisation substrates was of particular interest to us and so we investigated the use of S_NAr in doing so. Attempted synthesis *via* S_NAr with 2-chloro or 2-fluoropyridine was unsuccessful but was instead successfully achieved *via* Buchwald-Hartwig coupling (scheme 3.10).[111] Amine **173** was treated with 2-bromopyridine in the presence of a palladium source ($Pd_2(dba)_3$), ligand (BINAP) and base (NaO*t*Bu) and heated at 70 °C for 16 h. Purification by mass-directed preparative HLPC gave aminopyridine **176** in 11%.



Scheme 3.10: Synthesis of spirocyclisation precursor amino pyridine **176** *via* Buchwald-Hartwig chemistry.

We also planned to investigate the use of tethered carboxylic acids and sulfonamides as nucleophiles in the cyclisation chemistry using Nicewicz's conditions.[57] To this end, we attempted the synthesis of carboxylic acid **178** (scheme 3.11). Carboxylic acid **171** was treated with an amino acid derivative to give ester **177** in a 48% yield. Subsequent hydrolysis, followed by acidification to pH 5 with citric acid, yielded the desired carboxylic acid in 64% yield. We additionally attempted the preparation of sulfonamide **179**, again starting with amine **173** (scheme 3.11). Treatment with Et_3N, followed by Tf_2O, however, was not successful.



Scheme 3.11: the synthesis of carboxylic acid **178** and attempted synthesis of sulfonamide **179**.

3.2.6 Construction of quaternary centres *via* photochemically mediated hydroamination chemistry

Following the syntheses of the desired β-functionalised scaffolds, we were then able to attempt further β-functionalisation using the photocatalysed-hydroamination methodology developed previously in the group, as described in section 3.1.2 (scheme 3.2).[42] An annotated photograph describing the hydroamination setup in a practical setting is presented in figure 3.1.

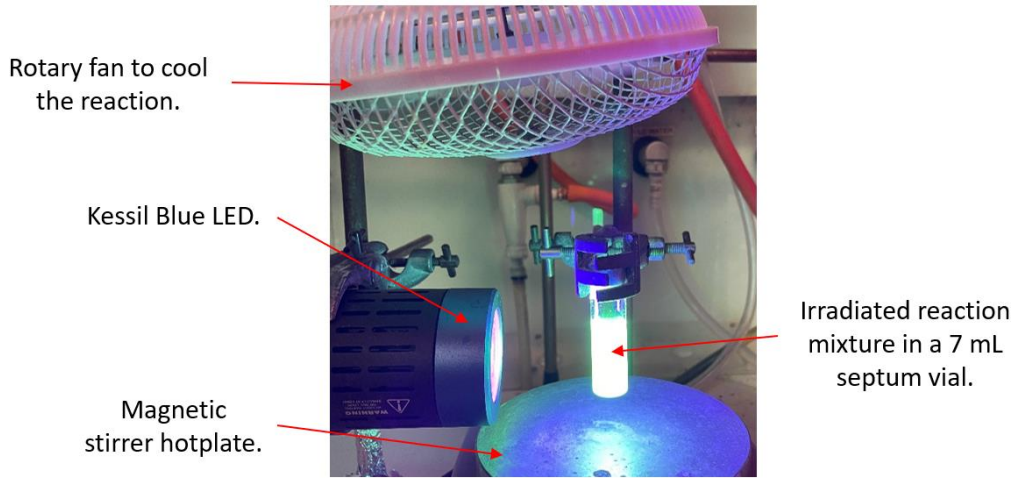
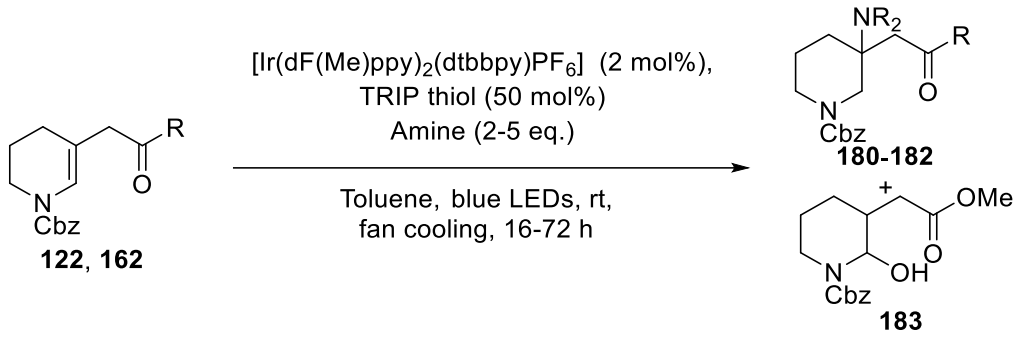


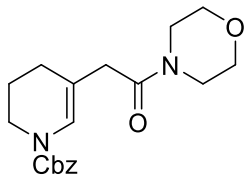
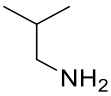
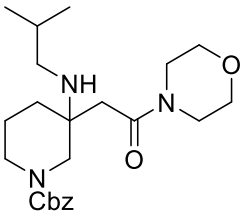
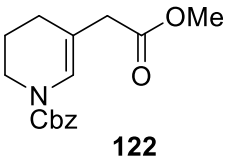
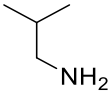
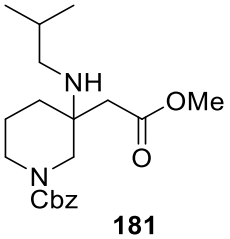
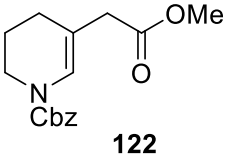
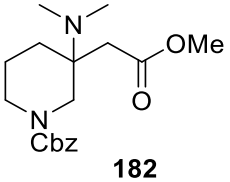
Figure 3.1: An annotated photograph describing the practical setup of the photocatalysed-hydroamination methodology carried out in batch.

To begin with, treatment of enecarbamate **162** with *iso*-butylamine, TRIP thiol **132** and Ir photocatalyst in a sealed septum vial under blue LED irradiation and rotary fan cooling provided desired β,β-difunctionalised *N*-heterocycle **180** in an isolated 19% yield (table 3.7, entry 1). The structure of **180** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, with a signal at δ_C 55.7 assigned to the newly formed quaternary centre. Unfortunately, the signals in the ^{1}H NMR spectrum were extremely broad due to the presence of rotamers caused by potentially both the Cbz and amide functionalities and so was only of limited use in the assignment. Efforts to resolve the broadness *via* VT NMR were unsuccessful within the available temperature windows. We therefore focused instead on employing alternative ester **122** in this chemistry

as we hoped that this may result in better resolved spectra. Unfortunately, reaction of ester **122** with *iso*-butylamine was unsuccessful; however interestingly, hemiaminal **183** was isolated in a 22% yield (entry 2). Reaction of ester **122** instead with a secondary amine (dimethylamine), gave the desired product **182** and hemiaminal **183** in respective isolated yields of 15% and 22% (entry 3). The structure of β,β-difunctionalised *N*-heterocycle **182** was again confirmed by ^{1}H and ^{13}C NMR spectroscopy, with key signals at δ_C 58.9, 58.8 assigned to the newly formed quaternary centre of each rotamer. Unfortunately, the presence of a mixture of rotamers again resulted in broadened signals in the ^{1}H NMR spectrum. The structure of hemiaminal by-product **183** was determined *via* HRMS and ^{1}H and ^{13}C NMR spectroscopic analysis. A key signal was identified at δ_H 5.72 corresponding to the C*H*OH proton.

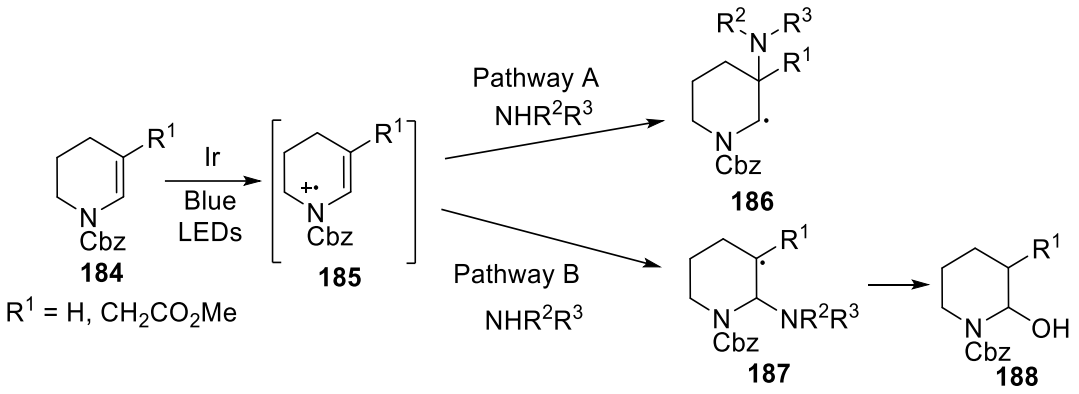
Table 3.6: Synthesis of β,β-difunctionalised *N*-heterocycles *via* photochemically-catalysed hydroamination methodology.



Entry	Enecarbamate	Amine	Product	Isolated product yield (%)	Isolated yield of 183 (%)
1	 **162**		 **180**	19	n/a
2	 **122**		 **181**	0	22
3	 **122**	$NHMe_2$	 **182**	15	22

Scheme 3.12 presents our proposed pathway towards the formation of hemiaminal by-product **183** as adapted from previous work carried out in the group.[42] It has

previously been suggested that irradiation of unsubstituted enecarbamate **184** (R^1 = H) and Ir catalyst with blue LEDs results in the formation of the photoexcited Ir catalyst of which can then be quenched by electron-transfer from enecarbamate **184** to form electrophilic radical cation species **185** (see section 3.1.2, scheme 3.3). From here, we have identified two potential reaction pathways which can take place when treated with primary and secondary amines. We propose that when unsubstituted systems are employed, pathway A will be favoured due to the increased stability of the α-amino radical over the β-amino radical, and therefore the formation of β-aminated heterocycles **186** would be favoured. When substituted enecarbamates are employed (e.g., $R^1 = CH_2CO_2Me$) it can be assumed that pathways A and B would compete due to the enhanced stability of the β-amino radical and therefore a mixture of β-substituted and α-substituted heterocycles **186** and **187** would be formed. It is likely that aminal **187** would be unstable and undergo hydrolysis during work-up or purification to yield hemiaminal **188**. In the reactions involving ester **122**, hemiaminal by-product **183** was only observed following purification by column chromatography, supporting the validity of this hypothesis. Due to this ambident reactivity displayed by substituted enecarbamate system **184**, we decided to focus our efforts on the development of the intramolecular hydroaminative methodology for the synthesis of β-spirocyclic scaffolds **157** (see section 3.2.1, scheme 3.6), where regiocontrol in the β-addition might be enforced by its intramolecular nature.

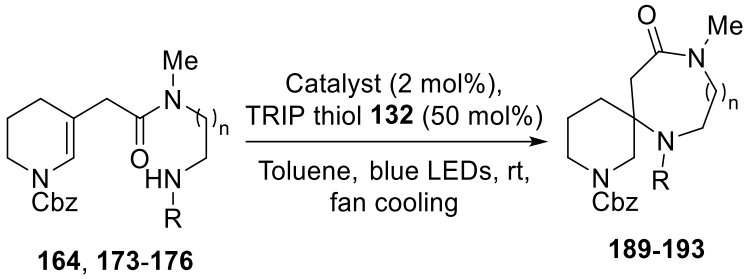


Scheme 3.12: The proposed synthetic pathway for the production of hemiaminal by-product **183**/**188**.

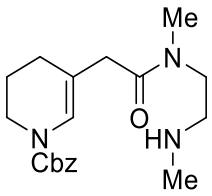
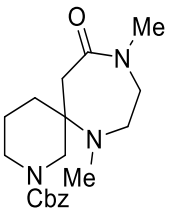
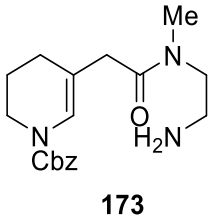
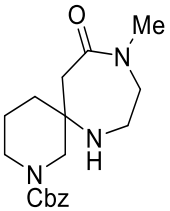
3.2.7 Synthesis of spirocyclic motifs *via* photochemically mediated hydroamination chemistry

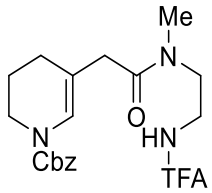
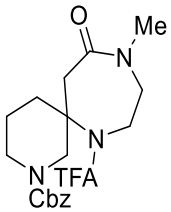
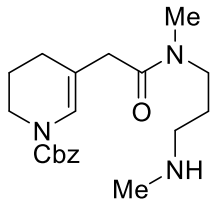
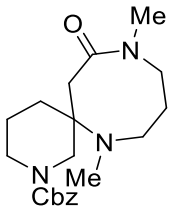
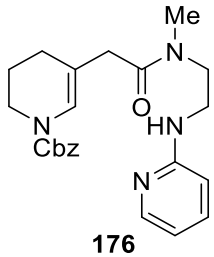
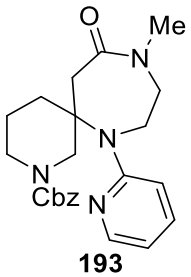
Using the precursor amines **164**, **173**-**186** prepared in section 3.2.5, we then explored the synthesis of spirocyclic motifs *via* intramolecular hydroaminative couplings. We began with the cyclisation of secondary amine **164** using the iridium photocatalyst ($[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$) and were delighted to isolate spirocycle **189** in a 57% yield after purification by column chromatography (table 3.8, entry 1). Alternative Ir catalysts were then employed and the results analysed *via* quantitative HPLC. High yields of 88% were obtained for $[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$ and $[Ir(dF(CF_3)ppy)_2(dtbbbpy)]PF_6$, however this was much lower for $[Ir(dF(CF_3)ppy)_2(4,4'\text{-}d(CF_3)bpy)]PF_6$ (23%, table 3.8, entry 1). Continuing with the initial Ir catalyst, alternative substrates **173**-**186** were then employed. *N*H spirocycle **190** was isolated in a moderate 21% yield (table 3.8, entry 2), whereas *N*-TFA spirocycle **191** was not isolated (table 3.8, entry 3). Reaction of secondary amine **175** provided an inseparable mixture of starting material and 8-membered spirocyclic heterocycle **192** after purification by column chromatography. The mixture was successfully separated *via* treatment with Boc_2O to functionalise the free amine to change its associated R_f, and subsequent purification by column chromatography allowed the isolation of spirocycle **192** in a 6% yield (table 3.8, entry 4). Finally, cyclisation of the aminopyridine-containing **176** was unsuccessful and corresponding spirocycle **193** was not isolated (table 3.8, entry 5).

Table 3.7: Synthesis of β,β-difunctionalised *N*-heterocycles *via* photochemically-catalysed hydroamination methodology.



164, **173-176** **189-193**

Entry	Enecarbamate	Product	Catalyst	Duration (h)	Yield (%)
1	 **164**	 **189**	[Ir(dF(Me)ppy)$_2$(dtbbbpy)]PF$_6$	72	52[a]
			[Ir(dF(Me)ppy)$_2$(dtbbbpy)]PF$_6$	72	(88)[b]
			[Ir(dF(CF$_3$)ppy)$_2$(dtbbbpy)]PF$_6$	72	(88)[b]
			[Ir(dF(CF$_3$)ppy)$_2$(4,4'-d(CF$_3$)bpy)]PF$_6$	72	(23)[b]
2	 **173**	 **190**	[Ir(dF(Me)ppy)$_2$(dtbbbpy)]PF$_6$	96	21[a]

3	 **174**	 **191**	$[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$	96	0[a]
4	 **175**	 **192**	$[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$	72	6[a,c]
5	 **176**	 **193**	$[Ir(dF(Me)ppy)_2(dtbbbpy)]PF_6$	96	0[a]

[a]Isolated yields determined following purification by column chromatography. [b]Yields determined *via* quantitative HPLC analysis of the crude compound. [c]Inseparable unreacted starting amine **175** removed *via* reaction with Boc_2O and further purification *via* column chromatography.

Broadened ^1H NMR spectra were obtained for spirocyclic heterocycles **189**, **190** and **192** due to the presence of rotamers, as exemplified by the ^1H NMR spectrum of **189** presented in figure 3.2. Therefore, characterisation was performed using a combination of 1D and 2D NMR spectroscopy. For 7-membered spirocycle **189**, a key signal at δ_C 54.4 corresponding to the newly formed quaternary centre was identified. Furthermore, analysis of the HMBC spectrum indicated an interaction between this quaternary carbon and the adjacent *N*-Me environment (δ_H 2.45–2.31,

3H, m) as highlighted in figure 3.3. The structures of spirocyclic heterocycles **190** and **192** were assigned by analogy. Variable temperature NMR was also explored to reduce the spectral broadening. Figure 3.4 shows the ^{1}H NMR spectrum in DMSO at 383 K for [6,7] spirocycle **189** which exhibits sharper and more resolved peaks, most noticeably in the region of 3.10–3.60 ppm. Unfortunately, due to limited material, a sufficiently resolved associated ^{13}C NMR spectrum and associated 2D spectroscopic data were not obtained.

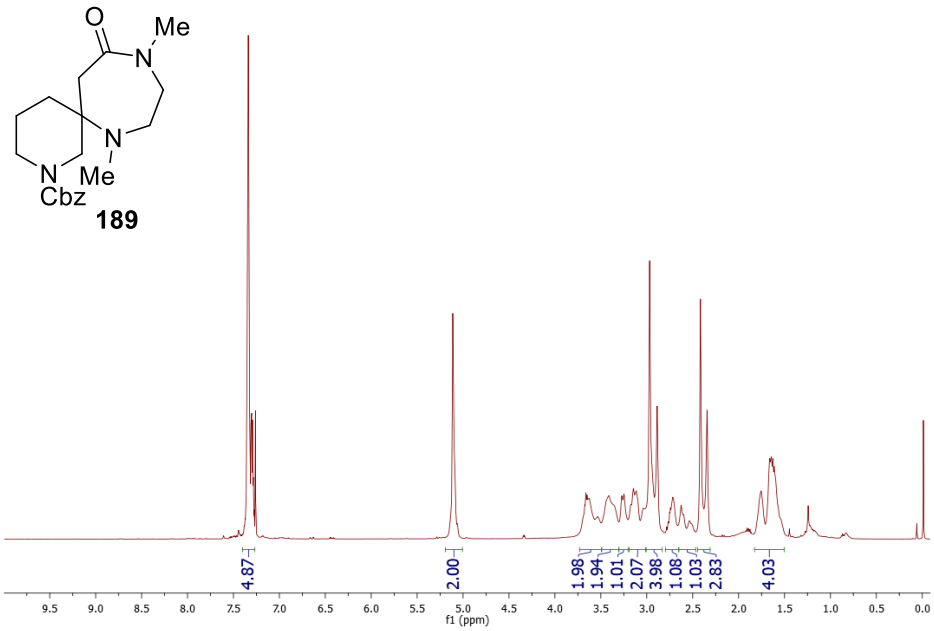


Figure 3.2: The ^{1}H NMR spectrum of rotameric [6,7] spirocycle **189** in $CDCl_3$.

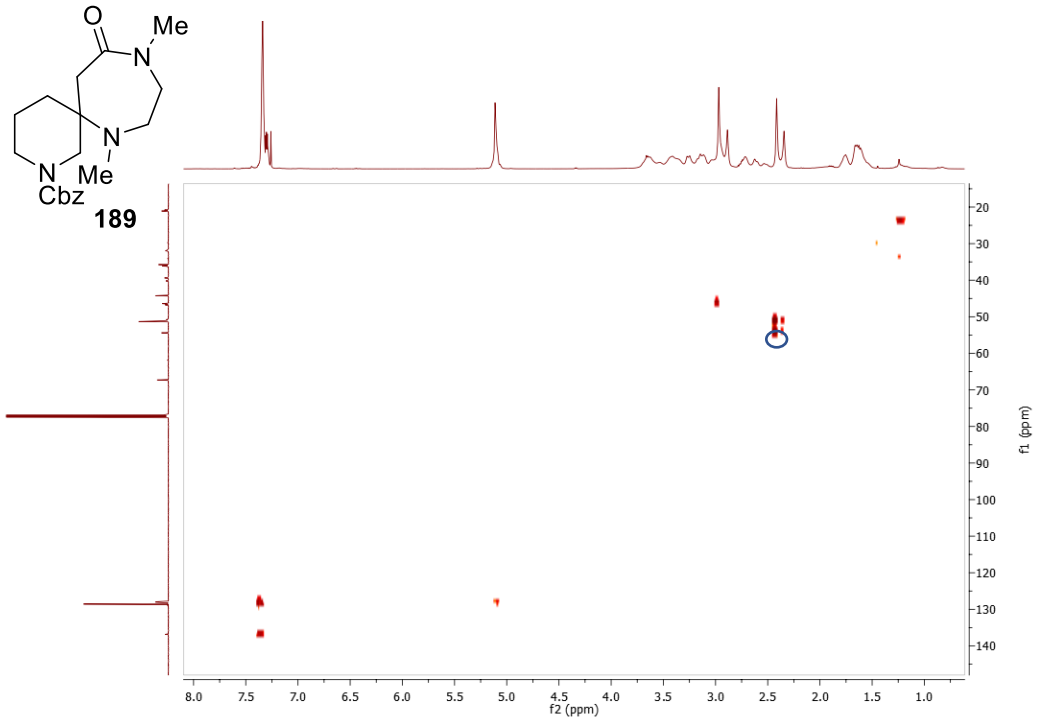


Figure 3.3: The HMBC spectrum of spirocycle **189** ($CDCl_3$), illustrating the interaction between the quaternary centre and *N*-Me environment.

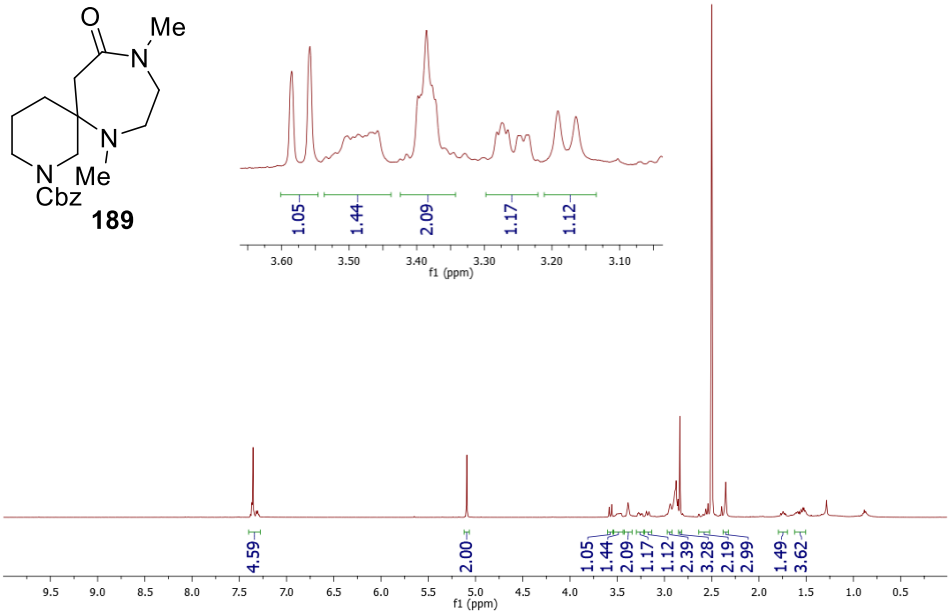
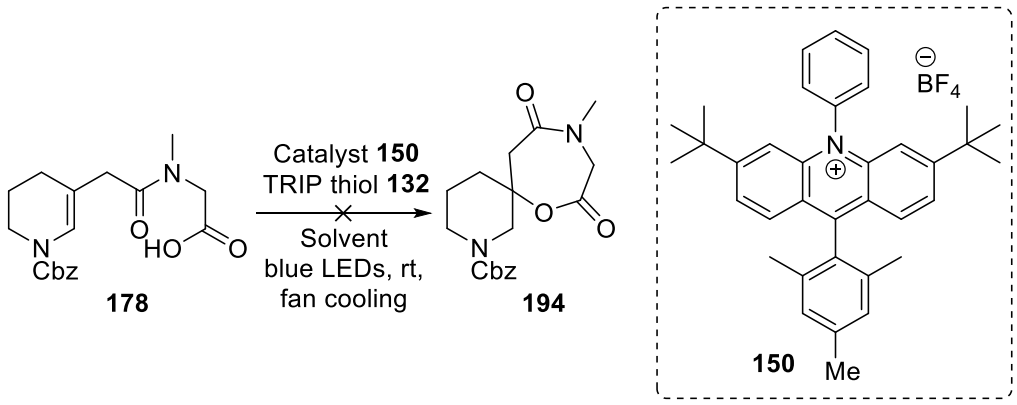


Figure 3.4: The ^1H NMR spectrum of rotameric [6,7] spirocycle **189** in d_6-DMSO at 383 K.

Cyclisations employing acid **178** were also briefly attempted, using both Nicewicz's[57] hydrofunctionalisation conditions and those developed in our group,[42] however, these efforts were unsuccessful (scheme 3.13).



Scheme 3.13: Attempts towards the synthesis of β,β-difunctionalised *N*-heterocycle **194** *via* photochemically-catalysed hydroamination methodology. Conditions: **150** (2.5 mol%), TRIP thiol (20 mol%), NaOAc (0.25 eq.), DCE, blue LEDs (455 nm), 16 h or **150** (2 mol%), TRIP thiol (50 mol%), toluene, blue LEDs (390 nm), fan cooling, 16 h.

3.2.8 Summary of results

We have successfully developed synthetic routes towards a series of β-functionalised *N*-heterocycles containing ester and amide functionalities and subsequently employed hydroamination chemistry to deliver several β,β-difunctionalised scaffolds. We have additionally been able to modify this chemistry for the preparation of a range of highly valuable β,β-difunctionalised spirocyclic heterocycles **189**, **190** and **192**.

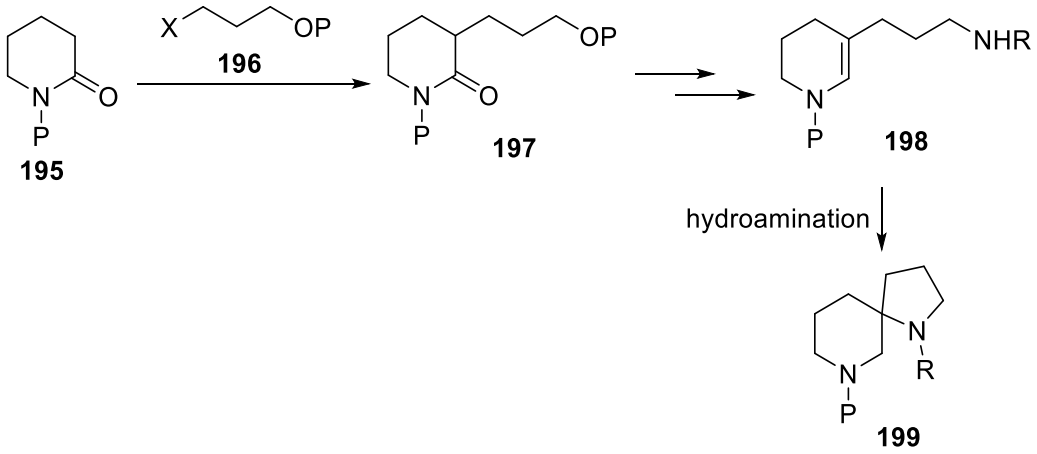
3.3 A complementary synthetic approach towards the synthesis of [6,5] spirocyclic motifs from lactams

3.3.1 Introduction

Section 3.2 describes the successful syntheses of several β,β-difunctionalised spirocyclic heterocycles employing either a two-step photocatalysed process or a

combination of photochemical and conventional synthetic approaches. The methodologies were limited to the inclusion of an amide functionality at the β-position with respect to the heterocyclic ring as well as only 7- and 8-membered appended rings being accessible. Another significant limitation is the difficulty in the preparation of the enecarbamate-based spirocyclic precursors. The photocatalysed alkylation chemistry was low yielding and highly substrate specific, whereas the alternative non-photocatalysed approach was lengthy and bespoke in nature, not allowing for facile variation in the ring size of the original heterocycle.

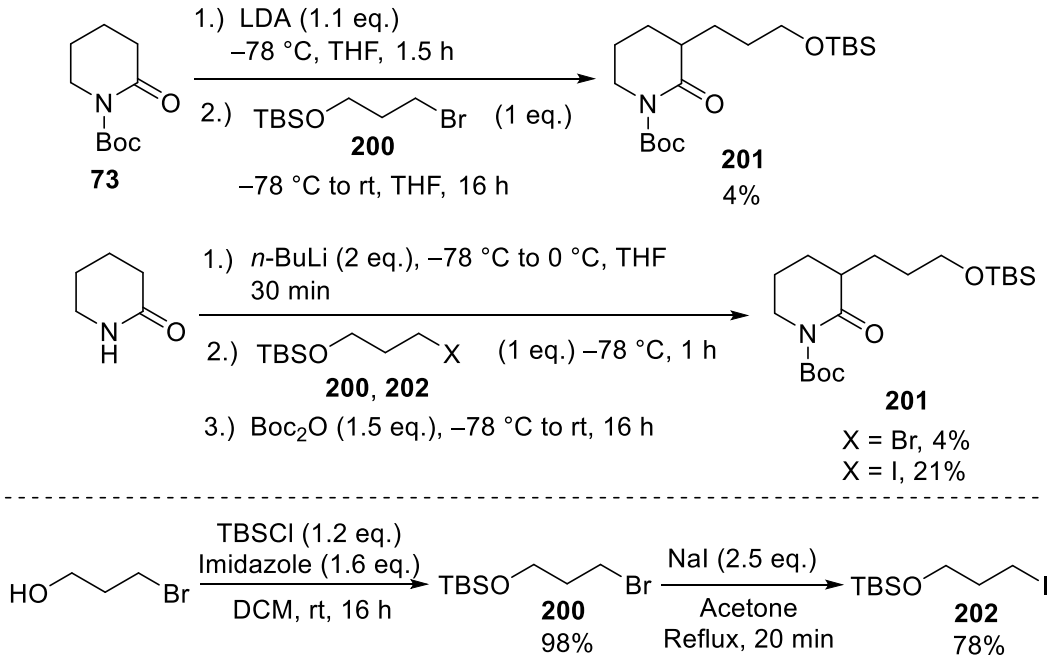
This section describes an alternative and complementary approach to the synthesis of [6,5] spirocyclic motifs starting from lactams as described in scheme 3.14. Initially lactams **195** would be functionalised with protected haloalcohols **196** *via* enolate chemistry. Substituted lactams **197** would then undergo the reduction and elimination methodology described previously (see section 2.2.3) to access the corresponding β-substituted enecarbamates. The desired amine tether would then be installed *via* a series of functional group conversions to access amines **198**. Finally, cyclisation could then be achieved using the same hydroamination methodology as described in section 3.2 to provide [6,5] spirocycles **199**. We envisaged that this methodology would enable access to alternative ring sizes through variation of both the starting lactam and haloalcohol.



Scheme 3.14: An overview of the synthetic approach towards [6,5] spirocyclic motifs **199**.

3.3.2 Results and discussion

We began with the β-functionalisation of 6-membered *N*-Boc lactam **201** *via* lithiation and trapping with TBS protected haloalcohol **200**, which provided lactam **201** in a low yield of 4% (scheme 3.15). To improve the low yield, δ-valerolactam was employed as the starting substrate *via* formation of its dianionic enolate, followed by reaction with the alkyl halide and an *in-situ* Boc protection step, which afforded lactam **201** again in a 4% yield. We suspected that the low yield many be resulting from poor reactivity of protected haloalcohol **200** and so planned to instead employ the analogous iodide-substituted derivative *via* a Finkelstein reaction. Bromo-substituted alcohol **200** was obtained *via* TBS protection of 3-bromopropanol and treatment with NaI in acetone at reflux for 20 minutes afforded iodide-substituted alcohol **202** in 78% yield (scheme 3.15).[112,113] Treatment of the dianionic enolate of δ-valerolactam with iodide **202** successfully resulted in an improved 21% yield (scheme 3.15). To access the analogous five-membered β-substituted lactam, we treated 2-pyrrolidinone with these conditions, however no desired product was isolated in this case.

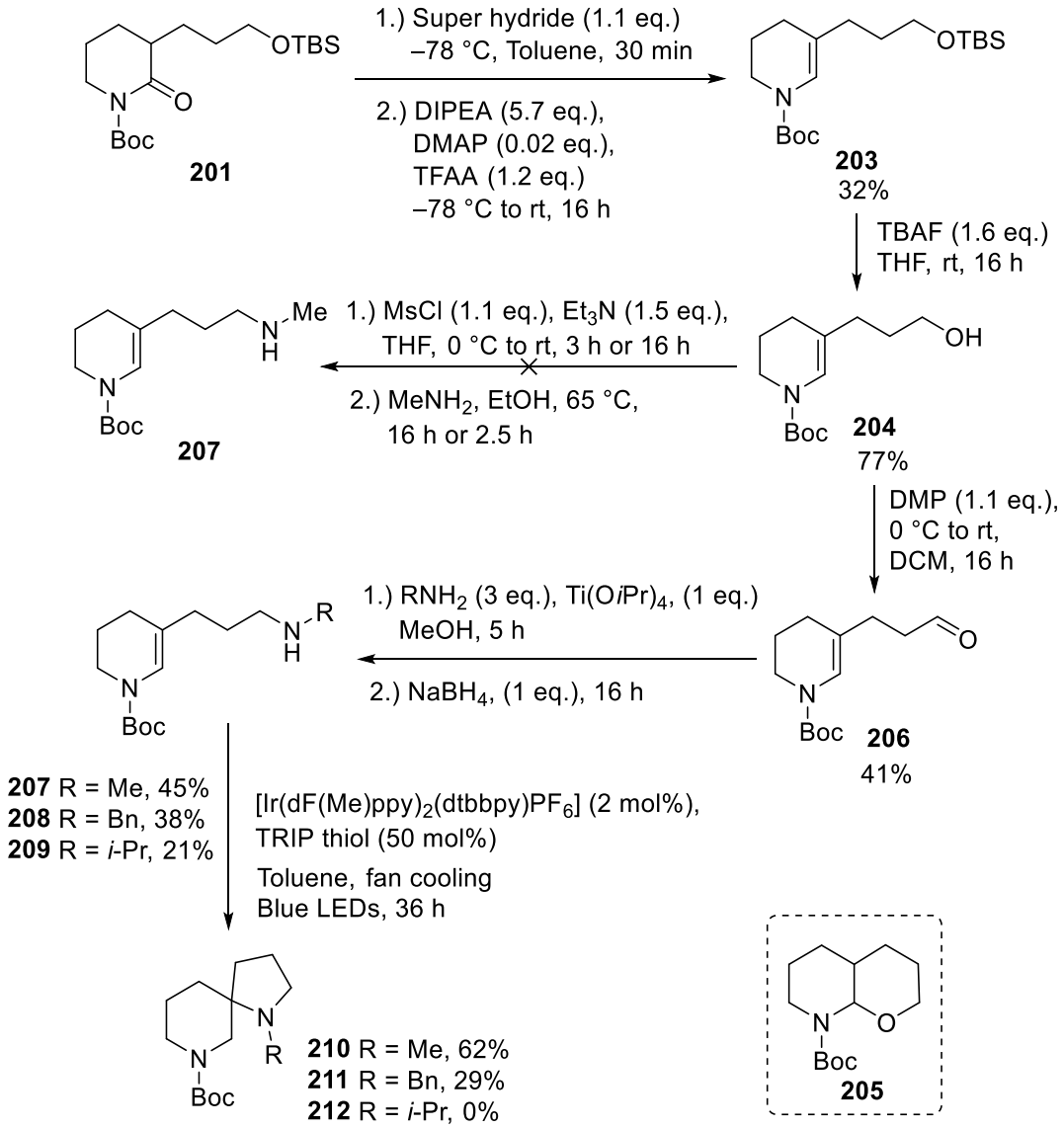


Scheme 3.15: The synthesis of β-functionalised lactam **201** and protected haloalcohols **200** and **202**.

With β-substituted lactam **201** in hand, we continued with the remainder of the route (scheme 3.16). Reduction and elimination were performed using Super hydride©, as described in section 2.2.3, providing enecarbamate **203** in 32% yield.[55] TBS deprotection using TBAF then gave impure alcohol **204** in approximately 77% yield.[114] The impurity was not removed due to the observed instability of alcohol **204** upon chromatographic purification (TLC and flash column chromatography). In efforts to understand this, it was discovered that upon treatment of alcohol **204** with aging $CDCl_3$, cyclised hemiaminal ether **205** was observed, presumably owing to residual HCl accumulation in solution. Indeed, the acid-catalysed cyclisation of alcohol **204** has been reported previously in the literature.[115] The structure of **205** was confirmed by ^1H and ^{13}C NMR spectroscopy ($CDCl_3$), with signals at δ_H 5.22 ppm (1H, br m) and δ_C 81.6 ppm, 82.6 ppm assigned to the hemiaminal ether CH position. Compound **205** was suggested to be formed as a single diastereomer based on the number of signals in the ^{13}C NMR spectrum, but an assignment of the relative stereochemistry was not possible due to broadened spectra occurring from the presence of rotamers. A single diastereomer with *cis* stereochemistry was assigned in the literature *via* VT analysis (80 °C in d_6-DMSO),[115] however in our case, the use of $CDCl_3$ means that an unambiguous assignment cannot be made. ^1H NMR spectroscopic data (d_6-DMSO) for alcohol **204** however is consistent with that reported in the literature and analysis in $CDCl_3$ was enabled *via* NMR solvent neutralisation.[115]

Next, conversion to the desired amines was attempted using an approach consisting of mesylation of the alcohol, followed by nucleophilic substitution with the required amine. Initial mesylation attempts were successful, however the reaction with methylamine resulted in preferential double alkylation of methylamine. To solve this issue, we performed an oxidation/reductive amination sequence. Oxidation of alcohol **204** using DMP furnished aldehyde **206** in 41% yield.[106] Subsequent reductive amination using $Ti(O\textit{i}Pr)_4$ and several primary amines resulted in the preparation of secondary amines **207**-**209** in yields of 45, 38, and 21%.[116] Finally, photochemically catalysed hydroamination successfully facilitated the cyclisation of amines **207** and **208**, affording [6,5] spirocyclic carbamates **210** and **211** in 62 and 29% yields.

Unfortunately, no desired product **212** was isolated in the reaction of amine **209**. Analysis by LCMS suggested the formation of a by-product with a mass of (M+2), presumably owing to a competing reductive pathway, however isolation of this compound was not achieved.



Scheme 3.16: The synthesis of [6,5] spirocycles **210**-**212** from β-substituted lactam **201**.

The structures of [6,5] spirocycles **210** and **211** were assigned by NMR spectroscopy. Like the spirocycles **189**, **190** and **192** discussed in section 3.2.7, broad spectra caused by the presence of rotamers led to difficult assignments. Despite this, the key

quaternary spirocyclic ^{13}C NMR signals were identified in both cases (61.5 ppm for **210**, 62.2 ppm for **211**) and furthermore, for *N*-Me spirocycle **210**, an interaction by HMBC was identified between this and the signal corresponding to the methyl substituent (figure 3.5). To improve the spectral resolution, spirocycle **210** was subjected to Boc deprotection, however no significant improvement in resolution was observed.

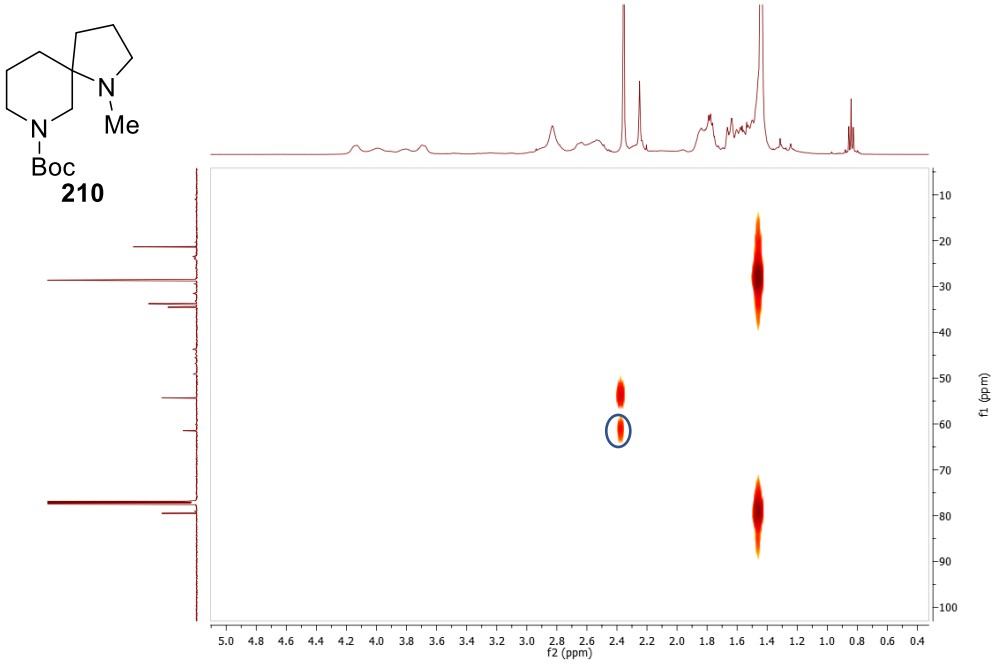


Figure 3.5: The HMBC spectrum of spirocycle **210** ($CDCl_3$), illustrating the interaction between the quaternary centre and *N*-Me environment.

3.3.3 Summary of results

This section describes the successful preparation of two novel [6,5] spirocyclic compounds **210** and **211** using a complementary approach to that presented in section 3.2. Whilst modification would allow access to alternative sizes in both the original and appended rings, its lengthy and stepwise nature meant that efforts to do so were not pursued further.

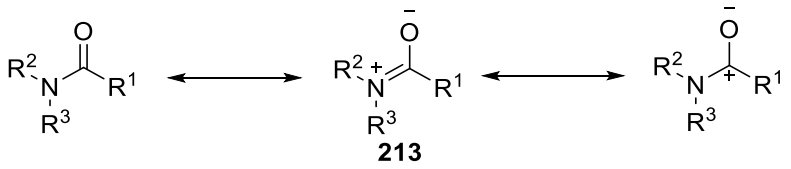
3.4 Chapter summary

This chapter has described the successful application of a toolkit of photocatalysed β-functionalisation approaches for the elaboration of enecarbamates and construction of novel and highly valuable spirocyclic systems. Subsequent chapters will explore further implementations of this hydroaminative-based methodology for the synthesis of alternative unique and three-dimensional polycyclic scaffolds through enecarbamate β-elaboration.

4 Chapter 4: Synthesis of diazabicyclic twisted amides and anilines

4.1 Background

Twisted cyclic amides have received significant attention in the literature over the last thirty years due to their unique characteristics and reactivity profiles in comparison to the conventional amide motif. In highly strained cyclic systems, the usual planarity and conjugation between the nitrogen lone pair and carbonyl π-system (n_N to $\pi^*_{C=O}$), as described by the resonance structures of amide **213** in scheme 4.1, is disrupted.[117,118]



213

Scheme 4.1: The typical resonance structures observed for the conventional unstrained amide **213** resulting from n_N to $\pi^*_{C=O}$ orbital overlap.[118]

This results in unique geometric effects such as lengthening of the N−C bond and shortening of the C=O bond and changes in the bond angles at N and C. Novel

hydrogen-bonding behaviour can also be observed, with an increased preference for protonation at nitrogen. Novel reactivity has also been observed including sensitivity to hydrolysis and N-C bond cleavage. In addition to bond length measurements, several other parameters as often used to observe the restricted overlap between the N-lone pair and C=O bond. These include ^{13}C NMR and IR spectroscopy as well as the sum of angles about N and the twist angle (τ, a descriptor of the magnitude of rotation around the N−C(O) bond) providing insight to the geometry and overall distortion easily calculated from X-ray crystallographic data.[117,118]

Figure 4.1 displays several examples of literature polycyclic twisted amides, with Kirby's twisted amide **214** (1-aza-2-adamantanone) as a pivotal example.[119] Twisted amide **214** exhibits minimal nitrogen lone pair and carbonyl π-bond overlap due to its rigidity and constraint within a ring, therefore displaying aminoketone-like properties (δ_C = 200 ppm for C=O by NMR), and deviated bond lengths (N-C = 1.475 Å and C=O = 1.196 Å) from those of typical unconstrained tertiary δ-lactams (for example: N-C = 1.352 Å and C=O = 1.233 Å).[120] Twisted amide **214** has pyramidal geometry at nitrogen (sum of bond angles at *N* = 325.7°) and a high calculated twist angle (τ = 90.58°). 2-Quinuclidonium tetrafluoroborate **215** has also recently been reported with a similar twist angle (τ = 90.9) and bond length deviations (N-C = 1.526 Å and C=O = 1.192 Å).[121] Tröger's base-derived 1-azabicyclo[3.3.1]nonan-2-one bridged systems **216** also display high distortion, though less extreme than the latter examples (τ = 41.0°, N−C = 1.430 Å, C=O = 1.210 Å).[122,123]

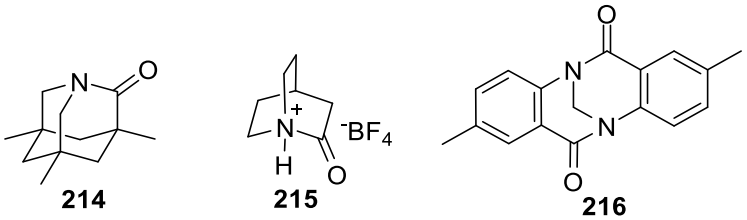
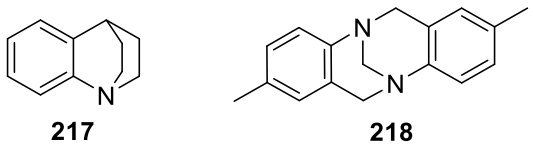


Figure 4.1: The structures of exemplar polycyclic twisted lactams Kirby's twisted amide **214**[119], 2-quinuclidonium tetrafluoroborate **215**[121], and Tröger's base-derived lactam **216**.[122,123]

This distortion can often result in interesting and novel reactivity. For example, Tröger's base-derived bridged systems **216** (figure 4.1) exhibit almost equienergtic behaviour in terms of N- and O-protonation as opposed to preferential O-protonation of non-twisted amides.[122,123] Derivatives of these have been employed in *N*-alkylation chemistry, facilitating C-N cleavage. Due to their tendency to undergo *N*-alkylation, twisted polycyclic amides can readily participate in reactions such as ring-opening polymerisation. An example of this concerns the halide-rebound polymerisation *via* alkyl iodide activation at nitrogen.[124]

Similar distortive effects can also be observed in aniline-based polycyclic systems where conjugation between the nitrogen lone pair and the aromatic π-system is disrupted, such as in benzoquinuclidine **217**[125,126] and Tröger's base **218**[127], presented in figure 4.2. Additional studies of benzoquinuclidine **217** have also reported the lack of typical diagnostic UV absorption bands typically observed for aromatic amines as well as anomalously low excited-state lifetimes. Furthermore, anomalous reactivity with diazonium salts and pK_aH have also been reported. Monoprotonated Tröger's base **218** has been shown to exhibit an abnormally low pK_aH (3.2) due to anomeric and substituent effects.



217 **218**

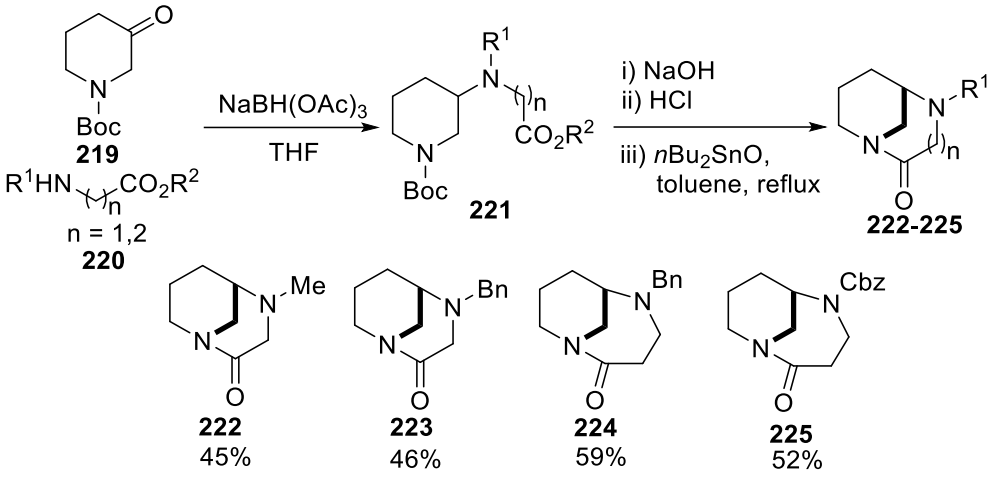
Figure 4.2: The structures of exemplar twisted anilines benzoquinuclidine **217**[125,126] and Tröger's base **218**[127].

4.2 Synthesis of diazabicyclic twisted amides

4.2.1 Introduction

Previous work in our group by Dr Haitham Hassan has focused on the synthesis of twisted bicyclic amides **222**-**225**, based on the bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane lactam scaffolds (scheme 4.2).[60] The approach consisted of initial reductive amination carried out between 1-Boc-3-piperidone **219** and amino

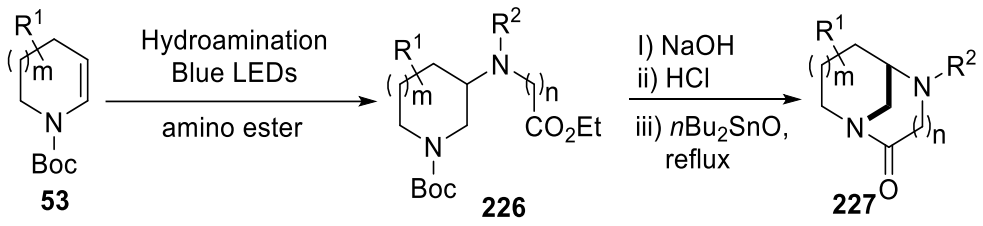
esters **220** under treatment with $NaBH(OAc)_3$ to yield intermediate amino esters **221**. Then, a one-pot, three-step procedure was carried out, first consisting of ester hydrolysis with NaOH, followed by sequential Boc deprotection using HCl and finally cyclisation *via* treatment with *n*-Bu_2SnO at reflux under Dean-Stark conditions to afford final twisted bicyclic amides **222**-**225**.



Scheme 4.2: The reductive amination and cyclisation approach towards the synthesis of bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane lactam scaffolds **222**-**225**, reported by Hassan *et al*.[60] Yields reported over steps i-iii.

Limitations of the approach regard its scope, with only bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane scaffolds accessed. This was mostly due to the poor accessibility of starting 3-ketoazacycles alternatives, especially those of alternative ring sizes, meaning that variation in the original ring was not easily achievable. We therefore planned to tackle these limitations by providing an alternative route towards the intermediate amino esters **221**. Scheme 4.3 describes our proposed procedure, instead employing starting enecarbamates and functionalising *via* β-hydroamination. To achieve this, *N*-Boc enecarbamates **53** would be treated with amino esters with appropriate photocatalysts under irradiation with blue LEDs to access amino ester intermediates **226**, followed sequentially by the cyclisation methodology previously described (scheme 4.2). The use of enecarbamates would allow facile variation in both the original and appended ring sizes, therefore expanding the scope. Furthermore, trisubstituted enecarbamates containing a substituent at the β-

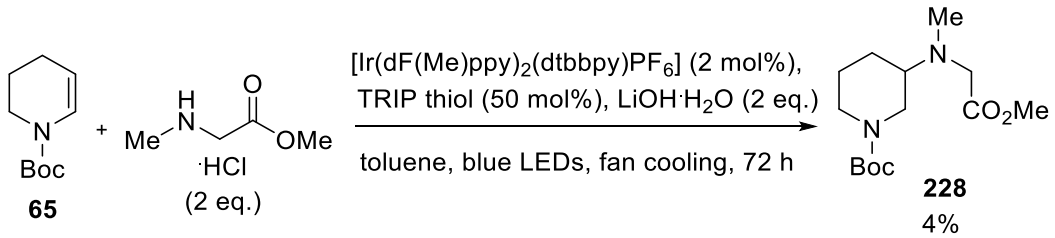
position could now be employed, allowing access to highly valuable tetrasubstituted-centre bearing scaffolds, not accessible through the original procedure.



Scheme 4.3: Our proposed approach towards the synthesis of bridged bicyclic lactams **227**, consisting of hydroamination followed by the cyclisation methodology.

4.2.2 Results and discussion

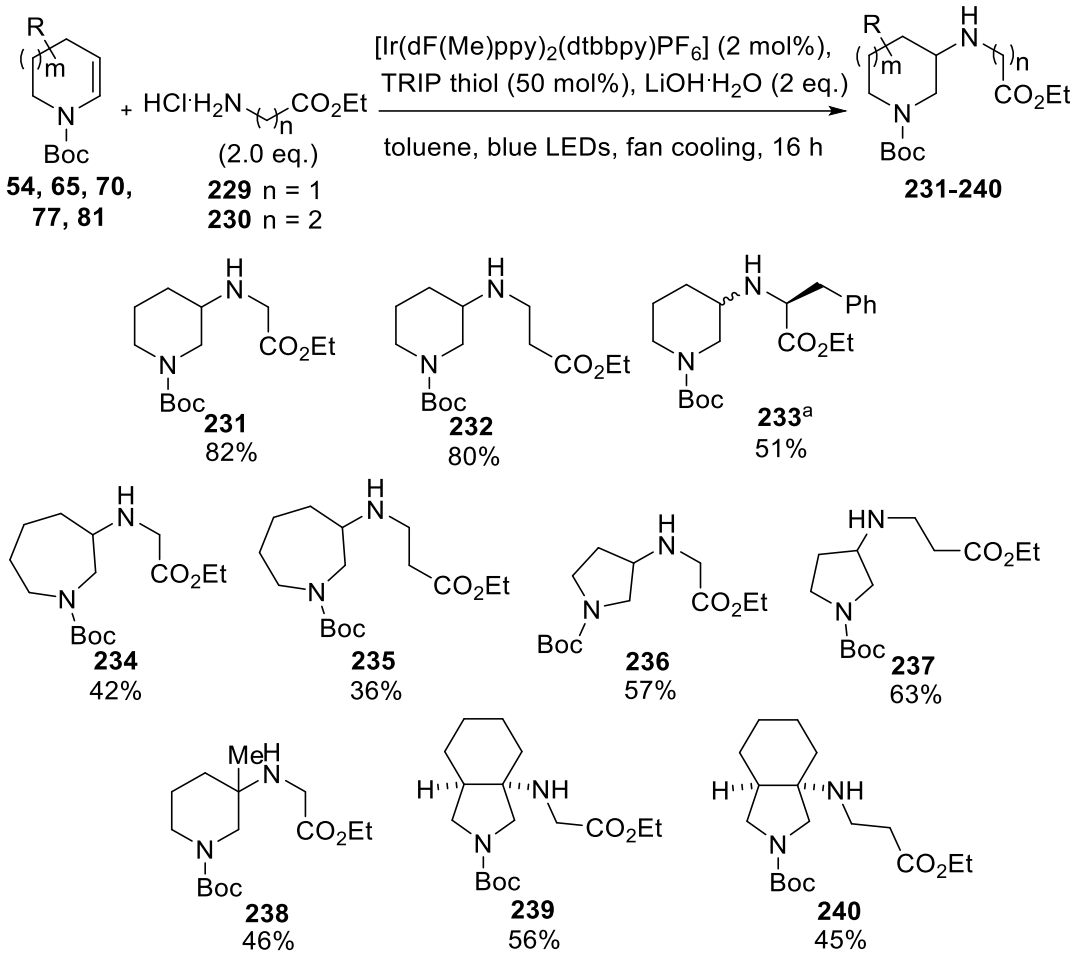
Efforts began with the hydroamination of enecarbamates with secondary amino esters to directly deliver tertiary amino esters as suitable precursors for cyclisation.[60] To achieve this, reaction of 6-ring *N*-Boc enecarbamate **65** with sarcosine methyl ester hydrochloride was carried out *via* treatment with an iridium catalyst, TRIP thiol and lithium hydroxide under blue LED irradiation for 72 h, which yielded tertiary amino ester **228** in 4% yield (scheme 4.4).



Scheme 4.4: Hydroamination reaction of *N*-Boc enecarbamate **65** with sarcosine methyl ester hydrochloride.

Due to the low yield, we instead employed primary amino esters. This would then be followed with protection of the resulting secondary amino group prior to cyclisation. Scheme 4.5 summarises the β-hydroamination of **54**, **65, 70**, **77** and **81** with primary

amino ester salts **229** and **230**, based upon conditions reported previously in our group[42]. Initial treatment of *N*-Boc enecarbamate **65** with primary amino ester **229**, an iridium catalyst, TRIP thiol and lithium hydroxide, followed by irradiation with a blue LED (with fan cooling) for 16 h successfully afforded secondary amino ester **231** in 82% yield. Analysis by ^{1}H NMR spectroscopy clearly showed the loss of enecarbamate alkene protons as well as the incorporation of ester signals at 4.16 ppm (q) and 1.24 ppm (t). Furthermore, the indicative β-CH position could be easily identified by DEPT or HSQC analysis. The analogous reaction with alternative amino ester **230** was also successful, delivering **232** (previously prepared by Hassan *et al*.[60]) in 80% yield. Enecarbamate **65** was also used to access a pair of diastereomeric substituted amino esters **233** *via* the use of L-phenylalanine methyl ester hydrochloride in 51% yield. We then explored the enecarbamate scope, with a particular focus on alternative ring sizes. The use of 7-membered enecarbamate **54** was also successful in accessing secondary amino esters **234** and **235**, albeit in somewhat lower yields of 42 and 36%. The 5-membered analogous examples **236** and **237** were also prepared by employing 5-membered enecarbamate **81** in good yields of 57% and 63%. Pleased with the reaction's tolerance of varying enecarbamate ring size, we then turned our attention to trisubstituted enecarbamates, as a means of installing new tetrasubstituted centres. To our delight, the hydroamination of trisubstituted enecarbamate **77** was also successful yielding tetrasubstituted amino ester **238** in 46% yield. Furthermore, we were also able to access related examples **239** and **240** in good yields of 56% and 45%, now containing both a tetrasubstituted centre and appended ring *via* the employment of [5,6] bicyclic enecarbamate **70**.



Scheme 4.5: The preparation of secondary amino esters **231**-**240** *via* hydroamination reactions of enecarbamates **54**, **65**, **70**, **77** and **81** and primary amino esters **229** and **230**. [a]Compound **233** accessed *via* the use of an alternative amino ester salt: L-phenylalanine methyl ester hydrochloride.

As expected, only the *cis*-fused diastereomers of bicyclic amino esters **239** and **240** were identified, determined by NOESY NMR spectroscopic analysis. A positive nOe interaction was observed in each case, between the two positions as indicated in figure 4.3, which presents the NOESY NMR spectrum and highlights this interaction of bicyclic amino ester **239**.

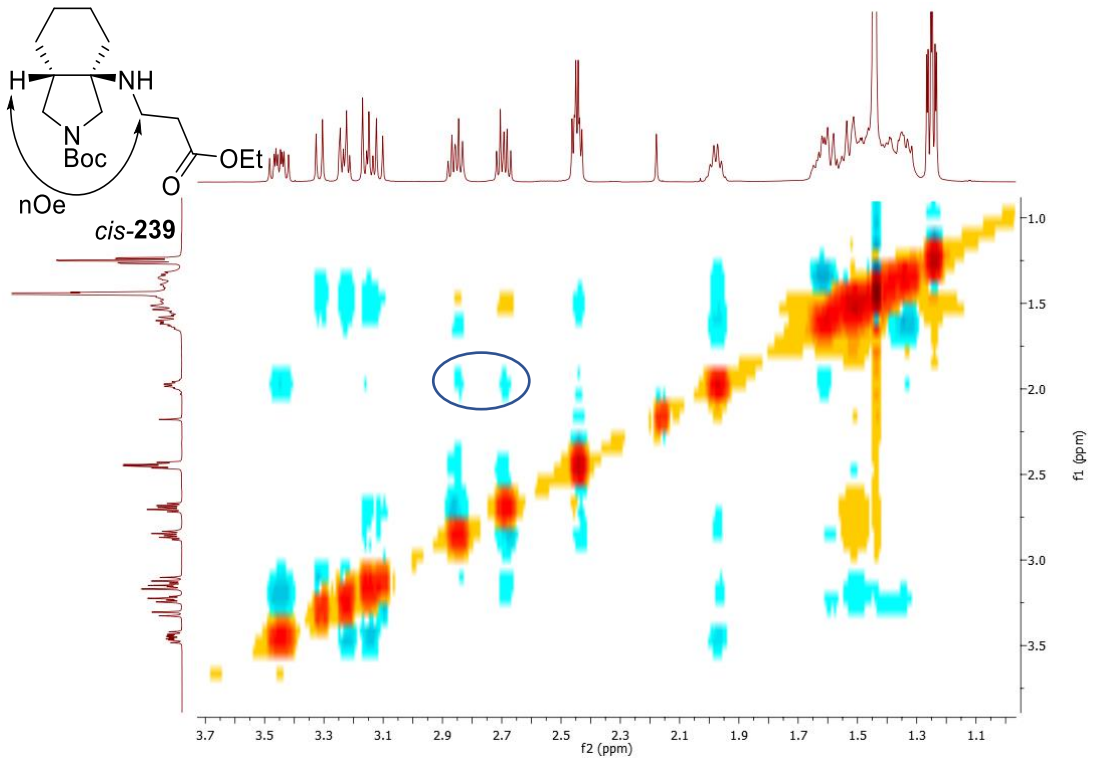
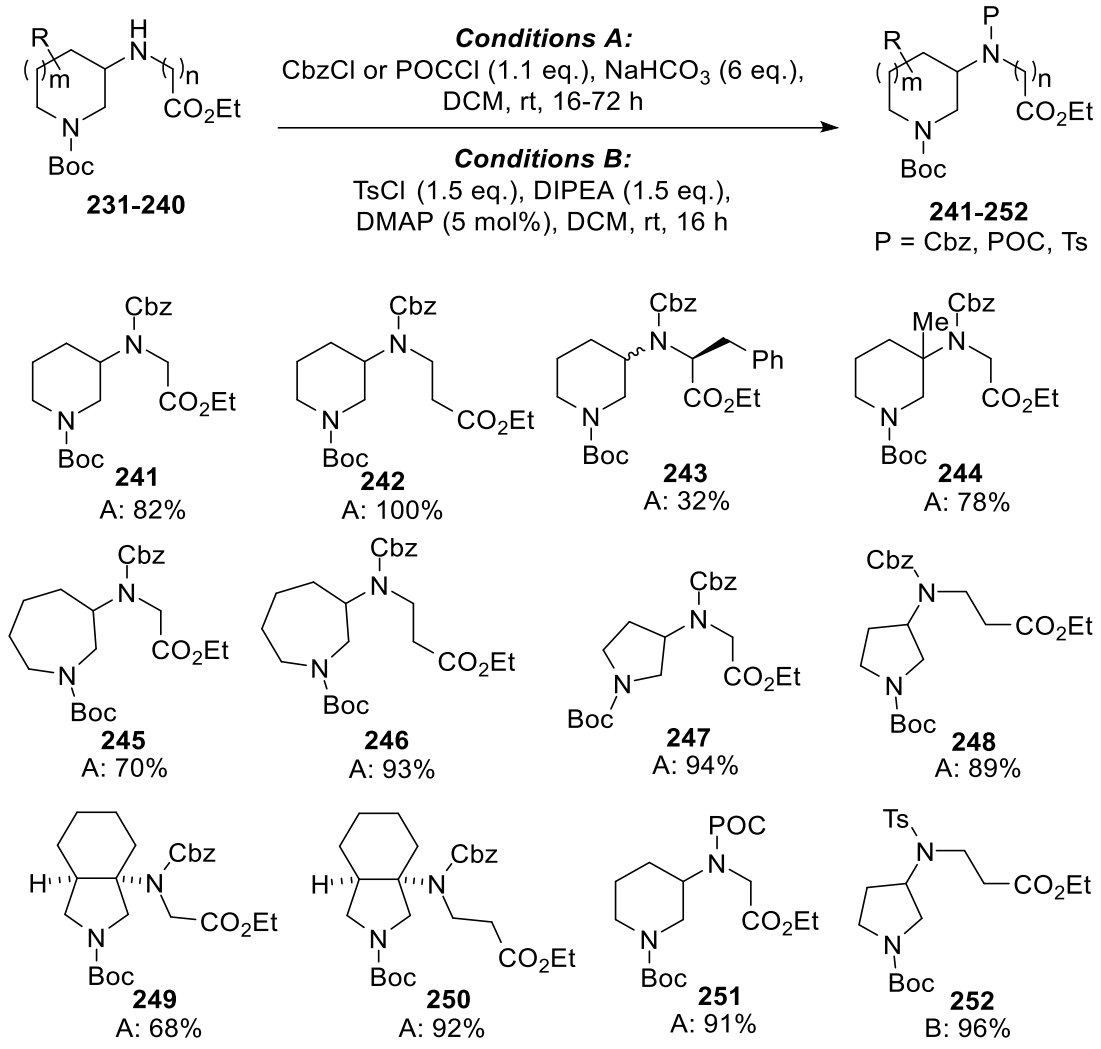


Figure 4.3: The NOESY NMR spectrum of bicyclic amino ester **239**, with a positive nOe interaction highlighted used for its *cis* assignment of relative stereochemistry.

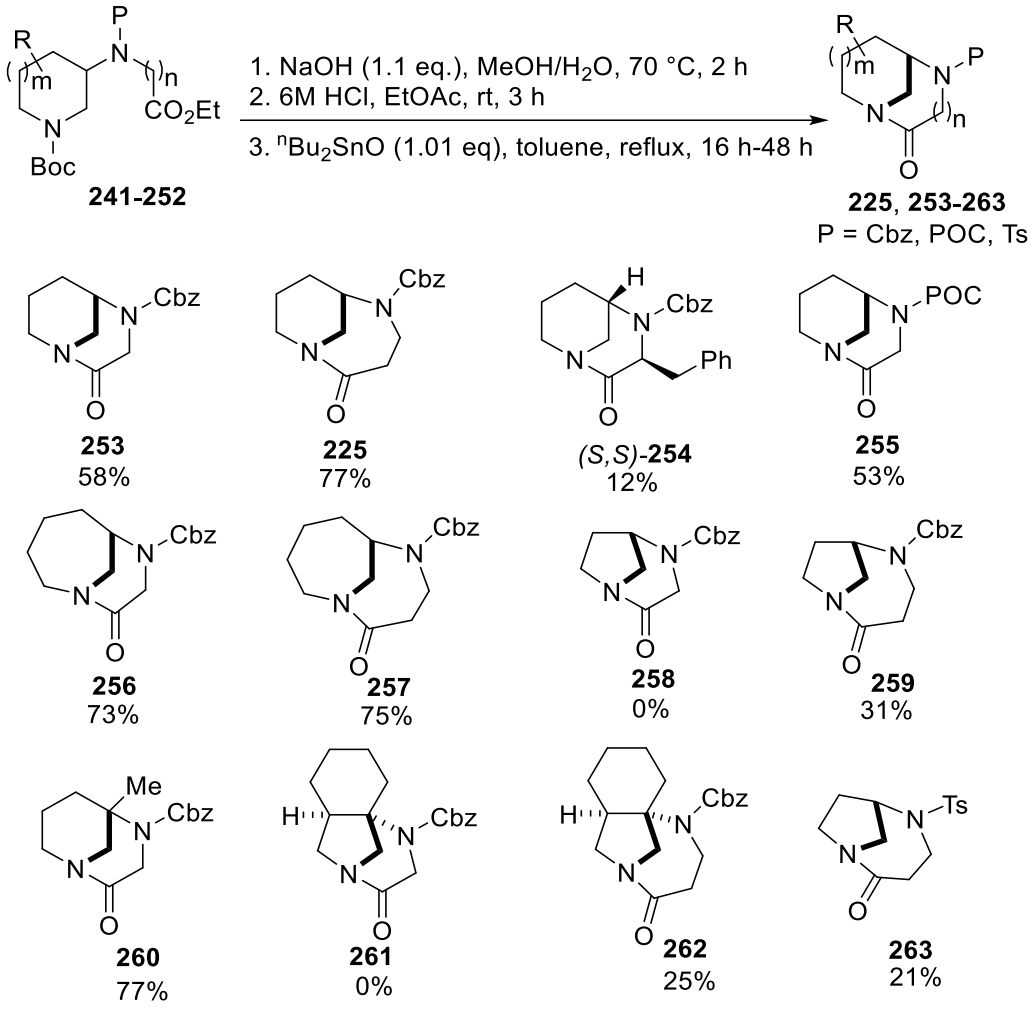
Amino esters **231**-**240** then underwent Cbz protection at the exocyclic nitrogen *via* treatment with benzyl chloroformate and $NaHCO_3$, delivering protected amino esters **241**-**252**, in mostly high yields except for a lower yielding reaction with the phenylalanine-derived substrate **233**, presumably owing to increased steric hindrance at this site (scheme 4.6, conditions A). Cbz was chosen as an orthogonal protecting group that would allow for subsequent selective removal of the Boc group in addition to being easily removable itself to allow for further potential elaboration. We also employed an alternative carbamate (POC) as shown by example **251** *via* the analogous reaction with propargyl chloroformate. Installing this handle would then enable *N*-POC amino ester **251** to be used as a probe in protein labelling experiments *via* click reactions with the alkyne substituent. A sulfonamidyl (*N*-Ts) amino ester **252** was also prepared in high yield *via* treatment with tosyl chloride, DIPEA and DMAP (scheme 4.6, conditions B), as an attempt to enhance the crystallinity of the final bridged bicyclic lactam.



Scheme 4.6: The protection of amino esters **231**-**240** to produce *N*-Cbz, *N*-POC and *N*-Ts protected amino esters **241**-**252**.

With *N*-Cbz, *N*-POC and *N*-Ts protected amino esters **241**-**252** in hand, we then turned our attention to the final hydrolytic, deprotection and cyclisation-based sequence. As summarised in scheme 4.7, initial ester hydrolysis was carried out *via* treatment with NaOH in MeOH/water at 70 °C for 3h to produce the corresponding carboxylic acid. Following removal of the solvent, Boc deprotection was achieved using 6N HCl in EtOAc at rt for 3 h, yielding the corresponding ammonium salt. Finally, after a second solvent removal, cyclisation was carried out *via* treatment with *n*-Bu_2SnO in toluene and heating at reflux under Dean-Stark conditions for 16-48 h. Subsequent solvent removal, work up and purification by column chromatography then afforded

each final bicyclic lactam. Bicyclo[3.3.1]nonane lactam **253** and bicyclo[4.3.1]decane lactam **225** were accessed in high yields (58% and 77%), with the latter previously prepared by Hassan *et al*.[60] Related bicyclo[4.3.1]decane lactams (*S,S*)-**254** and **255** were also accessed, showing that substituents on the appended ring and alternative carbamate protecting groups could be tolerated. Bicyclo[4.3.1]decane lactam (*S,S*)-**254** was isolated as a single diastereomer, with no evidence of the minor diastereomer undergoing cyclisation, *via* both the analysis of the crude ^{1}H NMR spectrum and LCMS chromatogram (see figure 4.5 for detailed assignment). We were pleased to discover that bicyclo[3.4.1]decane and bicyclo[4.4.1]undecane scaffolds **256** and **257** could also be prepared in high respective yields of 73 and 75%. *N*-Cbz bicyclo[4.2.1]nonane lactam **259** was too accessed, however in a considerably lower yield than previous examples (31%), however bicyclo[3.2.1]octane lactam **258** could not be accessed at all. We were delighted to discover that tetrasubstituted bicyclo[3.3.1]nonane lactam **260** (bearing a Me substituent) and bicyclo[4.2.1]nonane lactam **262** (bearing an appended ring) could also be prepared, though in varying yields (77% and 25%). Unfortunately, once again, the analogous bicyclo[3.2.1]octane lactam **261** could not be accessed. Finally, we were also able to access sulfonamide bearing bicyclo[4.2.1]nonane lactam **263** in a 21% yield. Consistently low yields were observed for the cyclisation of bicyclo[4.2.1]nonane lactams **259**, **262** and **263**, whereas cyclisation of bicyclo[3.2.1]octane lactams **258** and **261** did not take place. We presume these findings to be a result of increasing strain within these smaller scaffolds.



Scheme 4.7: The cyclisations of amino esters **241**-**252** to produce a library of bridged bicyclic lactams **225**, **253**-**263**.

The success of the cyclisation reactions described in scheme 4.7 were determined by ^{1}H NMR spectroscopic analysis in all cases, with an indicative loss of the ester and Boc related signals. Furthermore, an X-ray crystal structure was generated for bicyclo[4.4.1]undecane lactam **257**, as shown in figure 4.4.

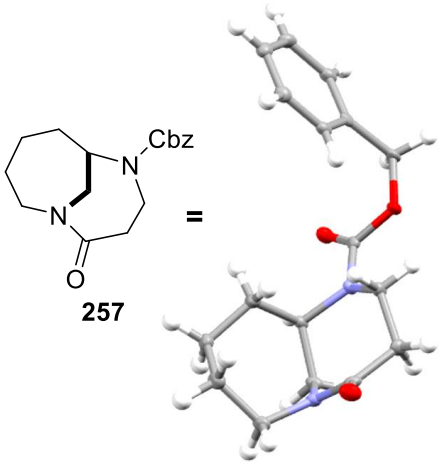


Figure 4.4: The X-ray crystal structure of bicyclo[4.4.1]undecane lactam **257**.

Bicyclo[4.3.1]decane lactam *(S,S)*-**254** was isolated following purification as a single diastereomer and enantiomer (scheme 4.7) as indicated by ^{1}H and ^{13}C NMR spectroscopic analysis. Figure 4.5 presents the 3-dimensional conformations of both possible diastereomers formed in the reaction. The absolute stereochemistry was elucidated to be *(S,S)* by a positive nOe interaction between signals corresponding to the 3-H and 7-H_A positions as indicated in the NOESY NMR spectrum shown in figure 4.6, an interaction which cannot occur for the *(S,R)* diastereomer.

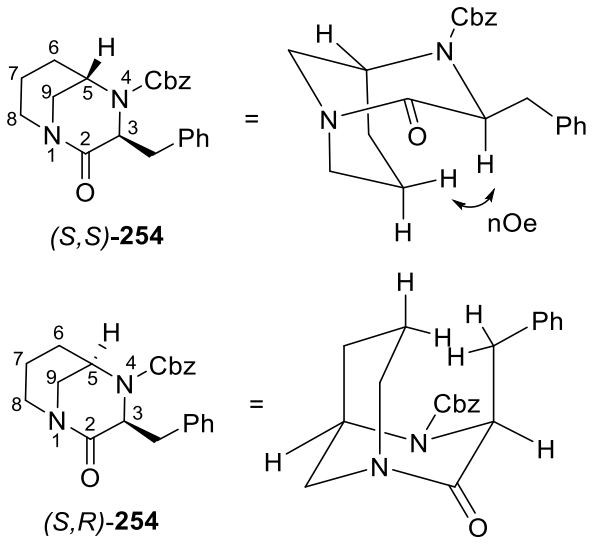


Figure 4.5: 3D conformations of the two possible diastereomers formed in the cyclisation procedure.

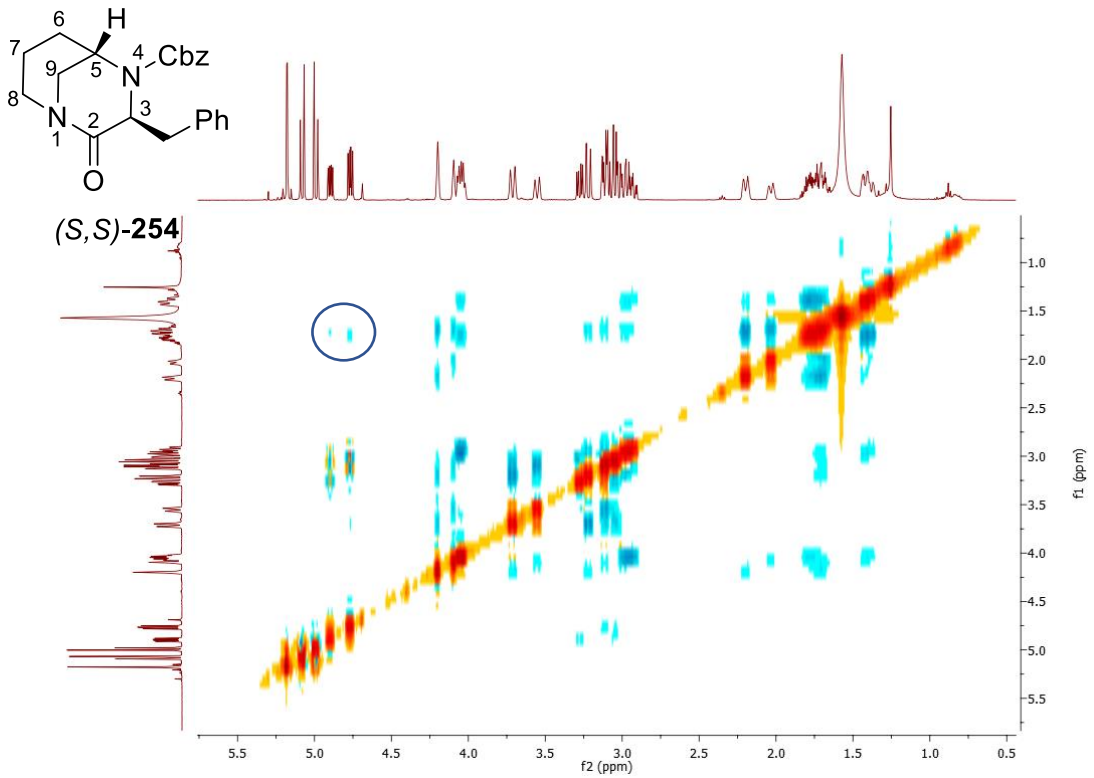


Figure 4.6: The NOESY NMR spectrum of bicyclo[4.3.1]decane lactam *(S,S)*-**254**, with a positive nOe interaction highlighted between the 3-H and 7-H_A positions used for its stereochemical assignment.

4.2.3 Summary of results

In this section we have described the successful preparation of a series of highly valuable twisted bicyclic amides. We have successfully adapted chemistry previously published in our group to exploit the benefits of enecarbamates and their subsequent functionalisation *via* photocatalysed β-hydroamination chemistry. This approach has enabled the preparation of a much broader range of ring systems than previously achieved *via* a single strategy. Highly three-dimensional systems based on the bicyclo[3.3.1]nonane, bicyclo[4.3.1]decane, bicyclo[3.4.1]decane, bicyclo[4.4.1]undecane and bicyclo[4.2.1]nonane cores were accessed in mostly high yields. Finally, complex ring systems containing tetrasubstituted centres as well as an additional appended saturated ring were prepared.

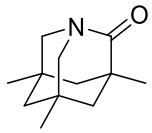
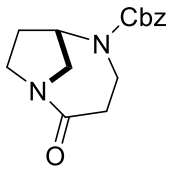
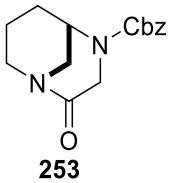
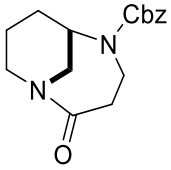
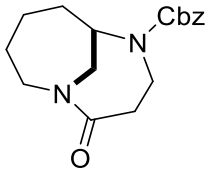
4.3 Assessment of properties of twisted amides

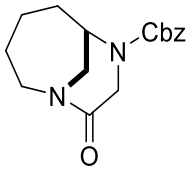
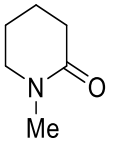
Section 4.2 describes the synthesis of a range of bicyclic ring systems exhibiting differing degrees of twist. This section will explore the assessment of physical properties to investigate this distortion and its subsequent effects on chemical reactivity and biological activity.

4.3.1 Physical properties

Two of the most accessible techniques for measuring amide twist include ^{13}C NMR and IR. Table 4.1 presents the ^{13}C NMR C=O δ and IR C=O stretching frequency for an exemplar bicyclic lactam of each ring system (**225**, **253**, **256**, **257** and **259**, entries 2-6) alongside comparative, representative strained and unstrained literature examples: Kirby's most twisted amide **214**[119] (entry 1) and *N*-Me valerolactam **264**[128] (entry 7). A decrease in ^{13}C NMR C=O δ can be observed from entries 1-7 with Kirby's most twisted amide **214** showcasing a high ketone like chemical shift (200 ppm) and *N*-Me valerolactam **264** showing a typical amide chemical shift (165 ppm). In between these extremes, the smallest bicyclo[4.2.1]nonane lactam scaffold **259** indicated the largest δ (182.1 and 182.0) decreasing to the larger scaffolds such as bicyclo[3.4.1]decane lactam **256** (δ = 170.9). A similar trend can be observed from the IR C=O stretching frequencies with a general decrease from entries 1-7. Anomalies in this data may be present due to the inconsistent overlap of amide C=O and carbamate C=O stretching frequencies, which occasionally provided coalescing broad signals and making accurate/unambiguous assignments difficult.

Table 4.1: ^{13}C NMR and IR data for twisted lactam ring systems **225**, **253**, **256**, **257**, **259** and comparative strained and unstrained literature compounds **214** and **264**.[119,128] See appendix section 9.2 for complete ^{13}C NMR and IR data for all twisted lactams.

Entry	Lactam	^{13}C NMR C=O δ (ppm)	IR C=O ν_{max} (cm^{-1})
1	 **214**	200	1732
2	 **259**	182.1, 182.0	1680
3	 **253**	180.2	1686
4	 **225**	176.8	1657
5	 **257**	172.80, 172.75	1647

6	 **256**	170.9	1667
7	 **264**	165	1650

An additional plethora of information can be generated *via* analysis of the compounds' X-ray structures, however, requires that a single crystal can be obtained. Pleasingly, bicyclo[4.4.1]undecane lactam **257** provided suitable X-ray data for structural determination (see figure 4.4); this, however, was the only *N*-Cbz bicyclic lactam isolated in solid form. Attempts to remove the Cbz group *via* hydrogenation to enhance crystallinity of bicyclo[3.3.1]nonane lactam **253** were unsuccessful and resulted in cleavage of the N-C lactam bond by the reaction solvent (MeOH), which is in itself indicative of the enhanced electrophilicity of these species versus 'simple' amides. Furthermore, the inclusion of an alternative *N*-Ts group throughout the synthetic route provided a solid bicyclo[4.2.1]nonane lactam **263** but did not sufficiently enhance crystallinity to allow a sample suitable for X-ray analysis to be prepared.

Table 4.2 therefore presents a series of measured properties for bicyclo[4.4.1]undecane lactam **257** compared with some of the twisted amides previously prepared by Hassan:[60] **265**-**267**, based on the bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane cores, from their respective X-ray data. Entries 1-7 present the distortion parameters used to calculate Winkler-Dunitz parameters, such as twist angle (τ) as an overall distortive measure. ω values represent angles measured about the amide group and were used to calculate distortion parameters χ_C, χ_N and τ (figure

4.7).[117,129,130,131] The twist angle (τ) increases as expected from bicyclo[4.4.1]undecane lactam **257** to bicyclo[3.3.1]nonane lactam **265** suggesting a trend in increasing distortion. Kirby's most twisted amide displays a high twist angle of 90.58° fitting this trend as an exemplar highly distorted amide.[119]

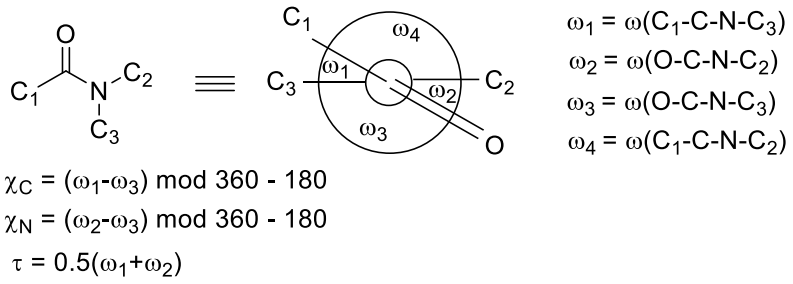
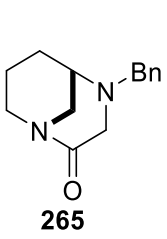


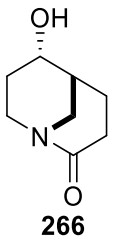
Figure 4.7: Distortive parameters as introduced by Winkler and Dunitz,[129,130] and summarised by Szostak.[117]

Entries 8-9 present the experimentally determined N-C(O) and C=O bond length which are expected to respectively lengthen and shorten with increasing distortion. N-C(O) bond length increases from bicyclo[4.4.1]undecane lactam **257** to bicyclo[3.3.1]nonane lactam **265** and therefore distortion (entry 8). C=O bond length, however, is more ambiguous and does not follow this trend (entry 9). Kirkby's most twisted amide presents longer and shorter bond lengths of 1.475 Å and 1.196 Å for N-C(O) and C=O respectively as expected. The sum of angles about the lactam nitrogen were also calculated as a geometrical assessment of nitrogen pyramidalisation and hence hybridisation (entry 10). This value is large and close to 360° for bicyclo[4.4.1]undecane lactam **257** indicating a near-planar structure, increasing to a smaller value of 334° for smaller ring system **265** indicating increased pyramidalisation at *N* (Kirby's most twisted amide = 325.7°; idealised sp^3 value = 328.5°).

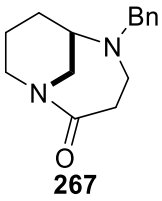
Table 4.2: Properties regarding twist of lactams **265**-**267** and **257** calculated from the associated X-ray structures of both this and previous work.[60]



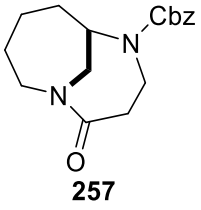
265



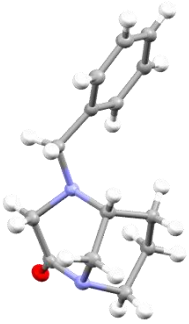
266



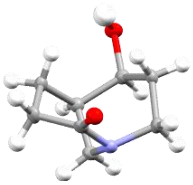
267



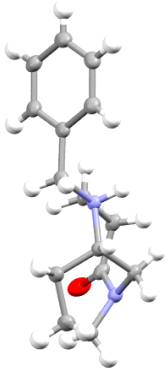
257



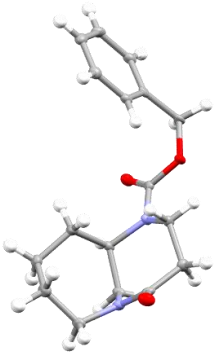
CCDC 1588303



CCDC 1588305



CCDC 1588304



CCDC 2192693

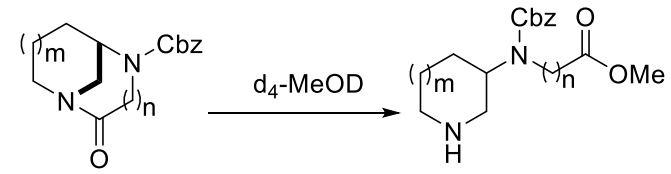
Entry			265[a]	266[a]	267[a]	257
1	**Distortion parameters (°)**	ω^1	0.06	-0.58	8.61	-4.22
2		ω^2	46.86	-43.17	-26.54	11.36
3		ω^3	173.98	-174.15	-168.55	173.82
4		ω^4	-127.06	130.39	150.62	-166.68
5		χ_C	6.08	6.4	2.84	1.96
6		χ_N	52.88	49.02	37.99	17.54
7		τ	23.45	21.8	8.9	3.57
8	**Bond lengths (Å)**	**N-C(O)**	1.38	1.372	1.361	1.355

9		**C=O**	1.233	1.232	1.218	1.233
10	**Sum of bond angles at N (°)**		333.7	341.2	348.8	357.8

[a]Compounds and associated data reported previously by Hassan *et al*.[60]

4.3.2 Chemical reactivity

To probe effects of this distortion on chemical reactivity we planned to investigate the rate of methanolysis on bicyclo[4.2.1]nonane lactam **259** and bicyclo[4.4.1]undecane lactam **257**, by accessing ring-opened amino esters **268** and **269**, as exemplified in scheme 4.8. It was found that strained bicyclo[4.2.1]nonane lactam **259** had undergone hydrolysis upon standing in air after a period of several days, whilst treatment of bicyclo[4.4.1]undecane lactam **257** with d_4-MeOD at rt for one week and at reflux for 5 h did not facilitate solvolysis of the amide bond whatsoever. Whilst these preliminary findings do not offer a means to quantifiably compare the rates of hydrolysis, they do illustrate the significant deviations in chemical reactivity. Further studies were not pursued due to the preparation of limited material.



m = 0, n = 2 **259**
m = 2, n = 2 **257**

m = 0, n = 2 **268**
m = 2, n = 2 **269**

Scheme 4.8: An overview of panned hydrolysis studies performed on bicyclo[4.2.1]nonane lactam **259** and bicyclo[4.4.1]undecane lactam **257**.

4.3.3 Biological activity

Novel biological applications may also be anticipated for some of the more reactive twisted lactams, due to their suspected acylating ability. *N*-POC bicyclo[4.3.1]decane

lactam **255** was prepared as an example of a strained lactam bearing an alkyne functionality and was used in protein labelling experiments carried out previously in our group. These experiments were performed by Dr Jack White and comprise initial incubation of the alkyne-bearing 'probe' with cell lysate to enable reactions with nucleophilic protein residues to occur. A fluorescent tag can then be attached to the alkyne *via* click chemistry, and then an electrophoretic gel is run and visualised for fluorescence to identify bands indicating labelled proteins (*vide infra*, see section 7.5.2 for experimental details). However, for *N*-POC bicyclo[4.3.1]decane lactam **255**, no clear fluorescent bands were observed, suggesting that no successful labelling had occurred. This may be due to insufficient reactivity of the probe or decomposition taking place before labelling can occur. Future work could therefore explore this further, perhaps *via* the synthesis of the analogous *N*-POC bicyclo[4.2.1]nonane lactam if suitably stable.

Furthermore, it is known from penicillins and cephalosporins that bacteria can be killed by covalent inactivation of enzymes involved in cell-wall biosynthesis through acylation.[132] Hence, antimicrobial screening was performed by Mr Julian Chesti, against *Staphylococcus Aureus* $ATCC_{29213}$, on a series of bicyclic lactams prepared in this chapter, encompassing each of the ring systems (see experimental section and appendix 9.3 for full details). Bicyclo[4.2.1]nonane lactam **259** (see scheme 4.7), bearing an appended cyclohexane ring, presented moderate activity, at 32 μg/mL (97% growth inhibition), agreeing with the hypothesis that scaffolds bearing the most twisted bicyclo[4.2.1]nonane core would display the largest biological activity. All other twisted lactams unfortunately did not present activity. Instability of bicyclo[4.2.1]nonane lactams **262** and **263**, towards the screening conditions, could explain the observed lack of expected activity.

4.3.4 Summary of results

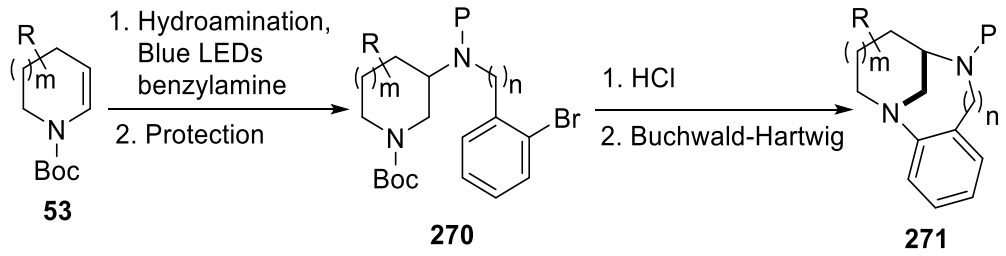
We have assessed and evaluated the physical properties of the potentially twisted lactams prepared in section 4.2. A clear trend of increasing distortion from the larger

to smaller ring systems was deduced with those bearing the bicyclo[4.2.1]nonane core exhibiting the highest degree of twist. These properties have been compared to literature benchmark highly strained and unstrained systems such as Kirby's most twisted amide which correlate with our findings.

4.4 Synthesis of diazabicyclic twisted anilines

4.4.1 Introduction

With the successful procedure for the synthesis of twisted bicyclic amides described in section 4.2 in hand, we envisaged opportunities for its modification to include complementary twisted ring systems. This section will describe the preparation of bicyclic bridged anilines **271** using a modification of this methodology. It was planned that enecarbamates **53** would again undergo β-hydroamination, this time with a brominated benzylamine or homologue, followed by protection at nitrogen to deliver intermediate bromoarenes **270** (scheme 4.9). Sequential one-pot Boc removal and Buchwald-Hartwig cross coupling methodology would facilitate cyclisation delivering a range of bicyclic bridged anilines **271**, varying in ring size in both the original and appended rings.

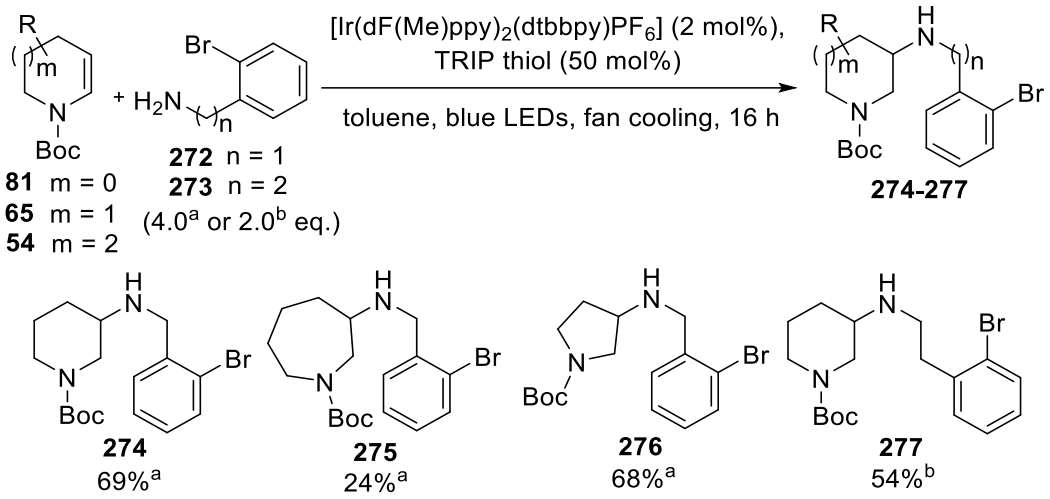


Scheme 4.9: Our proposed approach towards the synthesis of bridged bicyclic anilines **271**, consisting of hydroamination followed by Buchwald-Hartwig coupling.

4.4.2 Results and discussion

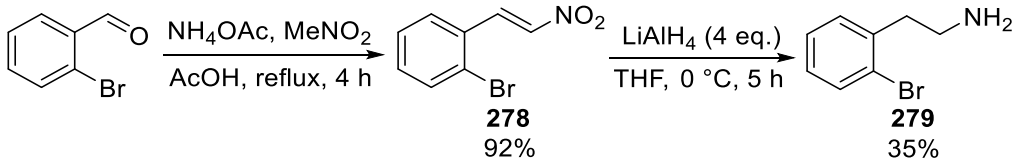
Scheme 4.10 describes the preparation of secondary bromoarenes **274**-**277** *via* the β-hydroamination of enecarbamates **54**, **65** and **81** with primary brominated-

benzylamines **272** and the homologous **273**. Initially, treatment of 6-membered *N*-Boc enecarbamate **65** with 2-bromobenzylamine **272**, an iridium catalyst, and TRIP thiol, under irradiation with a blue LED for 16 h afforded secondary brominated-benzylamine **274** in a high yield of 69%. Both the seven- and five-membered analogues **275** and **276** were also accessed in respective yields of 24% and 68%. Furthermore, brominated-aromatic amine **277** was prepared *via* the reaction with alternative starting amine **273**, enabling access to a longer appended chain (see scheme 4.11 for preparation). Attempts to introduce an aryl halide bonded directly to the amine through the reaction of 2-bromoaniline were unsuccessful, with the hydroamination failing.



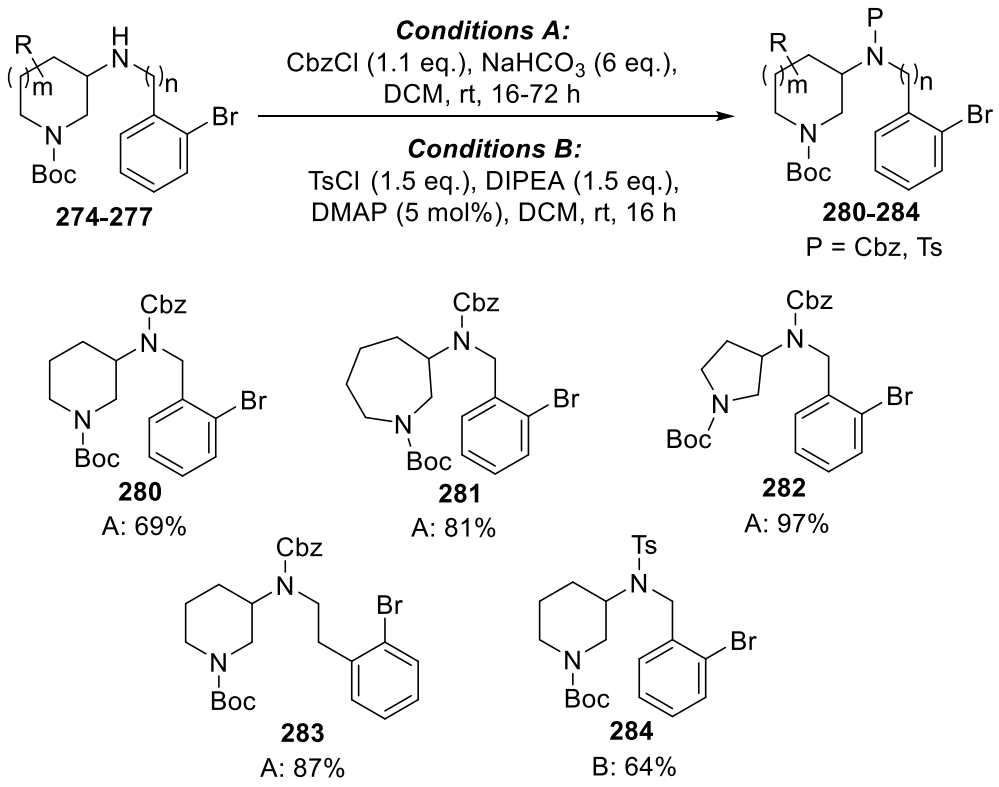
Scheme 4.10: The preparation of secondary brominated-benzylamines **274**-**277** *via* hydroamination reactions of enecarbamates **81**, **65** and **54** and primary brominated-benzylamines **272** and **273**.

Due to the poor commercial accessibility of alternative brominated-aromatic amine **273**, its preparation was instead achieved from 2-bromobenzaldehyde (scheme 4.11). Treatment of 2-bromobenzaldehyde with ammonium acetate, nitromethane and AcOH, under reflux for 4 h, afforded intermediate β-nitrostyrene **278** in 92%. Subsequent global reduction of both the nitro and alkene moieties with $LiAlH_4$ gave the desired brominated-aromatic amine **279** in 35%.



Scheme 4.11: Synthesis of alternative aromatic amine **279** from 2-bromobenzaldehyde.

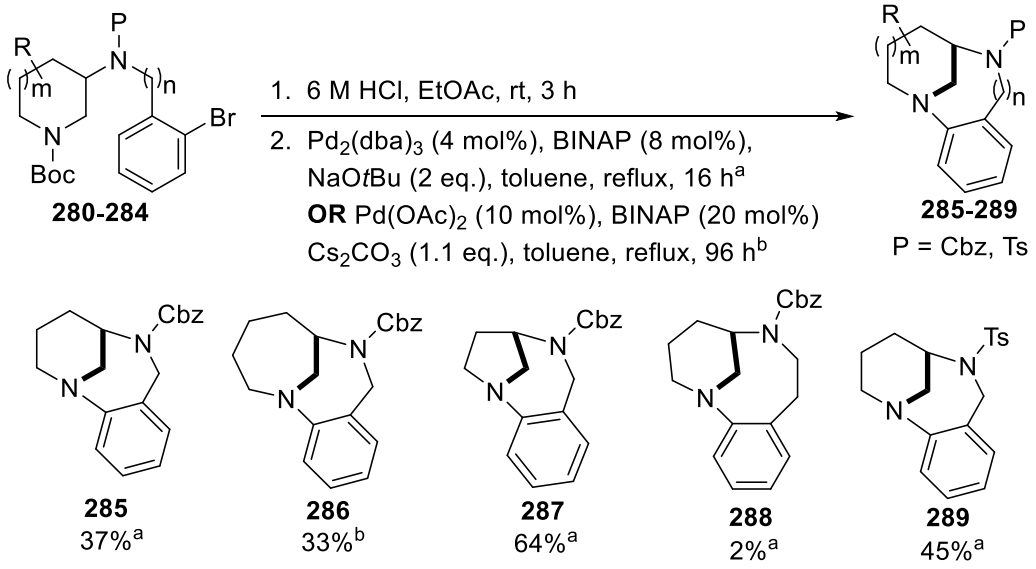
N-Cbz and *N*-Ts protection of secondary bromoarenes **274**-**277** was then achieved using the conditions described in section 4.2, delivering *N*-Cbz bromoarenes **280**-**283** and *N*-Ts benzylamine **284** in good yields of 64-87% (scheme 4.12).



Scheme 4.12: The preparation of *N*-Cbz and *N*-Ts secondary brominated-benzylamines **280**-**284**.

Cyclisations of *N*-Cbz and *N*-Ts secondary bromoarenes **280**-**284** were then carried out, using a modified version of the procedure described in section 4.2. Initially, Boc deprotection was performed as previously described to yield the crude cyclisation precursors (scheme 4.13). Buchwald-Hartwig coupling conditions were then employed to access the final bicyclic bridged anilines in mostly moderate to good

yields. For bicyclic bridged anilines **285** and **287**-**289**, this consisted of treatment with $Pd_2(dba)_3$, BINAP, NaO*t*Bu in toluene at reflux for 16 hours (conditions A); however, azepane-containing bicyclic bridged aniline **286** was not formed under these conditions. In this case, incorporation of a *t*-BuO moiety was suggested by LCMS and so alternative conditions avoiding the use of NaO*t*Bu were selected. Aniline **286** was therefore accessed *via* treatment with $Pd(OAc)_2$, BINAP and Cs_2CO_3 in toluene at reflux for 96 h in 33% yield (conditions B). The cyclisation of bicyclic bridged aniline **288** was low yielding under both conditions (A = 2%, B = 0%), presumably owing to unfavourable medium ring formation.



Scheme 4.13: The preparation of bicyclic bridged anilines **285**-**289** *via* sequential Boc removal and Buchwald-Hartwig coupling of *N*-Cbz and *N*-Ts secondary brominated-benzylamines **280**-**284**.

4.4.3 Summary of results

This section describes the successful synthesis of a range of novel twisted bicyclic anilines using a complementary approach to that described in section 4.2, consisting of sequential β-hydroamination and cyclisation *via* Buchwald-Hartwig coupling. Variation in the existing and appended rings were tolerated, including the successful incorporation of an 8-membered ring.

4.5 Assessment of properties of twisted anilines

Similarly to the assessment of distortion for bicyclic lactams, the investigation of *N* lone pair and arene overlap in anilinic systems can provide insight regarding distortion. The bicyclic anilines prepared were all isolated as oils, so limiting the accessibility of tools which can be used to investigate this, such as those based on crystallographic techniques. Some alternative methods for the investigation of this distortion will therefore be presented and discussed in this section.

4.5.1 Nonaqueous pK_aH determinations

Assessment of this distortion can be performed *via* pK_aH measurements, and therefore, in the case of bicyclic anilines **285**-**287**, and for many additional organic compounds, limited by aqueous solubility, including many APIs and drug candidates, nonaqueous-compatible methods for pK_aH determination are vital.[133] Many traditional techniques for aqueous-based determinations are not easily adaptable to nonaqueous solvents, due to the unsuitability of existing equipment (e.g., pH electrodes) and lack of commercially available consumables.[134]

We therefore underwent a collaborative project with the University of Liverpool to deploy their recently-reported method for the NMR-based determination of pK_aH measurements in DMSO (see experimental section 7.6 for full details).[135] This method is an extension of a previous related strategy[136] for aqueous-based pK_aH measurements and enables a one-shot approach, solely requiring a single measurement per single sample of each analyte. This both reduces the laborious nature of preceding, traditional NMR-based titration strategies and allows for the analysis of compounds prepared on a small scale. All experimental work was carried out at the University of Liverpool, under guidance.

Sample preparation was performed initially *via* the addition of the selected solid acid into the NMR tube followed by several glass beads to prevent rapid diffusion (schematic presented in figure 4.8). A solution of chosen chemical shift indicators

(compounds of known pK_aH that exhibit an observed chemical shift change with varying pH), and analyte in DMSO-d_6 was then carefully added and a pH gradient allowed to establish over the course of 8-32 h at rt. Spectroscopic NMR analysis then allowed the generation of an NMR 'image', comprising 128 individual ^{1}H spectra at varying pH, as illustrated in figure 4.8. See appendix section 9.4 for experimentally determined and annotated NMR images.

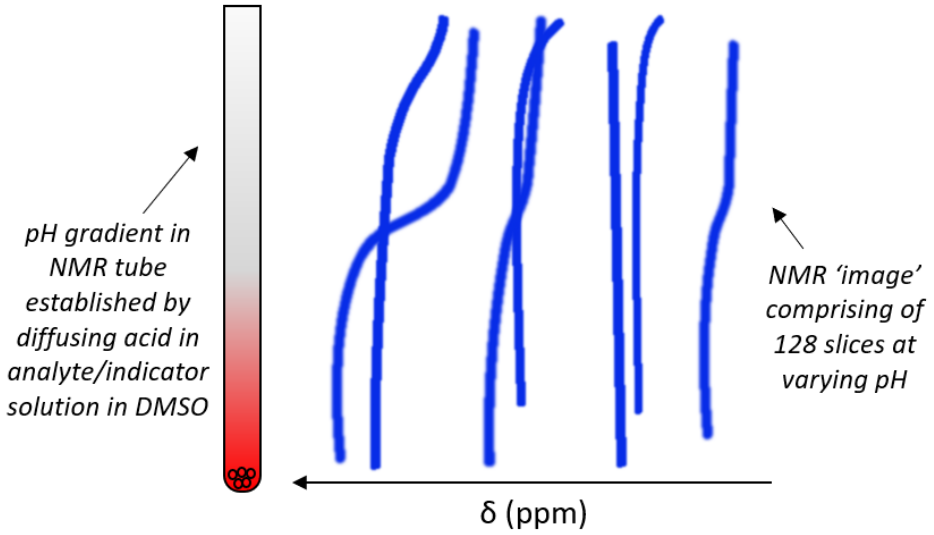
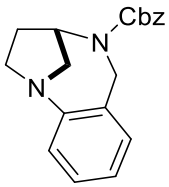
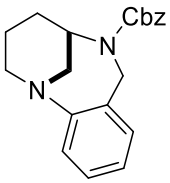
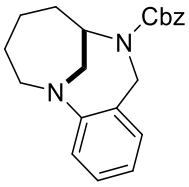


Figure 4.8: A schematic illustrating the generation of a chemical shift NMR image adapted from Schenck *et al*.[135] The NMR tube is initially equipped with solid acid, protected with a layer of glass beads, followed by a solution of analyte, and chosen indicators in d_6-DMSO. A pH gradient is established over a period of 8-32 h and a chemical shift image collected, comprising of 128 slices at varying pH. See appendix section 9.4 for collected NMR images.

Two to four basic indicators were selected for each analyte individually as described in table 4.3. Indicators were selected based on their literature pK_aH values, ensuring an appropriate range surrounding the expected analyte pK_aH, whilst maintaining a suitably complete titration curve under the required diffusion conditions for analysis of the analyte. Furthermore, the selected titration curve for each indicator must be suitably resolved, ideally avoiding overlap with other resonances, therefore requiring careful tuning of the choice of indicators and their respective concentrations.

Table 4.3: Basic indicator selection for each analyte and their corresponding literature pK_aH values.

Entry	Basic indicator[a]	Lit. pK_aH	 **287**	 **285**	 **286**
1	dma	2.51[137] ± 0.1		✓	✓
2	py	3.45[137] ± 0.1	✓	✓	✓
3	lut	4.46[138] ± 0.03	✓		✓
4	meimd	6.15[139] ± 0.01	✓		✓
5	dmb	7.60[140] ± 0.1	✓		

[a]dma = *N*,*N*-dimethylaniline, py = pyridine, lut = 2,6-lutidine, meimd = 1-methylimidazole, dmb = *N*,*N*-dimethylbenzylamine.

Following the selection of suitable analyte and indicator resonances, the observed chemical shifts (δ_{obs}) were extracted from the NMR image per slice and normalised versus the respective standard (HMDS) shifts. The solution pH values for each NMR titration were determined using the modified Henderson−Hasselbalch equation (equation 1). Limiting basic (fully deprotonated, δ_L) and acidic (fully protonated, δ_H) chemical shifts for each indicator were experimentally determined *via* ^{1}H NMR analysis of additional samples excluding acid and containing an excess of fully diffused (premixed) acid respectively.

$$pH = pK_a + log_{10}\left[\frac{\delta_{obs} - \delta_H}{\delta_L - \delta_{obs}}\right] \quad (1)$$

Analyte pK_aH was then determined by least-squares fitting of the solution pH data to the rearranged modified Henderson−Hasselbalch equation (equation 2), where pK_aH, δ_H and δ_L are free variables.

$$\delta_{obs} = \frac{\delta_H 10^{(pK_a - pH)} + \delta_L}{1 + 10^{(pK_a - pH)}} \quad (2)$$

All associated titration curves and determined pK_aH values are presented in appendix section 9.4 and table 4.4 for analytes **285**-**287** respectively. The largest magnitude error in the pK_aH determinations originates from the uncertainty associated with the literature pK_aH values of chemical shift indicators, and so this error has been applied.

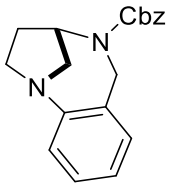
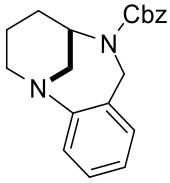
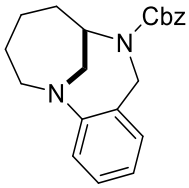
4.5.2 Physical properties

The nonaqueous pK_aH values, measured in section 4.5.1 are presented in table 4.4. As expected by the trends identified for the library of bicyclic amides, the smallest ring system **287** presented the highest pK_aH (3.85), therefore indicating the most significant distortion and enhanced basicity. These values then decreased with increasing ring size (2.10 for **285** and 0.81 for **286**), indicating an increase in conjugation. Agreement with this trend was also confirmed *via* the prediction of associated pK_aH values in water, as computationally determined using the Jaguar *p*K$_a$H prediction method by Krzysztof Baj[141] (table 4.4, entry 2, see experimental section 7.6).

Structural calculations were too performed computationally by Krzysztof Baj[141] (see experimental section 7.6), in both the gaseous phase and solvated in water or DMSO (table 4.4, entry 3). This revealed a similar trend regarding hybridisation to that reported for the twisted amide library, with the smallest ring system **287** showcasing enhanced pyramidalisation at nitrogen (331.5°), and the largest **286** indicating a near-planar structure (350.5°).

^{13}C NMR spectroscopic analysis can also provide insight regarding the planarity of the aniline nitrogen with respect to the aromatic ring, *via* the chemical shift measurement of the *para*-carbon to nitrogen (table 4.4, entry 4).[142] The value of ~129 ppm for smallest ring system **287**, is higher than that observed for benzoquinuclidine **217**[125,126] (see section 4.1, figure 4.2), indicating significant distortion. This shift then deceases with increasing ring size, with analogues **285** and **289** displaying an equal shift of 121.4 ppm. Finally, values of 118.1 and 119.2 ppm indicate mostly planar structures for larger systems **286** and **288**, which can be confirmed by comparison with exemplary planar systems (e.g., *N*-phenylpiperidine = 118.9 ppm).[142]

Table 4.4: Physical properties of bicyclic anilines **285**-**287**, as exemplar substrates for each key ring system.

Entry	**Property**	 **287**	 **285**	 **286**
1	Measured pK_aH$_{(DMSO)}$[a]	3.85	2.10	0.81
2	Calculated pK_aH$_{(water)}$[b]	5.64	3.56	1.27
3	Σ_{angles} (°)[b,c]	331.5	342.6	350.5
4	^{13}C NMR (ppm)[d]	130-128[e]	121.4	118.1

[a]Measured using the method reported by Schenck *et al*,[135] as described in section 4.5.1. [b]Measurements performed by Krzysztof Baj.[141] [c]Calculated using DMSO solvation. [d]Analogous comparative ^{13}C NMR measurements were performed for the additional prepared anilines: *N*-Ts **289** = 121.4 ppm, *N*-Cbz **288** = 119.2, 119.3 ppm. [e]Unambiguous assignment not possible due to overlapping signals.

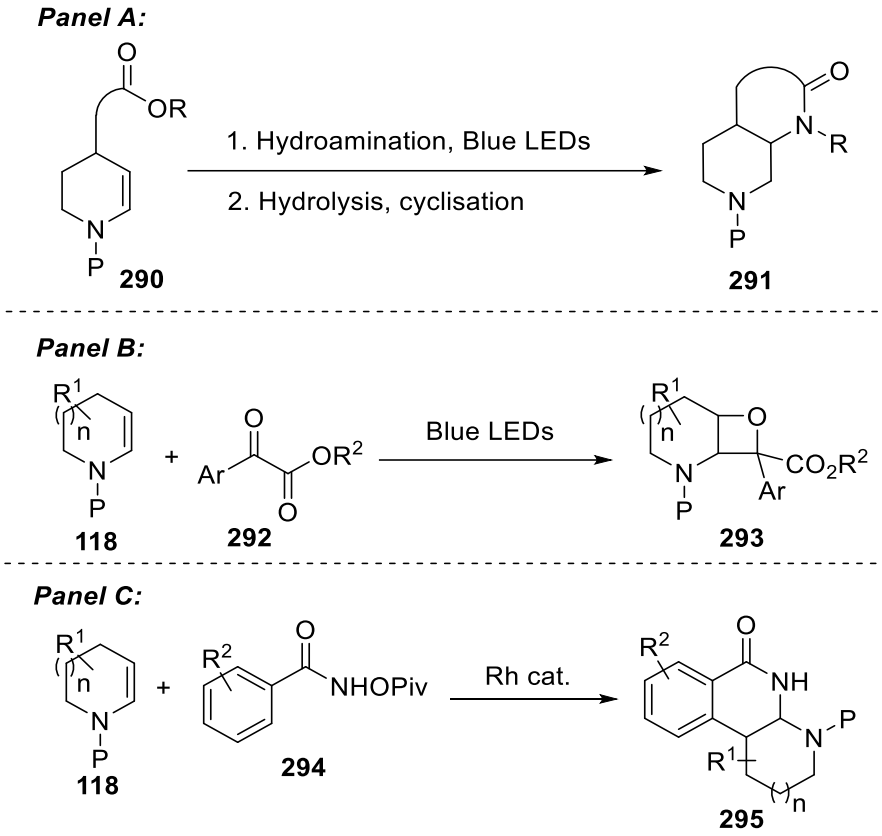
4.6 Chapter summary

This chapter describes the successful preparation of a novel library of highly three-dimensional, bridged bicyclic lactams and anilines *via* the development of a convergent approach comprising of the sequential β-hydroamination and cyclisation of enecarbamates. The twisted nature of these scaffolds has been investigated *via* various studies of their physical properties including nonaqueous pK_aH studies, carried out in collaboration with the University of Liverpool. Consequentially, we have identified complementary trends in twist for both systems and explored their chemical and biological impact.

5 Chapter 5: Enecarbamates in annulative chemistries

5.1 Introduction

In organic synthesis, annulations describe the addition or appendage of a new ring system, onto a pre-existing structure.[143] Applying these chemistries to the elaboration of enecarbamates would enable growth through two vectors, either in a stepwise or simultaneous manner, therefore providing a desirable and alternative strategy to those presented thus far. Strategies for enecarbamate difunctionalisation (mostly α, β) are known in the literature; however annulative approaches for cyclic systems are limited.[99] In this chapter, three annulative reactions of enecarbamates will be explored, based on photocatalysed (panel A, section 5.2), photochemical (panel B, section 5.3), and metal-catalysed (panel C, section 5.4) chemistries as summarised in scheme 5.1. We envisage that this would allow the construction of a novel library of complementary and varied, three-dimensional fused scaffolds, including lactams (**291**), oxetanes (**293**) and cyclic aminals (**295**), exhibiting a range of functionalities and ring sizes.

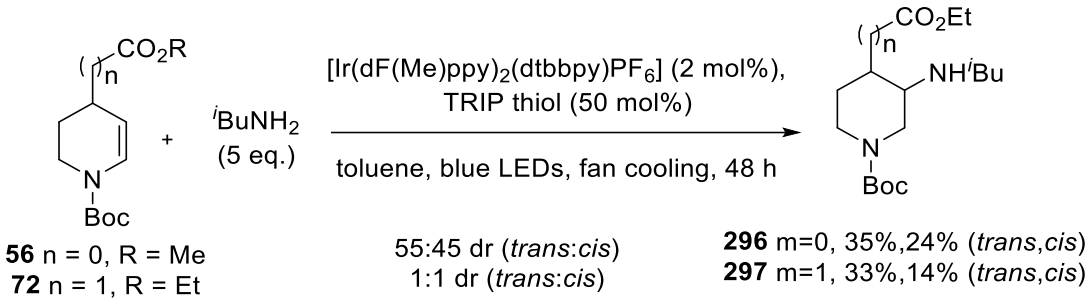


Scheme 5.1: An overview of the annulative chemistries employed in this chapter for the synthesis of lactams **291**, oxetanes **293** and cyclic aminals **295**.

5.2 Synthesis of diazabicyclic fused systems using hydroamination chemistry of ester-containing enecarbamates

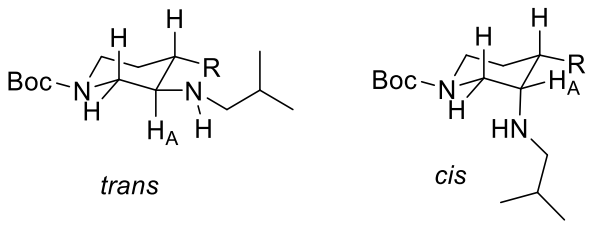
Initially, it was considered whether a simple annulative strategy could be borne by applying the successful hydroamination-cyclisation methodology, described in chapter 4 for the synthesis of twisted bicyclic lactams, to alternative enecarbamate precursors. To achieve this, ester-bearing γ-substituted enecarbamates **56** and **72** were prepared, designed with preinstalled reactive handles that could potentially undergo cyclisation following β-amination (scheme 5.2). Using the hydroamination methodology as previously described, enecarbamate **56** underwent β-amination *via* the reaction with *iso*-butylamine, delivering the corresponding amino ester product as 55:45 mixture of *trans*:*cis* diastereomers. Purification by column chromatography allowed the isolation of each diastereomer *trans*-**296** and *cis*-**296** in respective yields

of 35% and 24%. A similar result was observed for enecarbamate **72**, where diastereomeric amino esters *trans*-**297** and *cis*-**297** were isolated in respective yields of 33% and 14%.



Scheme 5.2: The preparation of diastereomeric, secondary amino esters **296** and **297** *via* hydroamination reactions of ester-bearing enecarbamates **56** and **72**.

The stereochemical assignment of *cis* and *trans* configuration for each amino ester was carried out *via* ^{1}H NMR spectroscopic analysis. Figure 5.1 depicts the favourable *trans* conformer and a possible *cis* conformer for each amino ester. H_A was selected as the signal of interest due to the two diagnostic transdiaxial interactions associated with it, which is not a possibility for either conformer of the *cis* diastereomer. This interaction was identified in both cases (9.9 Hz for *trans*-**296** and 9.8 Hz for *trans*-**297**), as illustrated by in figure 5.2, and so the *trans* diastereomers were assigned. It was not possible to interrogate the respective *cis*-isomers in this way due to the diagnostic signal (H_A) not being resolved in either case, and therefore *cis*-**296** and *cis*-**297** were assigned by analogy.



296 R = CO_2Me	H_A = app. td, 9.9, 5.0 Hz	H_A not resolved
297 R = CH_2CO_2Et	H_A = app. td, 9.8, 4.1 Hz	H_A not resolved

Figure 5.1: The stereochemical analysis of *trans*-**296** and *trans*-**297** as determined by ^{1}H NMR spectroscopic analysis. *Cis*-**296** and *cis*-**297** were assigned by analogy.

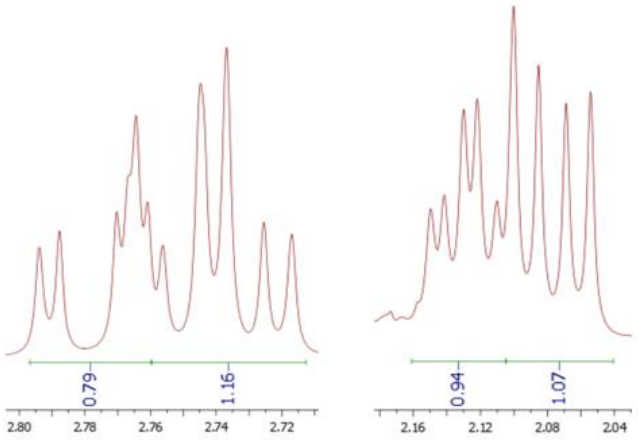
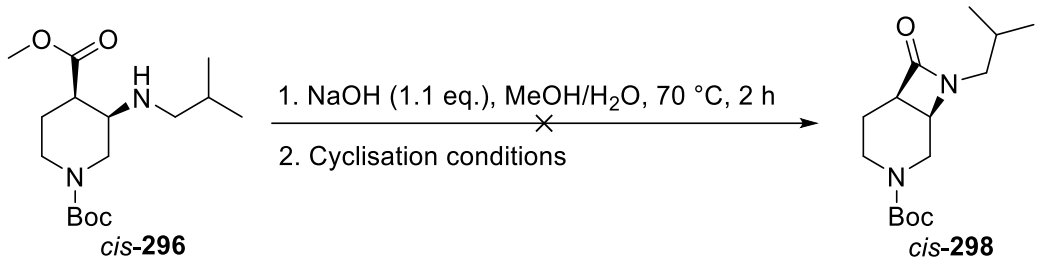


Figure 5.2: The ^{1}H spectroscopic apparent td signals corresponding to each H_A environment of *trans*-**296** (left) and *trans*-**297** (right). In each case, the diagnostic signal is overlapping slightly with a non-diagnostic signal, however this does not impact *J* value measurements and therefore stereochemical determination.

We then turned our attention towards the subsequent cyclisations of these amino esters to deliver novel [6,4]- and [6,5]-fused rings systems *via* the appendage of a new ring. Initial hydrolysis of *cis*-**296** was readily achieved using the conditions previously described; however, unfortunately, cyclisation was unsuccessful, presumably owing to increased strain associated with the formation of a β-lactam moiety (table 5.1, entry 1). Alternative literature cyclisation conditions applied to similar ring systems were also investigated but were also unsuccessful, returning the unreacted amino acid in each case (table 5.1, entries 2 and 3).[144,145]

Table 5.1: Efforts towards the synthesis of fused β-lactam *cis*-**298**.

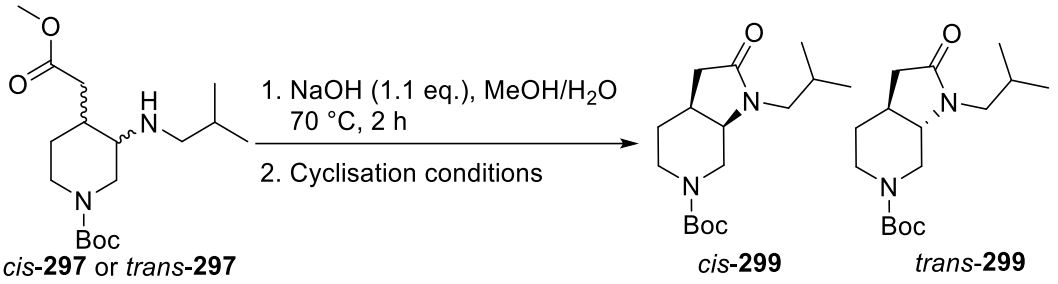


Entry	Cyclisation conditions	Isolated yield (%)
1	nBu$_2$SnO (1.01 eq), toluene, reflux, 16 h[60]	0
2	PPh$_3$ (1.2 eq.), NBS (1.2 eq.), Et$_3$N (1.2 eq.), MeCN, rt, 16 h[144]	0
3	PySSPy (1.3 eq.), PPh$_3$ (1.3 eq.), MnO$_2$ (2.5 eq.), MeCN, reflux, 16 h[145]	0

The analogous cyclisation attempts using *cis*-**297** were pleasingly however, much more successful (table 5.2). Both hydrolysis and the subsequent cyclisation were achieved delivering novel [6,5]-fused lactam *cis*-**299** as a single diastereomer in a high yield of 69% (table 5.2, entry 1). Furthermore *cis*-**299** could also be accessed by employing alternative conditions scoped during the attempted synthesis of β-lactam *cis*-**298**. For example, treatment of the amino acid intermediate with PPh$_3$, NBS, and Et$_3$N in MeCN at rt afforded an impure mixture of *cis*-**299** and TPPO, which despite efforts, could not be separated (table 5.2, entry 2).[144] To our delight, we discovered that the analogous cyclisation of *trans*-**297** was also possible showcasing the methodology's ability to deliver both fused lactams *cis*-**299** and *trans*-**299** each as single diastereomers. Treatment of *trans*-**297** with the previously described tin-based conditions afforded *trans*-**299** in 49%, whereas treatment with PPh$_3$ and NBS gave a higher yield of 57% (table 5.2, entries 3 and 4). In this case, the

chromatographic separation of *trans*-**299** with TPPO was facile due to its difference in retention factor to that of *cis*-**299**.

Table 5.2: The synthesis of novel fused ring systems *cis*-**299** and *trans*-**299**.



Entry	Amino ester	Cyclisation conditions	Product	Isolated yield (%)
1	*cis*-**297**	*n*Bu_2SnO (1.01 eq.), toluene, reflux, 16 h[60]	*cis*-**299**	69
2	*cis*-**297**	PPh_3 (1.2 eq.), NBS (1.2 eq.), Et_3N (1.2 eq.), MeCN, rt, 16 h[144]	*cis*-**299**	Impure
3	*trans*-**297**	*n*Bu_2SnO (1.01 eq.), toluene, reflux, 16 h[60]	*trans*-**299**	49
4	*trans*-**297**	PPh_3 (1.2 eq.), NBS (1.2 eq.), Et_3N (1.2 eq.), MeCN, rt, 16 h[144]	*trans*-**299**	57

This section illustrates the applicability and synthetic versatility of the combined hydroamination and cyclisation-based approach for the installation of new amide-containing rings for alternative systems. A key limitation is the need to install a functional group handle (which must be tolerant of the hydroamination) which requires multi-step synthesis. The use of this approach for novel fused rings is therefore less modular in nature and does not easily allow for variation in each ring, as seen in the preparation of the diazabicyclic, twisted amides and anilines described

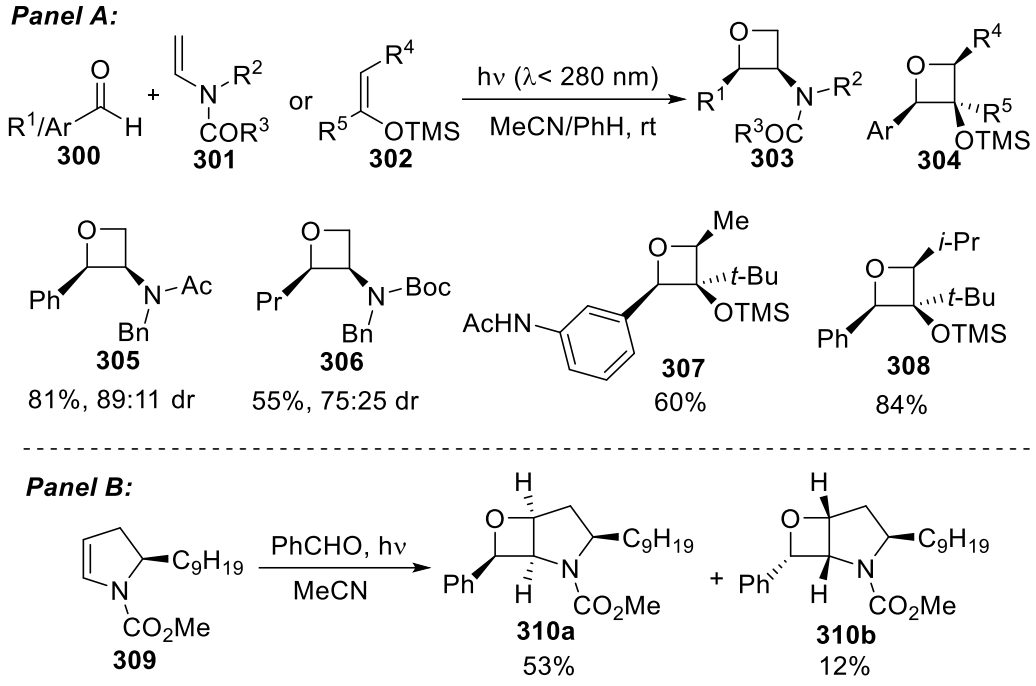
in chapter 4. Therefore, the remainder of this chapter will investigate alternative annulative strategies for the synthesis of novel fused rings systems from enecarbamates.

5.3 Photochemical annulation reactions of enecarbamates

5.3.1 Background

Oxetanes and their four-membered heterocyclic analogues are present in many medicinally important building blocks and hold pharmaceutical value as isosteric groups, and therefore their respective syntheses have been a long-lasting research focus. The Paternò-Büchi reaction is an established [2+2]-heterocycloaddition method for the rapid and facile preparation of substituted oxetanes *via* the reaction of a photoexcited carbonyl and alkene.[146] Related approaches, utilising this pivotal UV/visible light-mediated [2+2] cycloaddition, have been developed for the intermolecular and intramolecular syntheses of complementary four-membered systems such as azetidines[147] and bicyclic amines/ethers.[148]

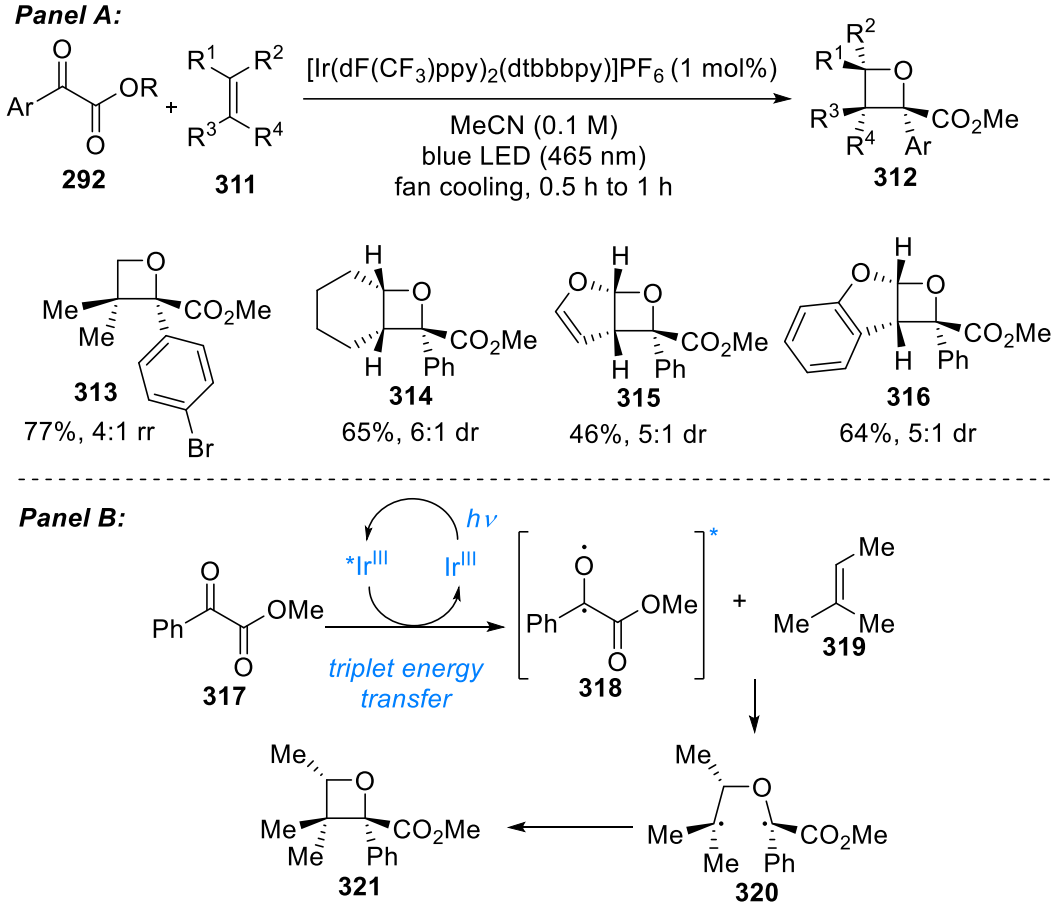
Via a series of studies, Bach *et al* reported the synthesis of oxetanes from their corresponding aldehyde (**300**) and either acyclic enamide/enecarbamate (**301**) or silyl enol ether (**302**) counterparts, facilitated by UV light (scheme 5.3, panel A). This allowed the preparation of aryl- or alkyl-bearing enamide- or enecarbamate-substituted oxetanes **303** (e.g., **305** and **306**), as well as highly functionalised silyl ether-bearing oxetanes **304** (e.g., **307** and **308**).[149,150,151] Bach *et al* has also reported the only accounts, to our knowledge, of the employment of cyclic enamides and enecarbamates in this chemistry (panel B).[152,153,154] For example, diastereomeric bicyclic oxetanes **310a** and **310b** were accessed under similar conditions in 53% and 12% respectively.



Scheme 5.3: The employment of acyclic enamides/enecarbamates and silyl enol ethers in the preparation of oxetane-based scaffolds (panel A).[149] Cyclic enecarbamates in the Paternò-Büchi reaction (panel B).[152,153]

To avoid the requirement of high-energy UV light needed for carbonyl systems absorbing at shorter wavelengths, common approaches involve the use of EDA complex intermediates or an energy transfer photocatalyst.[146,155] Based on the latter, Rykaczewski *et al* have reported a complementary method, instead employing visible light ($\lambda \geq 400$ nm) and an iridium photocatalyst (scheme 5.4, panel A).[156] Treatment of the selected ketoester **292** and alkene **311**, under these conditions, delivered a series of substituted oxetanes **312** in mostly high regioisomeric and diastereomeric ratios. Several ketoesters bearing a range of *p*-substituted aromatics (e.g., **313**) were tolerated, as well as a series of substituted and non-substituted alkenes including those present in cyclic (**314**) and heterocyclic (**315** and **316**) systems. Efforts using furan and benzofuran have also been reported elsewhere in the literature, and confirm the observed regio and stereochemical outcomes.[157] A triplet energy transfer mechanism for the formation of oxetanes under these photocatalytic conditions was proposed, supported by Stern-Volmer quenching studies (scheme 5.4, panel B).[156] Initial excitation of the photocatalyst would be followed by energy

transfer to ketoester **317**, resulting in formation of the carbonyl triplet state **318**. C-O bond formation would then take place with alkene **319**, furnishing stabilised biradical **320**, which would then undergo rapid ring closure to **321**. Use of these photocatalytic conditions demonstrate potential applicability towards carbonyl systems which are not able to absorb visible light.



Scheme 5.4: The synthesis of oxetanes under photocatalysed conditions and the proposal of a triplet energy transfer mechanism as described by Rykaczewski *et al*.[156]

5.3.2 Introduction

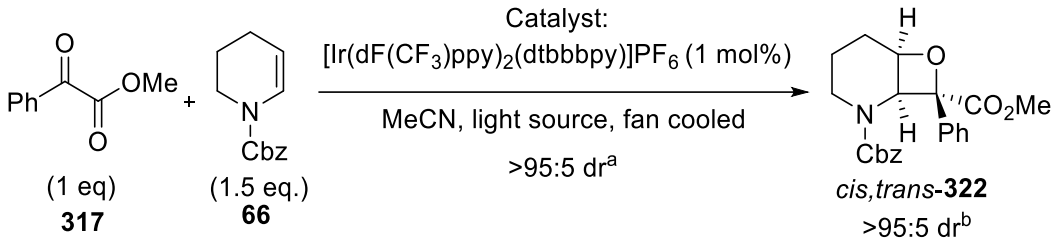
The elaboration of enecarbamates *via* the application of the Paternò-Büchi [2+2] cycloaddition methodology has received limited attention within the literature, and only accounts employing aldehyde-based substrates have been described, providing little scope for further derivatisation. This, therefore, provides a desirable opportunity for the preparation of a library of highly three-dimensional and novel

oxetane-based scaffolds. This section will explore this approach, with a particular focus on the scope and diastereoselectivity *via* modification of the method reported by Rykaczewski *et al*.[156]

5.3.3 Results and discussion

Initial efforts enabled the discovery of the successful Paternò-Büchi annulation between *N*-Cbz enecarbamate **66** and ketoester **317** to yield bicyclic oxetane *cis*,*trans*-**322** as a single diastereomer in good yield of 41% (this was a comparable yield to a previous account of the reaction performed by MChem student Harrison Tran, table 5.3). Upon changing *N*-Cbz enecarbamate **66** to its *N*-Boc equivalent or upon increasing the ring size, no oxetane formation was observed. To rationalise this, we performed a brief optimisation for *N*-Cbz enecarbamate **66** (table 5.3). Extending the reaction duration to 16 h provided little improvement on the yield (entry 2, 49%). Analysis of the crude ^{1}H NMR spectra for entries 1 and 2 clearly indicated the complete degradation of enecarbamate **66** (employed in excess) and suspecting the occurrence of potential competing SET processes between the excited iridium photocatalyst and enecarbamate **66**, we planned to investigate the role of the photocatalyst. Removal of the catalyst and inclusion of the CSTR fReactor platform, providing a shorter wavelength of light more suited to direct excitation of ketoester **317** (λ_{max} = 365 nm), as previously discussed in sections 3.1.2 and 3.2.2, resulted in an improved yield of 56%: importantly, remaining unreacted *N*-Cbz enecarbamate **66** was now observed in the crude ^{1}H NMR spectrum (entry 3). Entries 4-6 describe the effects of changing both the reaction duration and light source (reaction success measured with respect to the relative ratio of *cis*,*trans*-**322** to **66** in the crude ^{1}H NMR spectra). No improvement in conversion was observed and so conditions presented in entry 3 were employed in subsequent reactions.

Table 5.3: Optimisation of the Paternò-Büchi annulation reaction conditions for the synthesis of *cis,trans*-**322**. The relative stereochemistry has been denoted as *cis,trans* with respect to the *cis* ring junction and subsequent *trans* relationship to the ester tether.



Entry	Light source	Catalyst	Duration (h)	Conversion (*cis*,*trans*-322:66)[e]	Isolated yield (%)[g]
1	Kessil blue LEDs[c]	Yes	1	n/a[f]	41 (45)[h]
2	Kessil Blue LEDs[c]	Yes	16	n/a[f]	49
3	fReactor[d]	No	1	1:1.2	56
4	Kessil Blue LEDs[c]	No	1	1:1.5	-
5	fReactor[d]	No	16	1:1.4	-
6	Kessil Blue LEDs[c]	No	16	1:1.6	-

[a]dr determined *via* spectroscopic analysis of the crude ^{1}H spectrum. [a]dr determined *via* spectroscopic analysis of the ^{1}H NMR spectrum of the isolated product. [c]λ_{max} = 390 nm. [d]λ_{max} = 365 nm. [e]Conversion represented in terms of *cis*,*trans*-**322**:**66** ratio determined for crude reaction mixture by ^{1}H spectroscopic analysis. [f]Ratio not reported due to degradation of enecarbamate **66** observed when Ir catalayst present. [g]Isolated yields reported following chromatographic purification. [h]Reaction and associated yield as performed by Harrsion Tran.

Reaction success was determined by ^{1}H and ^{13}C spectroscopic analysis in each case. Formation of *cis*,*trans*-**322** was indicated by key diagnostic signals in the δ_H 5.54–5.30 ($CDCl_3$) and δ_H 5.40–5.00 (d_6-DMSO) ranges corresponding to the CH environments at the oxetane ring junction. The associated diagnostically high ^{13}C spectroscopic shifts ($CDCl_3$) were present at δ_C 76.8 (C-6, α-O) and 55.4 (C-1, α-*N*) and that of the newly formed quaternary centre was assigned at δ_C 89.5. *Cis*,*trans*-**322** contained a 1:1 mixture of rotamers in both the crude and isolated spectra, indicated by the doubling up of ^{1}H and ^{13}C signals. Rotamers are frequently observed with Cbz and other carbamates, due to hindered rotation about the C-N bond. This was confirmed using variable temperature (VT) NMR spectroscopic analysis as summarised in figure 5.3. The consistent coalescence of key rotameric signals in the ^{1}H NMR spectrum of *cis*,*trans*-**322** was observed upon heating from 298 K to 363 K in d_6-DMSO, therefore confirming *cis*,*trans*-**322** to be present as a single diastereomer.

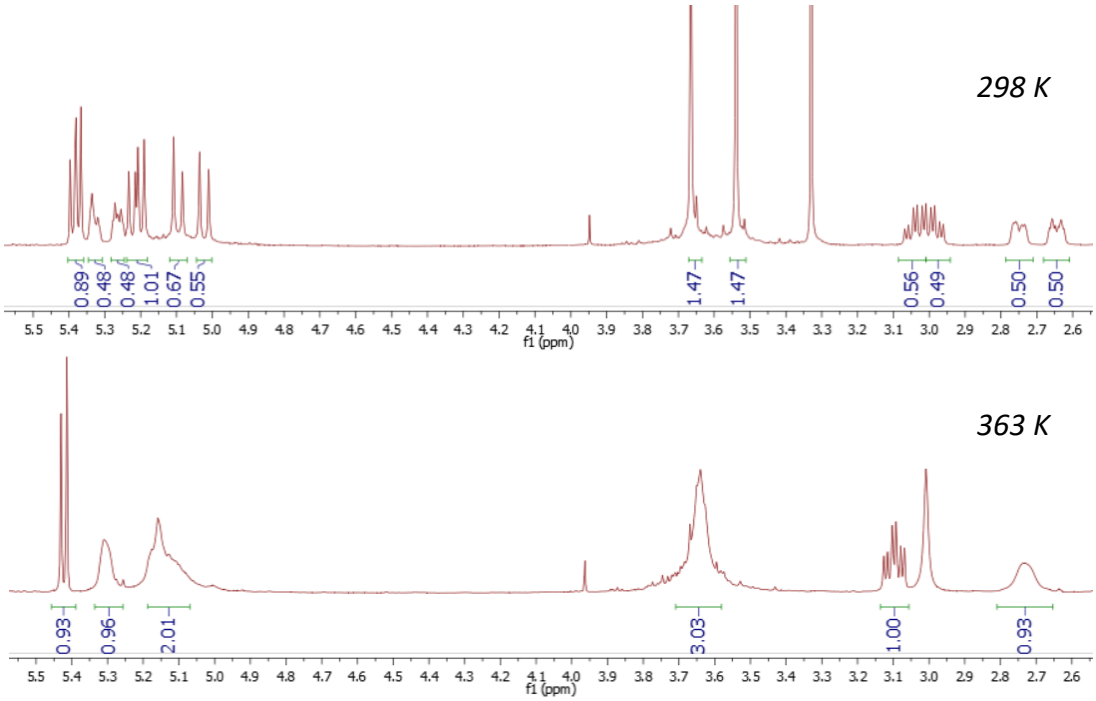
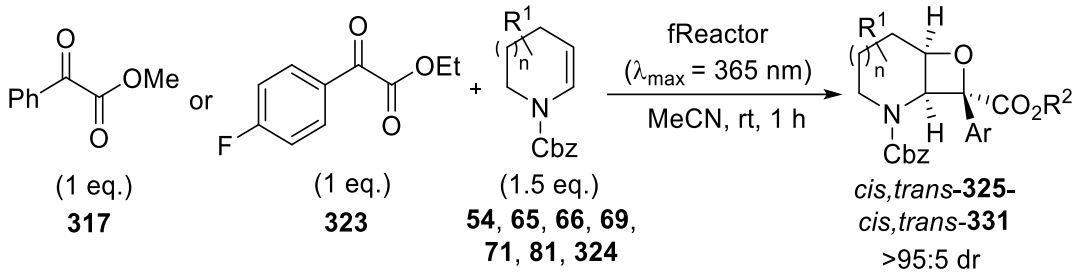


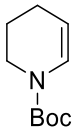
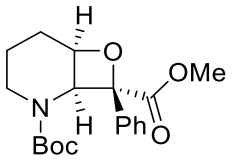
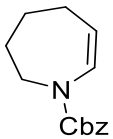
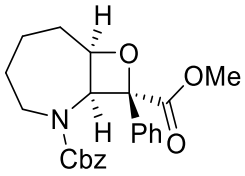
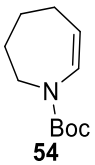
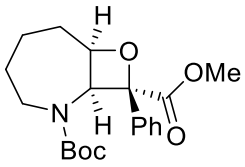
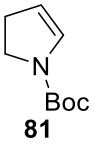
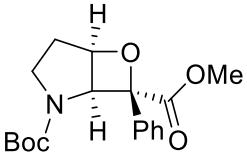
Figure 5.3: ^{1}H NMR spectra for *cis*,*trans*-**322** in d_6-DMSO at 298 K (top) and 363 K (bottom), showing the coalescence of rotameric signals upon heating.

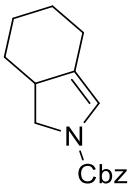
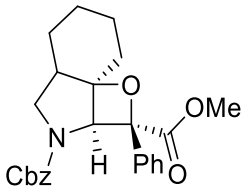
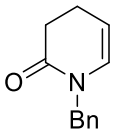
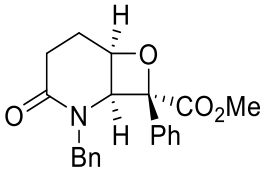
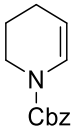
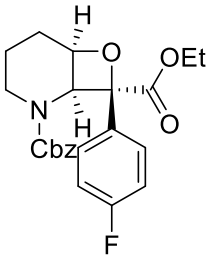
We then moved onto the exploration of the enecarbamate and ketoester reaction scope, employing the optimised conditions from table 5.3 (entry 3), as summarised

in table 5.4. We were delighted to find, that under these photochemical conditions, *N*-Boc enecarbamate **65** was now tolerated, affording *cis*,*trans*-**325** in 19% yield with full diastereoselectivity (entry 1). Employing seven-membered enecarbamates **69** and **54** and five-membered enecarbamate **81** was also successful, yielding the respective *cis*,*trans* products **326**-**328** for each reaction as single diastereomers, and in moderate to good yields (19-64%, entries 2-4). Employing the photocatalytic conditions as a comparative measure for these substrates resulted in approximately a 20% drop off in yield for the seven-membered analogues *cis*,*trans*-**326** and *cis*,*trans*-**327** and halted formation of five-membered oxetane *cis*,*trans*-**328** altogether (entries 2-4). Unfortunately, the reaction of bicyclic enecarbamate **71** was unsuccessful under both photochemical and photocatalytic conditions, potentially due to the more crowded transition state assembly that would be required for desired oxetane product *cis*,*trans*-**329** (entry 5). Conversely however, changing the enecarbamate to enamide **324** (prepared by Mr Harrison Johnson-Evans), successfully gave the analogous oxetane product *cis*,*trans*-**330**, as a single diastereomer in good yield (44%, entry 6). To investigate the ketoester scope, we initially selected previously employed alternative *p*-fluoro substituted ketoester **323** with *N*-Cbz enecarbamate, affording *cis*,*trans*-**331** as a single diastereomer in 40% yield (entry 7). This was a slight improvement on its previous employment under photocatalytic conditions, as performed prior by Harrison Tran (36%, entry 7). Changing the ketoester aryl substituent to a methyl group halted all reactivity under photochemical conditions, presumably due to its exhibition of weak absorption between 280 nm and 400 nm.[158] We also briefly explored the use of alternative carbonyl containing systems such as diketones (benzil), ketones (benzophenone) and α,β-unsaturated ketones (1,4-dibenoquinone), however these too were unsuccessful.

Table 5.4: The ketoester and enecarbamate scope of the Paternò-Büchi reaction employing the optimised conditions from table 5.3.



Entry	Ketoester	Enecarbamate	Product	dr[a]	Isolated yield (%)
1	**317**	 **65**	 *cis,trans*-**325**	>95:5	19, 0[b]
2	**317**	 **69**	 *cis,trans*-**326**	>95:5	56, 36[b]
3	**317**	 **54**	 *cis,trans*-**327**	>95:5	64, 44[b]
4	**317**	 **81**	 *cis,trans*-**328**	>95:5	19, 0[b]

5	**317**	 **71**	 *cis,trans*-**329**	-	0, 0[b]
6	**317**	 **324**	 *cis,trans*-**330**	>95:5	44
7	**323**	 **66**	 *cis,trans*-**331**	>95:5	40, 36[b,c]

[a]Determined *via* ^{1}H NMR spectroscopic analysis of the crude product. [b]Isolated yield when employing photocatalytic conditions (as per table 5.3, entry 1). [c]Reaction performed by Harrison Tran for a reaction duration of three hours.

All reactions presented in table 5.4 proceeded with full diastereoselectivity in accordance with *N*-Cbz oxetane *cis*,*trans*-**322**, yielding the corresponding *cis*,*trans* diastereomer in each case. The high diastereoselectivites obtained and associated stereochemical assignments of the major diastereomers were consistent with those presented in the literature for related examples.[156,152] Stereochemical assignments for six- and seven-based oxetane systems *cis*,*trans*-**325** and *cis*,*trans*-**327** were made by X-ray crystallographic analysis (X-ray structures presented in figure 5.4).

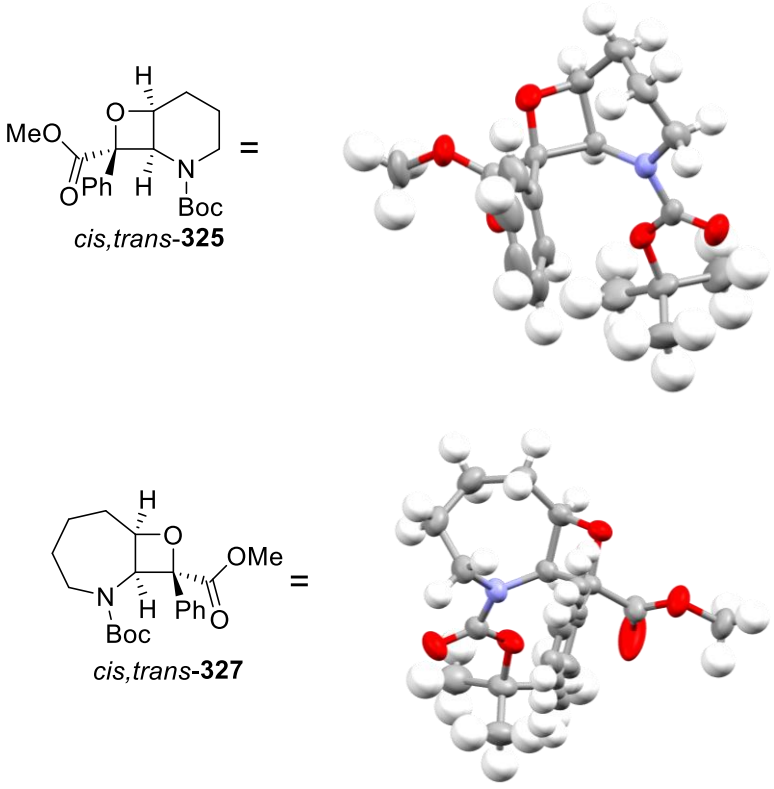


Figure 5.4: The X-ray crystal structures of *cis*,*trans*-**325** and *cis*,*trans*-**327**.

Furthermore, the stereochemical assignment of enamide-based *cis*,*trans*-**330**, displaying high spectral resolution due to the lack of rotamers, was performed using ^{1}H and ^{13}C spectroscopic analysis. A positive nOe between protons at the 4-H and *o*-Ph environments was observed as illustrated by the NOESY NMR spectrum shown in figure 5.5. The conformation provided by the X-ray crystal structure of six-membered *cis*,*trans*-**325** supports the possibility of this interaction for the *cis*,*trans* diastereomer. Coupling between the *o*-Ph environment and the quaternary carbon was identified *via* analysis of the HMBC NMR spectrum confirming that the nOe observed was associated with the desired phenyl ring. All further stereochemical assignments were made by analogy with these systems.

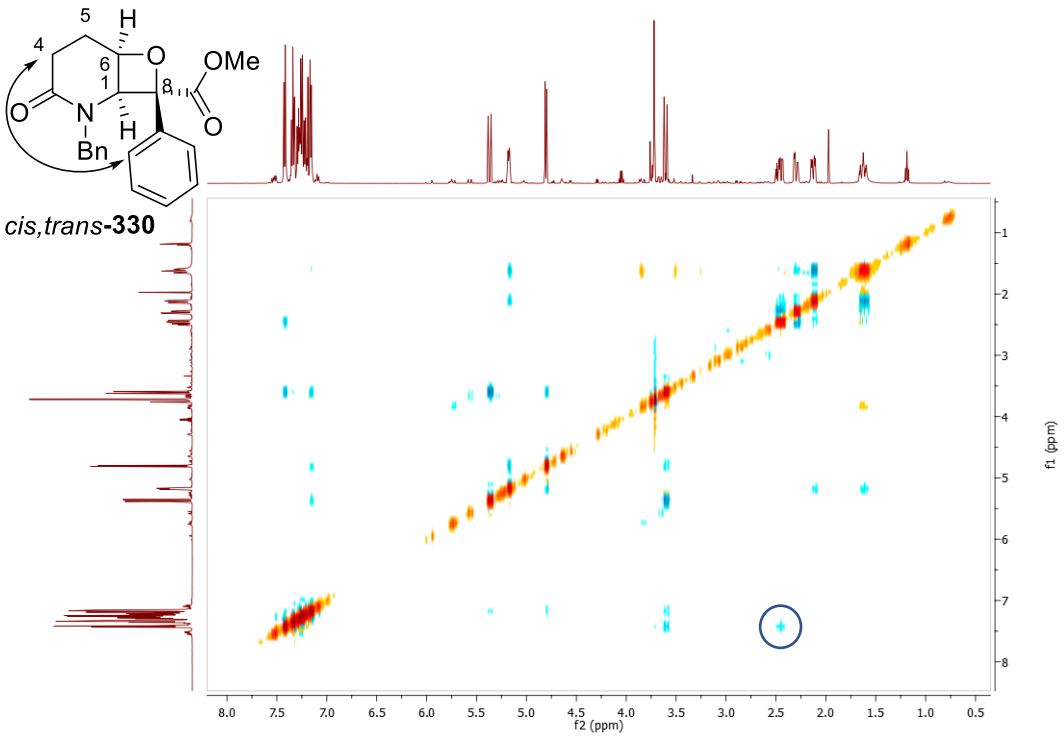


Figure 5.5: The NOESY NMR spectrum for *cis*,*trans*-**330** with the highlighted positive nOe interaction between 4-H_A and *o*-Ph.

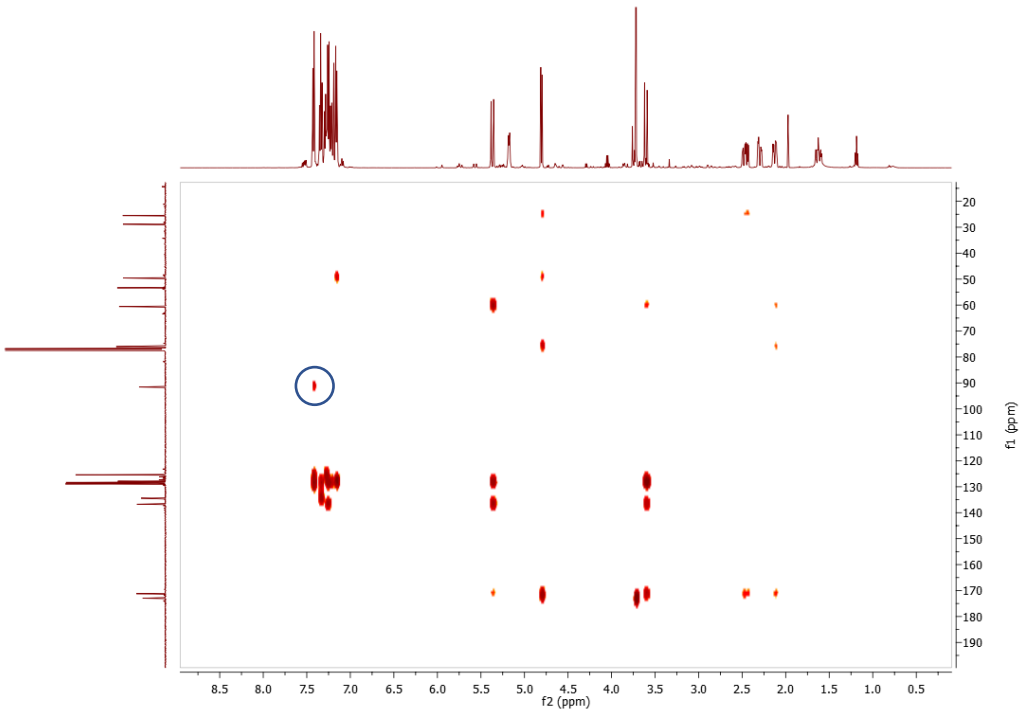
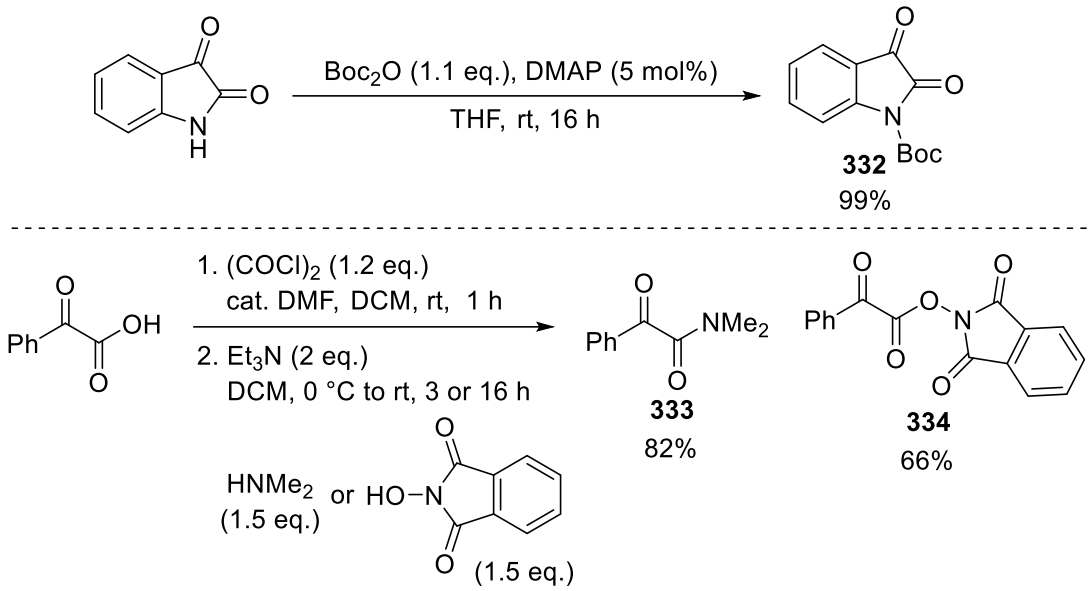


Figure 5.6: The HMBC NMR spectrum *cis*,*trans*-**330** with the highlighted coupling between the ^{1}H corresponding to the *o*-Ph, used in nOe determination, and ^{13}C signal corresponding to the quaternary centre.

We then set about the synthesis of ketoamides **332** and **333** and activated ketoester **334** to be employed as alternative substrates in the Paternò-Büchi annulation (scheme 5.5). *N*-Boc isatin **332** was easily accessed *via* treatment of isatin with Boc_2O and DMAP, according to a literature method, in high yield (99%).[159] As per another literature procedure, treatment of phenylglyoxylic acid with oxalyl chloride and catalytic DMF in DCM afforded the corresponding acid chloride.[160] Subsequent addition of Et_3N and either dimethylamine or *N*-hydroxy succinimide provided ketoamide **333** and ketoester **334** in high yields (82% and 66%).



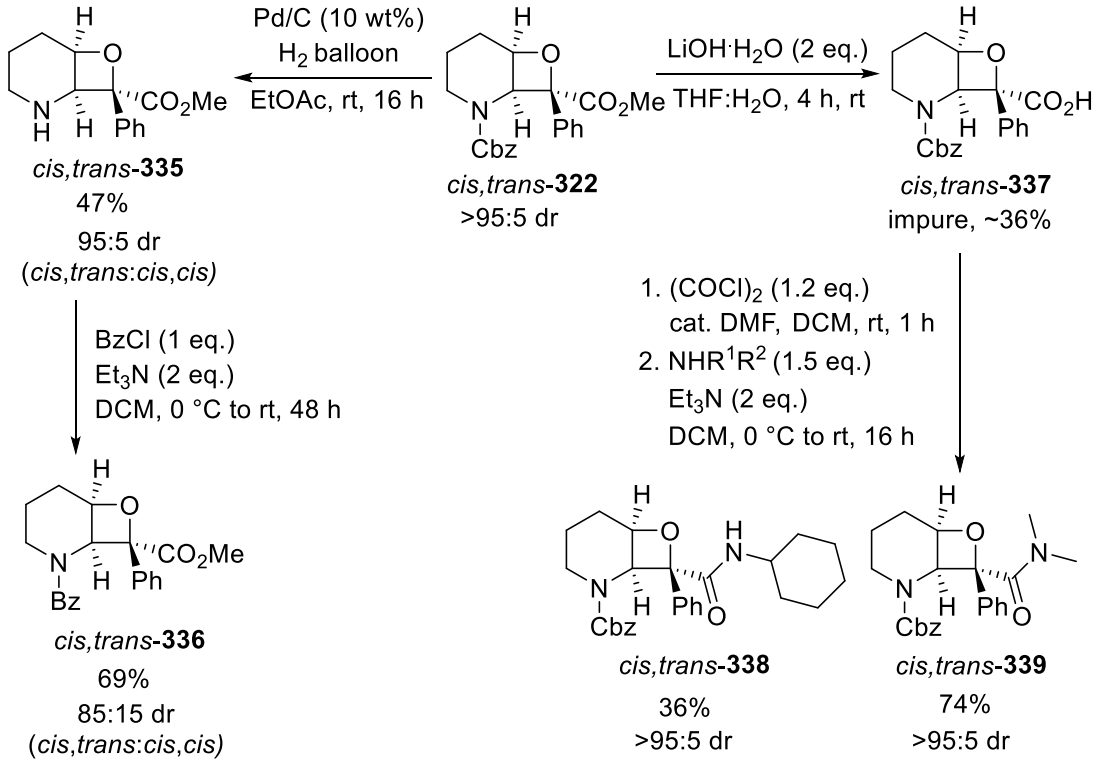
Scheme 5.5: The synthesis of ketoamides **332** and **333** and activated ketoester **334**.

Unfortunately, the use of ketoamides **332** and **333** in the Paternò-Büchi annulation with *N*-Cbz enecarbamate **66**, (under the photochemical conditions described in table 5.4) were unsuccessful, resulting in the return of unreacted starting materials. Assuming this to be a result of mismatched irradiated wavelength required for C=O excitation of ketoamides, we returned to the photocatalytic conditions described in table 5.3, entry 1. These were however also unsuccessful, for dimethyl ketoamide **333**, yielding a complex mixture of by-products, again presumably caused by a competing SET process. To bypass this issue, activated ketoester **334** was proposed for the synthesis of intermediate activated esters which could subsequently be

reacted with amines, furnishing the corresponding amides. Similarly, however, the photochemical annulation with activated ketoester **334** was unsuccessful, providing a complex mixture of by-products, and suggesting possible degradation of activated ketoester **334**.

To showcase the opportunities for further elaboration of these scaffolds and to provide alternative avenues for the preparation of oxetane scaffolds bearing amide tethers, we set about the exemplary decoration of *cis*,*trans*-**322**. Scaling out the photochemical synthesis of *cis*,*trans*-**322** by performing the reaction in six fReactor modules, set up in batch, provided an improved yield of 68%. Cbz removal would enable facile growth *via* the heterocyclic amine and so we initially planned to carry out deprotection and amide coupling sequentially (scheme 5.6). Treatment with a Pd/C catalyst system under hydrogenation conditions afforded a 95:5 mixture of inseparable diastereomeric amines *cis*,*trans*-**335** and *cis*,*cis*-**335** in 47% following purification (>95:5 dr by ^{1}H spectroscopic analysis of the crude product). The observation of a small amount of the minor diastereomer suggests unequal carry over from starting material *cis*,*trans*-**322** which presumably contained a negligible amount of the minor diastereomer, not readily visible by ^{1}H NMR spectroscopic analysis. This could also be rationalised by a small amount of a retro-Mannich reaction and Mannich ring closure sequence taking place, enabling scrambling of the stereocentre. This minor diastereomer has been assigned as *cis*,*cis*-**335** in analogy with literature accounts of preferential *cis* ring junction formation in bicyclic oxetanes (see section 5.3.1).[156,154,152] This was then coupled with benzoyl chloride to produce an 85:15 mixture of inseparable *N*-Bz diastereomeric oxetanes *cis*,*trans*-**336** and *cis*,*cis*-**336** in 69%, following purification. The observed deviation in dr is likely to be caused again by unequal recovery of each diastereomer during column chromatographic purification. We additionally identified the ester substituent of *cis*,*trans*-**322** as an alternative and complementary handle for elaboration (scheme 5.6). Initial hydrolysis of *cis*,*trans*-**322** was achieved using lithium hydroxide in THF:water, followed by isolation *via* acid-base extraction to deliver impure carboxylic acid *cis*,*trans*-**337** which was used without further purification. Treatment of acid

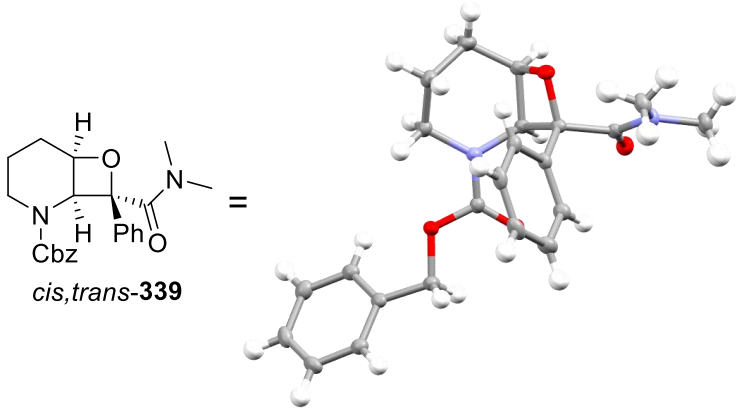
cis,*trans*-**337** with cyclohexylamine or dimethylamine under the amide coupling conditions described previously (see scheme 5.5) provided primary and secondary amides *cis*,*trans*-**338** and *cis*,*trans*-**339** respectively as single diastereomers (>95:5 dr by ^{1}H spectroscopic analysis of the crude products) in good yields (36% and 74%). These transformations successfully provided alternative synthetic routes towards analogues which were not previously accessible *via* the Paternò-Büchi reaction (e.g., *cis*,*trans*-**339**).



Scheme 5.6: The preparation of decorated analogues of *cis*,*trans*-**322** *via* elaboration of two individual vectors.

For each analogue prepared in scheme 5.6, ^{1}H NMR spectroscopy was used to determine the success of each derivatisation as well as ensuring that the oxetane ring did not undergo opening. To determine this, the diagnostic ^{1}H and ^{13}C signals observed for both ring junction proton environments as well as the ^{13}C signal corresponding to the quaternary centre were identified in all cases. Furthermore, analysis of tertiary amide *cis*,*trans*-**339** was performed using X-ray crystallography,

confirming the structure, and agreeing with the previous *cis*,*trans* stereochemical assignments and conformational observations provided (figure 5.7). As tertiary amide *cis*,*trans*-**339** was present as a mixture of suspected rotamers by ^{1}H NMR spectroscopy (65:35 in $CDCl_3$), this was once again confirmed using VT NMR studies. Figure 5.8 shows the coalescence of signals occurring at 363 K, confirming *cis*,*trans*-**339** as a single diastereomer.



cis,*trans*-**339**

Figure 5.7: The X-ray crystal structure of *cis*,*trans*-**339**.

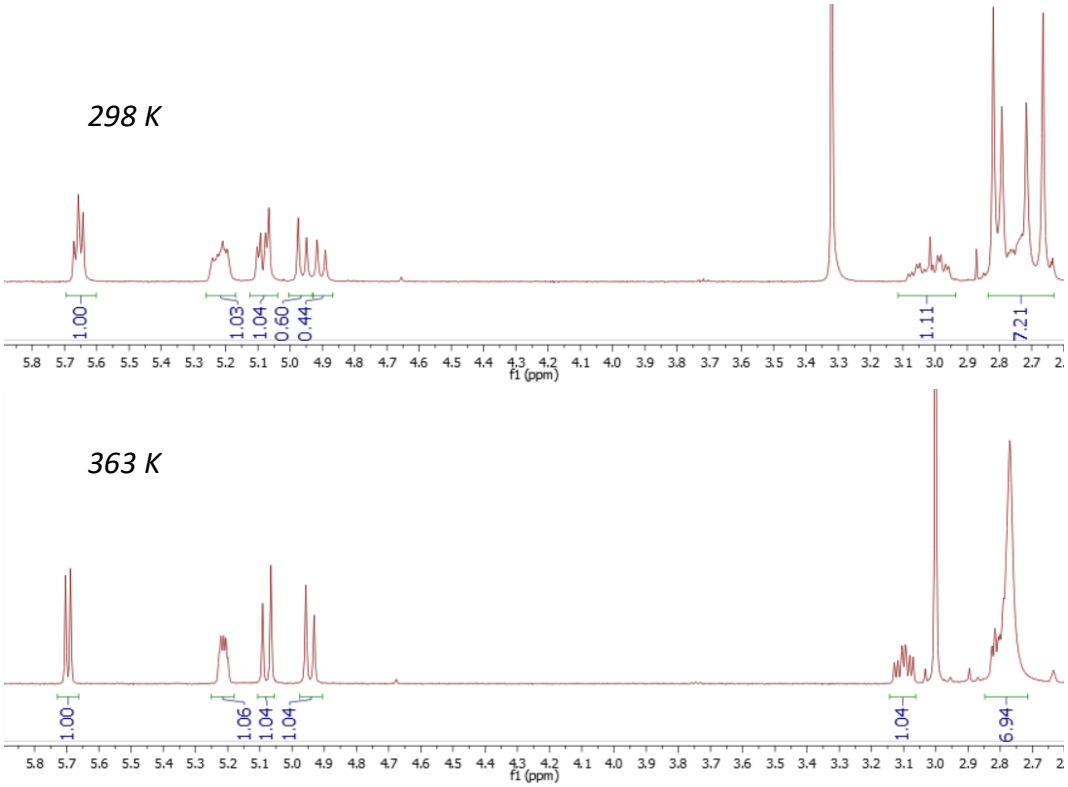


Figure 5.8: ^{1}H NMR spectra for *cis*,*trans*-**339** in d_6-DMSO at 298 K (top) and 363 K (bottom), showing the coalescence of rotameric signals upon heating.

5.3.4 Summary of results

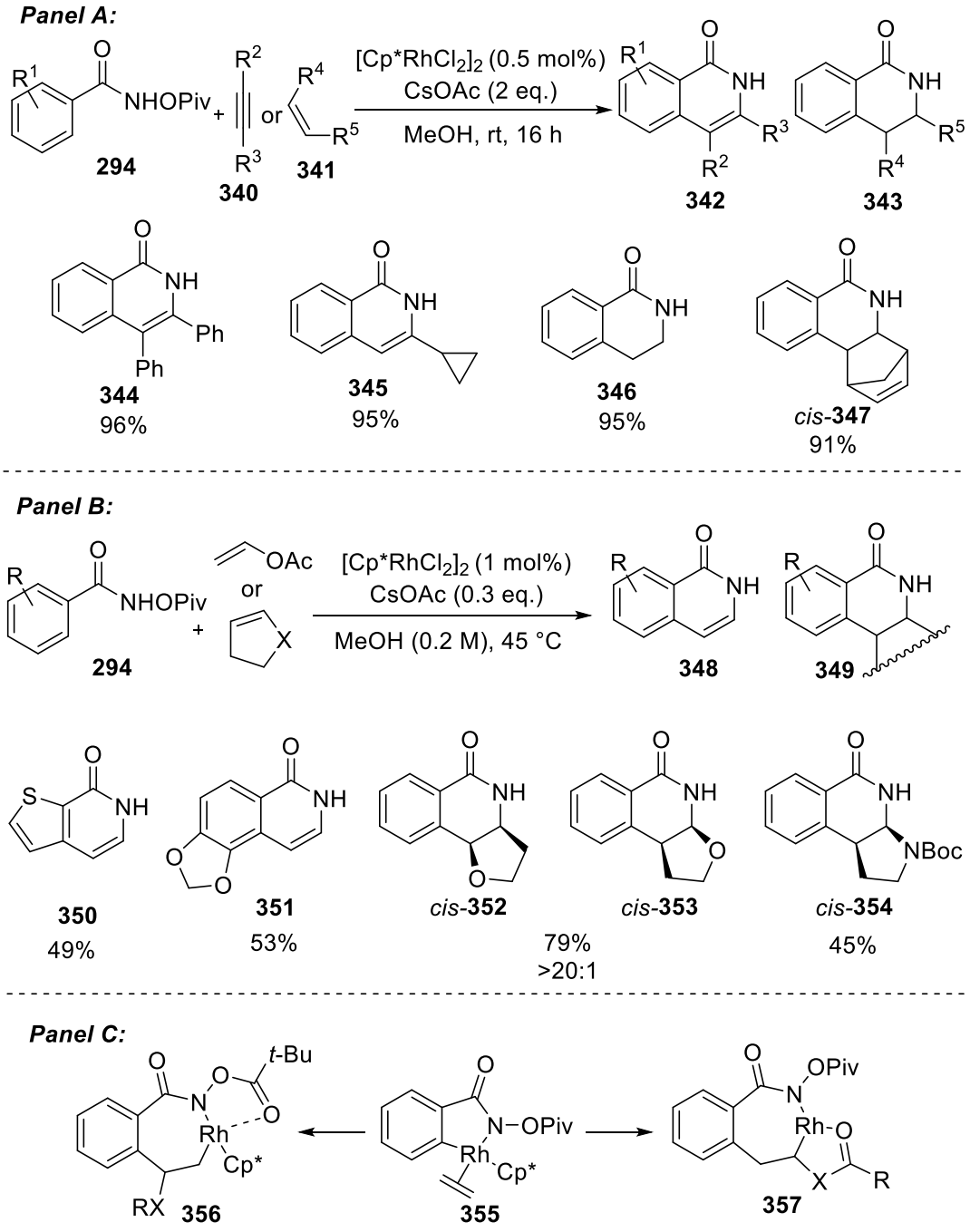
Herein this section, we have reported the successful employment of enecarbamates as alkene-based substrates in the Paternò-Büchi reaction. We have explored both photochemical and photocatalysed conditions and in doing so, have presented a library of highly functionalised and three-dimensional bicyclic oxetane-based scaffolds. An excellent scope was observed regarding the enecarbamate substrate, with all examples proceeding in full diastereoselectivity, however the scope was much more limited in regarding the ketoester, with ketoamides not tolerated.

5.4 Rhodium-catalysed annulation reactions of enecarbamates

5.4.1 Background

The application of rhodium(III)-catalysed C-H activation/annulation chemistry has been described in the literature for the successful preparation of isoquinolone and 3,4-dihydroisoquinolone-based scaffolds. Guimond *et al* have reported the preparation of both scaffolds *via* the use of either alkyne or alkene reactive partners, as summarised in scheme 5.7, panel A.[161] To achieve this, hydroxamate esters **294** were treated with alkynes **340** or alkenes **341**, CsOAc, and rhodium catalyst $[Cp^*RhCl_2]_2$ in MeOH at rt for 16 h delivering the corresponding isoquinolones **342** or 3,4-dihydroisoquinolones **343**. The methodology was tolerant of both disubstituted and terminal alkynes, shown by the formation of isoquinolones **344** and **345** respectively, as well as un-, mono- and di-substituted alkenes, including some examples of cyclic alkenes, providing a series of 3,4-dihydroisoquinolone examples such as **346** and *cis*-**347**. Dr Nicola Webb has carried out additional related studies, previously within our group, accessing both isoquinolone and 3,4-dihydroisoquinolone-based scaffolds from their alkene counterparts (scheme 5.7, panel B).[162] To achieve this, vinyl acetate was employed as a cheap and safe alternative to acetylene under similar reaction conditions (45 °C) facilitating the preparation of a library of isoquinolones **348**. A broad hydroxamate ester scope was reported, including both symmetrical and unsymmetrical substituents, illustrated by

exemplar isoquinolones **350** and **351**. Furthermore, a series of alkenes were also employed to deliver a library of 3,4-dihydroisoquinolones **349** including examples using heterocyclic alkenes, such as *cis*-**352**, *cis*-**353** and *cis*-**354**.



Scheme 5.7: Rhodium(III)-catalysed C-H activation/annulation chemistry for the preparation of a library of isoquinolone and 3,4-dihydroisoquinolone scaffolds *via* reactions with both alkyne and alkene partners as described by Guimond *et al* (panel A)[161] and Webb *et al* (panel B).[162] Regiochemical preferences regarding alkene insertion as described by Webb *et al* (panel C).[162]

Mechanistic rationale has also been proposed for the differing regiochemical outcomes observed for *cis*-**352**, cis-**353** and *cis*-**354** (scheme 5.7, panel C).[162] Electron rich enol ethers (where X = O, see panel B) may preferentially give rise to intermediate **356** *via* the migration of Rh to the most electron rich carbon, therefore governed by electronic factors. Conversely, those bearing potential coordinating groups (where X = *N*-Boc, see panel B), may instead favour the formation of intermediate **357**, therefore resulting in the opposite regiochemical outcome.

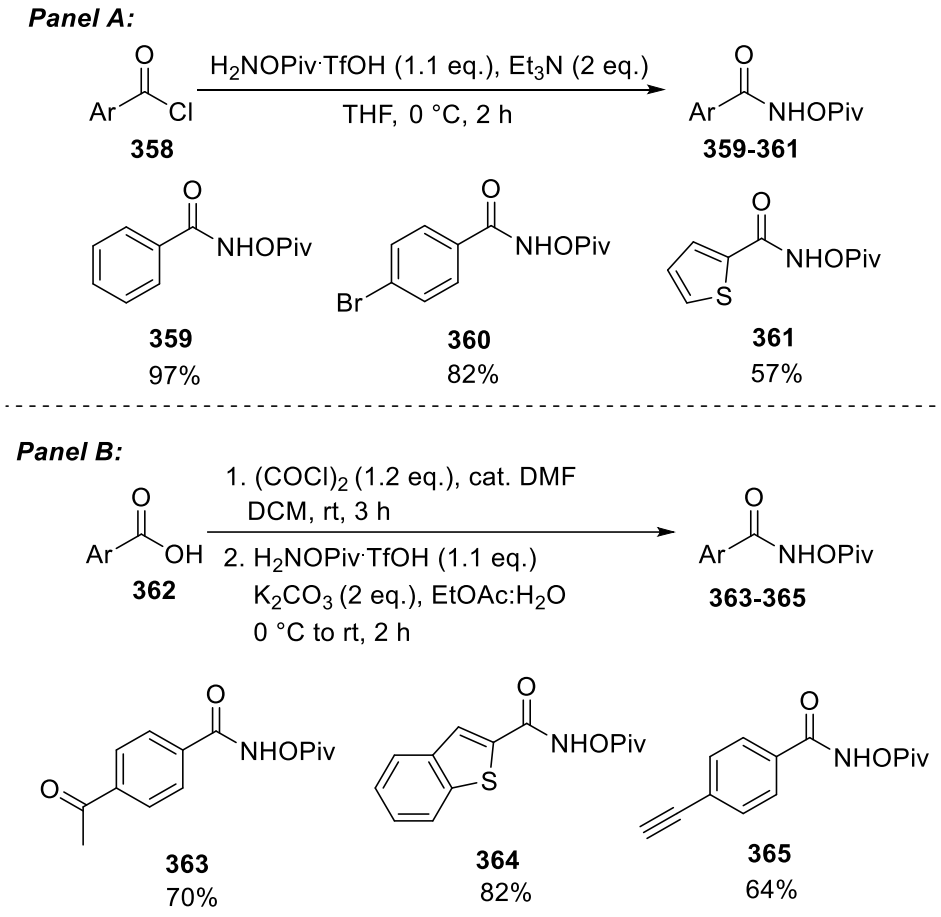
5.4.2 Introduction

This section will explore the applicability of the rhodium(III)-catalysed C-H activation/annulation chemistry, developed previously in our group, for the direct and simultaneous elaboration of enecarbamates through multiple vectors.[162] The hydroxamate ester and enecarbamate scope will be explored to deliver a series of novel polycyclic scaffolds. We envisage that the construction of such an unusual and novel core motif within these structures could give rise to interesting biological properties and we therefore plan to evaluate this *via* protein labelling experiments.

5.4.3 Results and discussion

Hydroxamate ester starting substrates were either previously prepared by Dr Sam Griggs or synthesised from their corresponding acid chlorides or carboxylic acids as described in scheme 5.8. Modifications of the methods published by Webb *et al*[162] and Guimond *et al*[161] were used for the amide couplings of acid chlorides where treatment of the appropriate acid chlorides **358** with $H_2NOPiv{\cdot}TfOH$ and Et_3N at 0 °C in THF for 2 h afforded hydroxamate esters **359**-**361** in good yields (scheme 5.8, panel A). For the desired hydroxamate esters where the corresponding acid chloride precursors were expensive or difficult to obtain, the associated carboxylic acids were instead employed. Treatment of these carboxylic acids **362** with oxalyl chloride and catalytic DMF in DCM afforded the corresponding intermediate crude acid chlorides

which were then subjected to treatment with $H_2NOPiv{\cdot}TfOH$ and K_2CO_3 in EtOAc and water at 0 °C for 2 h, yielding hydroxamate esters **363**-**365** again in high yields (scheme 5.8, panel B).[162] These methodologies enabled the preparation of hydroxamate esters bearing a variety of substituted phenyl groups (including those bearing halogen, acetyl and alkyne functionalities) and non-substituted aromatic functionalities (thiophene and benzothiophene). For all prepared hydroxamate esters, ^1H NMR spectroscopic analysis was used to determine the success of their syntheses, with a 9H singlet acting as a diagnostic signal for the incorporation of the pivalate group.



Scheme 5.8: The synthesis of hydroxamate esters **359**-**361** and **363**-**365** from their corresponding acid chloride (panel A) or carboxylic acid (panel B) precursors.

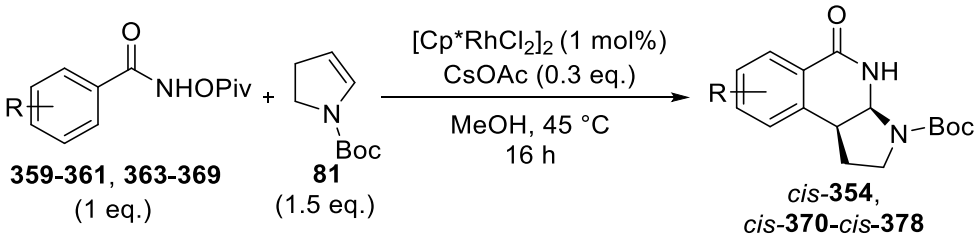
With a variety of hydroxamate esters in hand, we then turned our attention towards the rhodium(III)-catalysed C-H activation/annulation chemistry. We began by

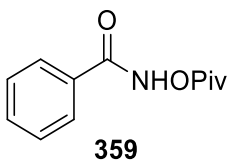
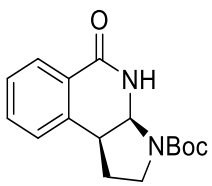
exploring the hydroxamate ester scope with five-membered enecarbamate **81**, previously employed in a single reaction by Webb *et al* (see scheme 5.7).[162] An initial repeat of this reaction was performed by treating unsubstituted hydroxamate ester **359** with *N*-Boc enecarbamate **81**, $[Cp^*RhCl_2]_2$ and oven-dried CsOAc in MeOH at 45 °C for 16 h, affording desired lactam *cis*-**354** in 62% yield, higher than that reported previously (45%), but agreeing with the previous regiochemical outcome (table 5.5, entry 1).[162] Expanding the scope to employ electron-deficient and neutral *p*-substituted aryl hydroxamate esters bearing bromo and acetyl functionalities was successful, delivering lactams *cis*-**370** and *cis*-**371** in good yields (44 and 55%, entries 2 and 3). Lactams *cis*-**370** and *cis*-**371** also provide easy avenues for further elaboration, such as cross-coupling strategies with the iodo functionality for the construction of new C-C bonds, or reductive amination of the acetyl group for the facile preparation of amines (*vide infra*). To achieve evaluation of the biological properties of this unique core motif, we planned to incorporate an alkyne functional handle into the amide product (*via* use of alkyne-containing hydroxamate ester **365**) for subsequent use in click-chemistry mediated protein labelling experiments. Unfortunately, alkyne-bearing hydroxamate **365** was not tolerated and no production of desired lactam *cis*-**372** was observed (entry 4). We then investigated the use of alternative heterocyclic and heteroaromatic containing hydroxamate esters. Electron-rich thiophene and benzothiophene-based hydroxamate esters were successful, delivering lactams *cis*-**373** and *cis*-**374** in moderate to good yields (39 and 26%, entries 5 and 6). Unfortunately, use of indole-based hydroxamate **366** was unsuccessful and did not provide any desired lactam product *cis*-**375**, instead forming a complex mixture of by-products potentially arising from the inclusion of a free nitrogen (entry 7). Interestingly, the formation of only one regioisomeric product was observed in each case, in accordance with that observed by Webb *et al*[162] for the reaction with *N*-Boc enecarbamate **81** (see scheme 5.7).

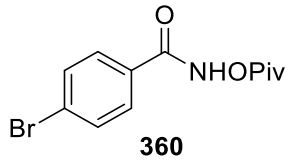
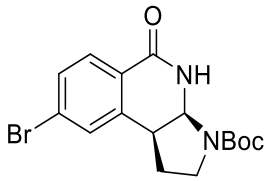
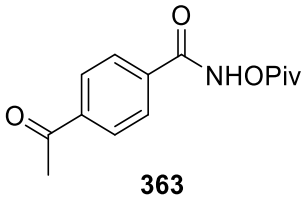
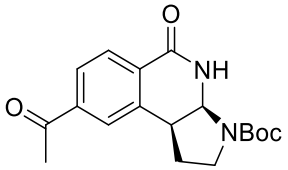
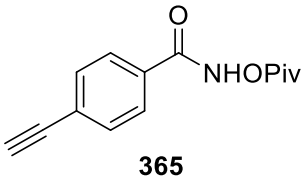
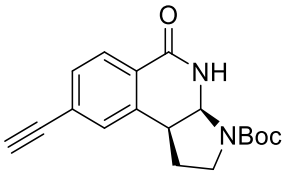
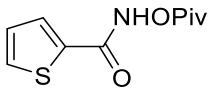
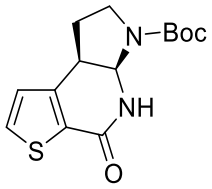
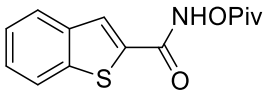
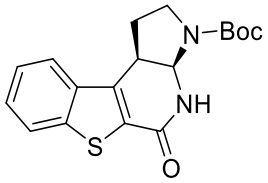
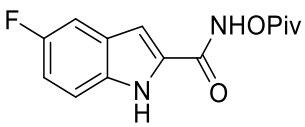
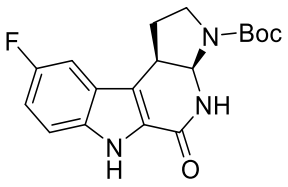
We then explored the use of non-symmetrical hydroxamate esters, offering multiple aromatic reactive C-H sites. The employment of difluorobenzodioxole-containing hydroxamate **367** was successful, furnishing *cis*-**376** as a single regioisomeric product

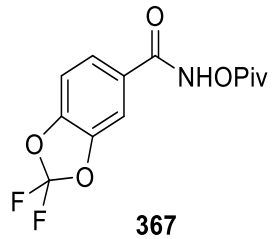
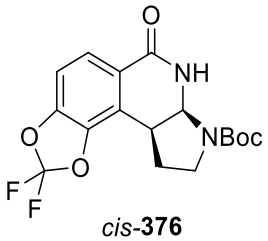
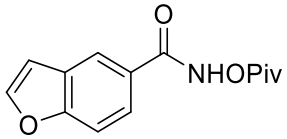
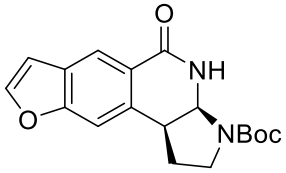
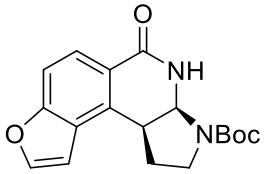
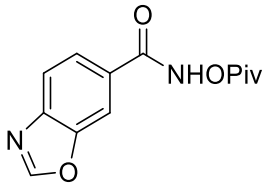
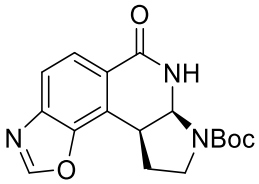
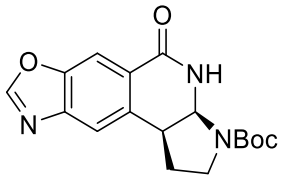
in 18% yield following purification (entry 8). The formation of this single contiguous regioisomer agrees with that observed for related acetal-bearing products reported by Webb *et al* (e.g **351** in scheme 5.7).[162] Benzofuran-based hydroxamate ester **368** was also successful, delivering a 1:1 mixture of regioisomeric lactams *cis*-**377a** and *cis*-**377b** as the crude and a 60:40 mixture following isolation in a good yield of 63% (entry 9). Finally, oxazole containing hydroxamate ester **369** delivered a 75:25 mixture of regioisomeric lactams *cis*-**378a** and *cis*-**378b**, which were isolated following purification as a 60:40 mixture in a low yield due to difficult separation from by-products (6%, entry 10). The lack of regioselectivity observed for benzofuran-based hydroxamate ester **368** (entry 9) likely reflects the dual directing ability of the benzofuran oxygen to both possible C-H insertion sites. For oxazole containing hydroxamate ester **369** (entry 10) however, this selectivity is more pronounced as the oxazole oxygen is only capable of activating one productive C-H environment.

Table 5.5: The results of the hydroxamate ester scope of the rhodium(III)-catalysed C-H activation/annulation using hydroxamate esters **359**-**361** and **363**-**369** and five-membered *N*-Boc enecarbamate **81**, employing conditions as reported by Webb *et al*.[162]



Entry	Hydroxamate ester	Desired product	Isolated yield (%)
1	 **359**	 *cis*-**354**	62

2	 **360**	 *cis*-**370**	44
2	 **363**	 *cis*-**371**	55
4	 **365**	 *cis*-**372**	0
5	 **361**	 *cis*-**373**	39
6	 **364**	 *cis*-**374**	26
7	 **366**	 *cis*-**375**	0

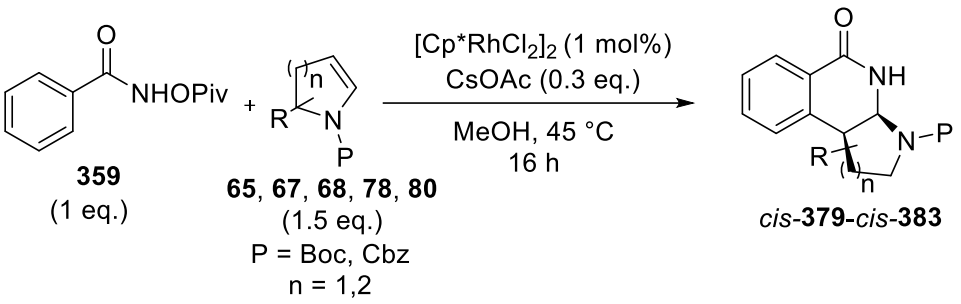
8	 **367**	 *cis*-**376**	18
9	 **368**	 *cis*-**377a**  *cis*-**377b**	63 (60:40)
10	 **369**	 *cis*-**378a**  *cis*-**378b**	6 (60:40)

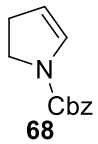
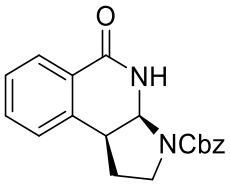
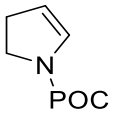
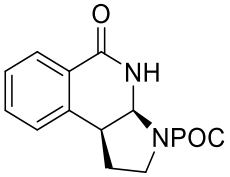
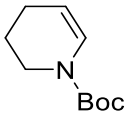
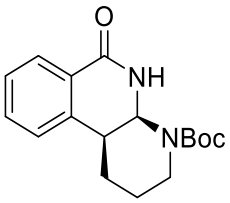
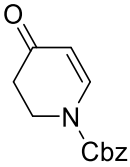
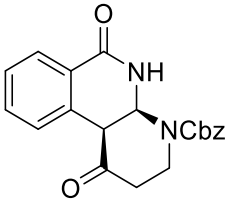
The success of each annulation was determined by ^{1}H and ^{13}C NMR spectroscopic analysis. In all cases two key diagnostic rotameric signals were observed for the aminal proton and carbon environments respectively. For example, for *cis*-**354** (entry 1) ^{1}H and ^{13}C signals were present at δ_H 5.54 (d, *J* 6.5), δ_H 5.60 (d, *J* 6.7), δ_C 80.9 and δ_C 81.5 respectively. The presence of this CH signal occurring at 80.9/81.5 ppm, consistent with an aminal and contrasting with the isomeric structure which might

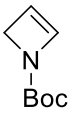
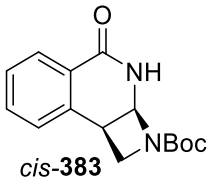
be expected to show a signal at ~68 ppm, was used to determine the formation of a single regioisomeric product with respect to the enecarbamate addition. For entries 8-10, where additional regioisomeric products arising from multiple CH sites were possible, the ^{1}H aryl signals and their associated couplings were used to identify each regioisomeric product. The regioselectivity was determined *via* ^{1}H spectroscopic analysis of either these signals or the aminal CH depending on which displayed suitable resolution.

We then set about exploring the enecarbamate scope in the reaction with hydroxamate ester **359** and associated results are presented in table 5.6. Changing the protecting group on the five-membered enecarbamate to Cbz was successful, affording *cis*-**379** in 43% (entry 1). The analogous *N*-POC enecarbamate **67** however, did not react and returned both starting materials (entry 2). Furthermore, no Lossen rearrangement of the hydroxamate ester was observed (as initially reported by Webb *et al*),[162] which has been noted to take place under these conditions where non-productive annulation reactions are seen. This observation, coupled with the reaction failure when employing alkyne-functionalised hydroxmate ester **365** (table 5.5, entry 4) indicates potential alkyne-mediated deactivation of the Rh catalyst (*vide infra*). Changing the enecarbamate to six-membered analogue **65** was unsuccessful and only Lossen rearrangement was seen to occur (entry 3). Altering reaction conditions to minimise this rearrangement (rt, longer duration) was unsuccessful at delivering desired amide *cis*-**381**. Suspecting insufficient enecarbamate reactivity as the hindering factor, we employed activated enecarbamate analogue **78** and four-membered enecarbamate **80**, the former again not displaying any reactivity (entry 4) and the latter producing a range of undesired by-products (entry 5).

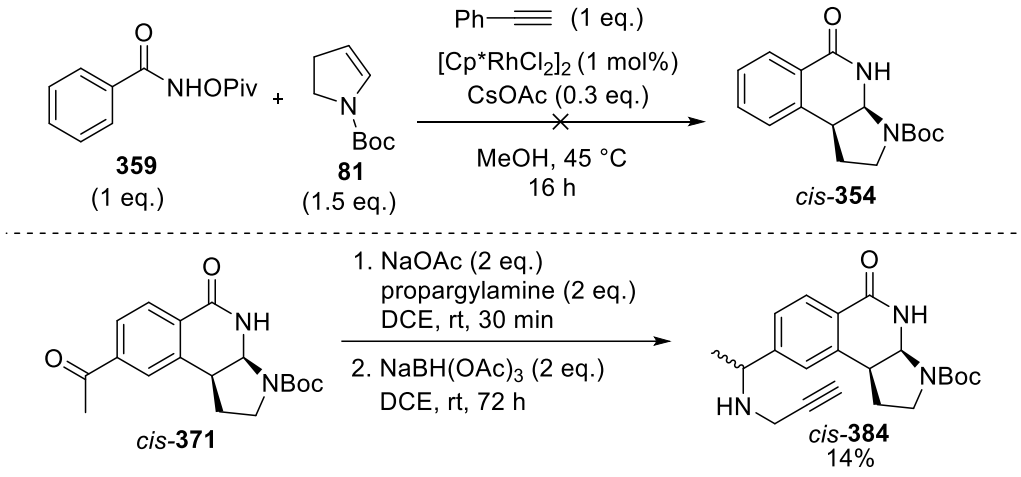
Table 5.6: The results of the enecarbamate scope of the rhodium(III)-catalysed C-H activation/annulation using hydroxamate ester **359**.



Entry	Enecarbamate	Desired product	Isolated yield (%)
1	 **68**	 *cis*-**379**	43
2	 **67**	 *cis*-**380**	0
3	 **65**	 *cis*-**381**	0
4	 **78**	 *cis*-**382**	0

5	 **80**	 *cis*-**383**	0

To explore the cause of the lack of reactivity observed in these reactions with alkynes present on either starting material (see table 5.5, entry 4 and table 5.6, entry 2) we doped a successful exemplar reaction with phenyacetylene (scheme 5.9). Indeed, the presence of the alkyne halted any desired product (*cis*-**354**) formation and delivered a range of by-products, including those formed from the annulation of phenylacetylene with hydroxamate ester **359**. The annulation of terminal alkynes is known in the literature,[161] however, interestingly wasn't observed in the reactions described above (see table 5.5, entry 4 and table 6.6, entry 2) therefore agreeing with our hypothesis of alkyne-induced catalyst deactivation. To achieve alkyne incorporation, we pursued an alternative approach, taking acetyl-decorated *cis*-**371** and installing a propargyl group *via* reductive amination (scheme 5.9).[163] Treatment of *cis*-**371** with NaOAc and propargylamine followed by sodium triacetoxyborohydride afforded alkyne-bearing amine *cis*-**384** as an undetermined mixture of diastereomers (dr not measurable due to rotamers).



Scheme 5.9: Doping of a successful exemplar rhodium(III)-catalysed C-H activation/annulation with phenylacetylene (top) and the synthesis of alkyne-bearing amine *cis*-**384** (bottom).

We suspected that alkyne-bearing *cis*-**384** could act as an electrophilic probe due to its inclusion of an aminal or masked aldehyde functionality, therefore potentially being able to react as such. With this in hand, protein-labelling attempts were pursued, using a commonly employed approach within our group. Figure 5.9 presents the experimental workflow where initial interaction between the probe and the protein takes place, then allowing the electrophilic warhead (presumably the aminal-like moiety), to undergo covalent binding to the protein (1). Then, attachment of a rhodamine-based fluorophore can be achieved *via* a biorthogonal copper-catalysed click [3+2] cycloaddition (CuAAc) reaction between the alkyne tag and the azide-functionalised fluorophore (2). This then allows visualisation of the reactivity using in-gel fluorescence of the rhodamine fluorophore.[164,165,166]

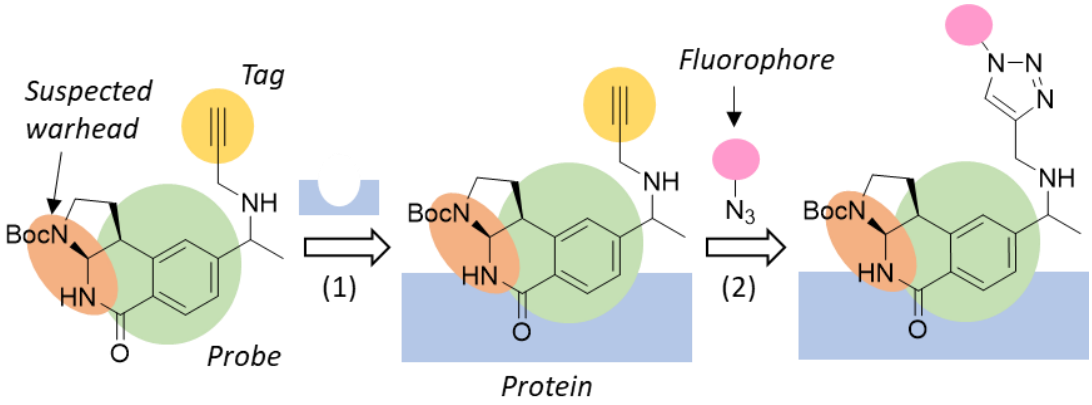


Figure 5.9: The summarised procedure of protein labelling. Initial protein binding of probe *cis*-**384** occurs facilitating covalent bonding between the protein and suspected warhead (1). Treatment with an azide-bearing fluorophore then undergoes a CuAAc reaction with the alkyne tag (2). Removal of excess click reagent and unreacted probe followed by visualisation *via* SDS-PAGE analysis can then take place to identify protein labelling.

To visualise labelling of probe *cis*-**384**, the click reaction and preparation of an SDS-PAGE gel was performed by Mr Julian Chesti, as presented in figure 5.10, using the method described in experimental section 7.5.2. Labelling of multiple protein residues can be observed, indicating sufficient electrophilicity of the reacting warhead and therefore potential biological applications of *cis*-**384**. Future work could investigate identification of the labelled protein residues as well as the mode of action of this core motif.

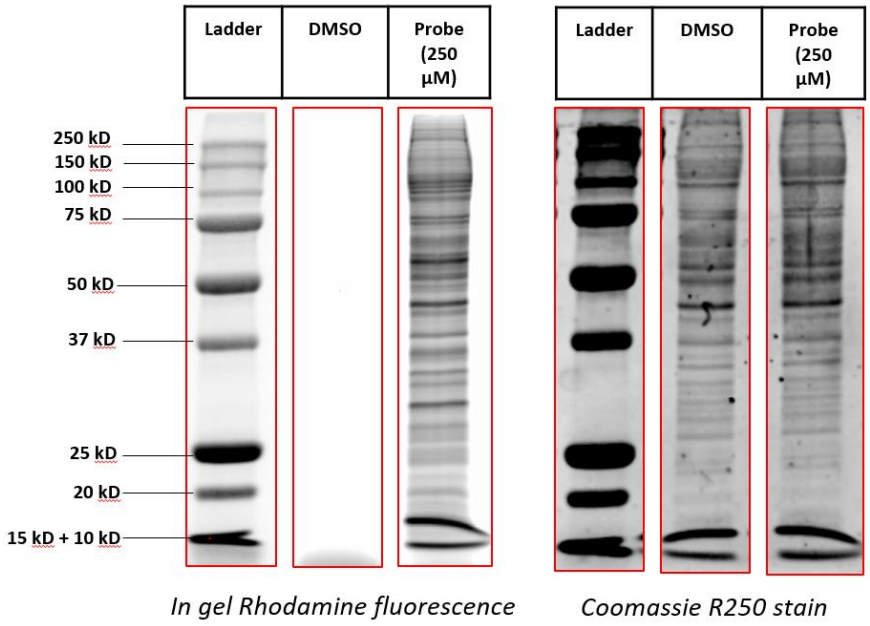


Figure 5.10: SDS-PAGE gel analysis of *cis*-**384** (probe). Obtained by incubation (25 µM, 1% DMSO) with HeLa cell lysate, loading 10 µg protein to each lane, running against a pre-stained molecular weight ladder, and reaction DMSO control containing lysate and DMSO (1%). Showing in-gel fluorescence using a DyLight 550 602/50 epifluorescence filter overlayed with Coomassie image of the pre-stained protein ladder using 715/30 far-red epifluorescence filter (left) compared to the total protein Coomassie stain (right).

5.4.4 Summary of results

We have successfully utilised the rhodium(III)-catalysed C-H activation/annulation chemistry to effectively elaborate enecarbamates *via* the α- and β-vectors simultaneously, facilitating the preparation of novel and fused polycyclic scaffolds. A broad substrate scope was discovered regarding the hydroxmate ester partner however this was much poorer in terms of the enecarbamate. Furthermore, evaluation of the biological activity of alkyne-bearing amine *cis*-**384** *via* click and gel analysis indicated successful protein labelling. Possible future work could include the identification of labelling sites and associated mode of action for this core motif.

5.5 Chapter summary

This chapter describes the successful application of a toolkit of annulation chemistries for the simultaneous elaboration of enecarbamates *via* multiple vectors (α, β and γ), facilitating the construction of new rings. We have adapted the hydroamination-cyclisation methodology described in chapter 4 for the novel and stereodivergent preparation of bicyclic fused lactams. We have described the application of the Paternò-Büchi annulation for the diastereoselective construction of a library of novel bicyclic oxetanes, performed stereochemical assignments and reported a broad enecarbamate scope. Finally, we have employed the rhodium(III)-catalysed C-H activation/annulation for the synthesis of a library of polycyclic 3,4-dihydroisoquinolone-based scaffolds and demonstrated potential biological value.

6 Chapter 6: Thesis conclusion

Via the application of three distinct synthetic strategies, we have been able to showcase the value of enecarbamate-based building blocks for the construction of diverse, lead-like polycyclic scaffolds. A modification of existing methodology[41] for the synthesis of enecarbamates **21** has been described, offering improved functional-group compatibility, delivering nine examples in good yields (scheme 6.1, Chapter 2). Preliminary efforts, regarding the elaboration of enecarbamates *via* the β-vector enabled the delivery of a series of low yielding arylations, providing few novel scaffolds. The α-elaboration of intermediate hemiaminal ethers, was pursued briefly, highlighting the diversity of functional groups able to undergo incorporation using a series of well documented methods (scheme 6.1, Chapter 2). Unfortunately, the inclusion of distal substituents, required for the preparation of novel scaffolds, delivered unresolvable, insufficient regioselectivity in the Shono oxidation.

The recent development of alternative β-functionalisation avenues for enecarbamates within our group,[41,42] provided a potential toolkit for the preparation of highly complex and diverse scaffolds. To showcase this, several highly three-

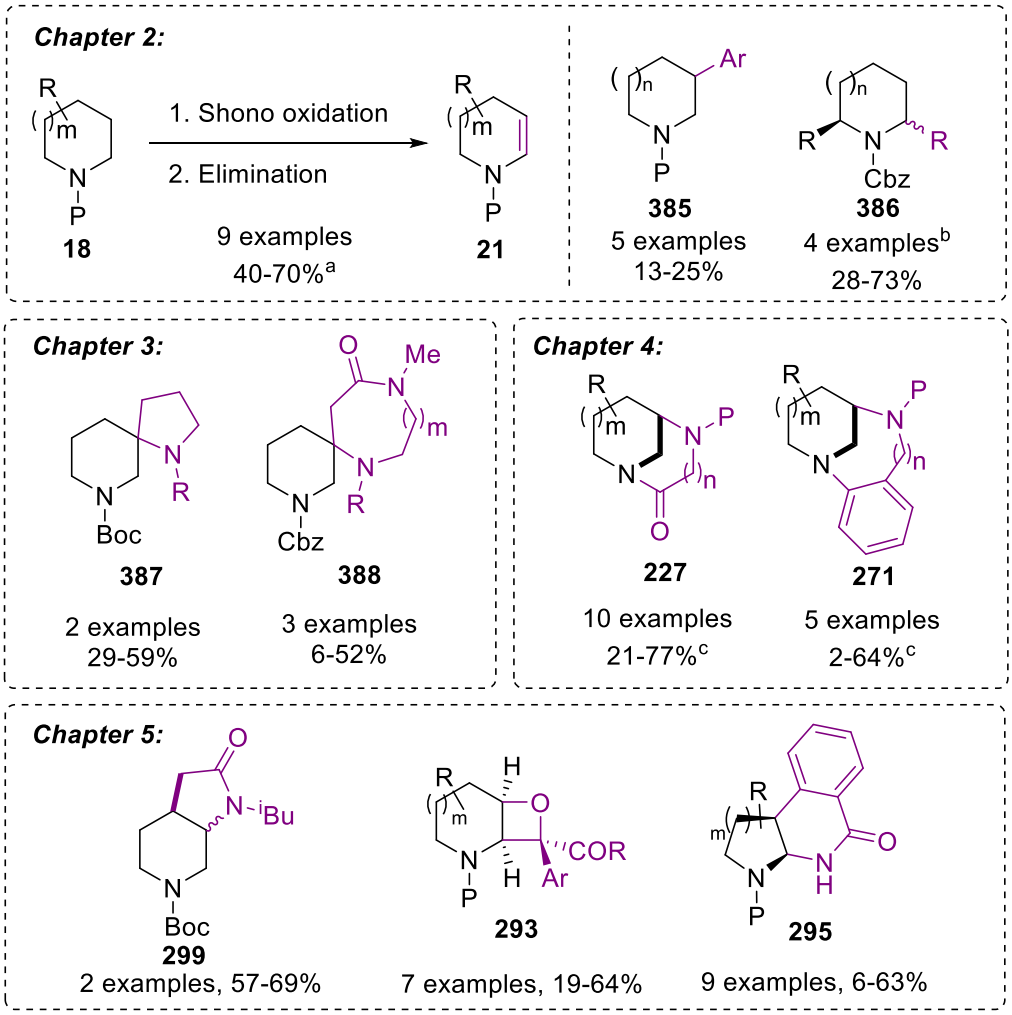
dimensional and novel spirocyclic scaffolds **388** were accessed *via* the sequential application of photoredox-mediated β-alkylation and β-amination methodologies (scheme 6.1, Chapter 3). The development of a conventional and complementary synthetic route towards spirocyclic precursors provided realistic scale-up opportunities and encouraged the preparation of alternative spirocyclic systems **387**. Unfortunately, lengthy synthetic routes and intrinsic by-product formation prevented the generation of a full compound library.

In response to these difficulties and to realise alternative opportunities for the employment of these methods, we explored photocatalysed β-amination as a complementary tool in the construction of diazabicyclic twisted amides (scheme 6.1, Chapter 4).[60] To our delight, we successfully delivered a library of ten twisted amides **227**, following subsequent protection and cyclisation of the β-aminated intermediates, demonstrating mostly high yields. These efforts greatly improved the scope from that previously reported, by enabling the inclusion of various ring sizes, appended ring systems and pre-existing β-substituents, not achievable by the previous approach. Modification of the cyclisation conditions enabled the preparation of a novel and complimentary library of five diazabicyclic twisted anilines **271**, again showcasing scaffolds of various ring sizes. Twisted amides exhibit a plethora of unique properties, explored frequently in the literature, and so we sought to investigate their relationship with ring size, showing twist to be most significant for the smallest ring systems. An exemplar strained lactam was shown to exhibit antimicrobial activity, highlighting the effects of twist on reactivity. An analogous relationship was too observed for the twisted aniline series, measured *via* their associated p*K*aHs in DMSO, carried out in collaboration with the University of Liverpool.[135]

Chapters 3 and 4 describe the synthesis of three-dimensional spiro- and bridged-ring systems and so, finally we pursued the construction of fused-systems, as a complementary scaffold and demonstration of diversity-oriented synthesis (Chapter 5). Initially we sought to exploit the β-aminative/cyclisation approach (Chapter 4) for this, and so bicyclic fused lactam **299** was prepared, with diastereomeric separation

of the precursors facilitating the access of each diastereomeric lactam (scheme 6.1). Achieving variation in ring size was problematic due to the prerequisite of a suitable tether being present in the starting heterocycle, and associated attempts at β-lactam cyclisation were unsuccessful. These approaches thus far describe a common method where β-elaboration is followed by appendage of a tether to construct a new ring. Instead, utilising annulative methods, where simultaneous α- and β-elaboration could be achieved in a single step would be highly desirable. Both the Paternò-Büchi [2+2]-cycloaddition and rhodium(III)-catalysed C-H activation/annulation methodologies[162] had received little literature attention regarding the use of enecarbamates and so these were explored. To our delight, the former delivered a library of seven bicyclic oxetanes **293**, all proceeding with full diastereoselectivity across a series of ring systems and providing ample opportunities for further decoration, as illustrated. Unfortunately, the carbonyl scope proved much more limited under our reaction conditions. The latter similarly delivered a large library of nine polycyclic 3,4-dihydroisoquinolones **295**, however whilst the hydroxamate ester scope was broad, only one enecarbamate ring system was successful. The unusual core motif accessed *via* these reactions underwent biological evaluation *via* protein labelling techniques and ultimately demonstrated activity. Future work could focus on the identification of labelled residues and associated biological mode of action.

In conclusion, we have successfully developed synthetic strategies for the construction of novel, highly three-dimensional, and valuable polycyclic scaffolds. The structurally diverse nature of the accessed scaffolds showcases the approaches' abilities to efficiently explore new areas of chemical space. Each chapter presents a different and complimentary approach for the synthesis of each diverse ring structure from simple enecarbamate building blocks and their associated successes and limitations discussed. Chapter four describes perhaps the most effective strategy, with the preparation of a broad library of interesting bicyclic twisted amides and anilines. A library of scaffolds was accessed in mostly high yields from a unified route, easily allowing variation in both structure and molecular properties due to its highly modular nature.



Scheme 6.1: A summary of the diverse and valuable three-dimensional, polycyclic scaffolds accessed in each chapter *via* the β-elaboration of their respective enecarbamate building blocks **21**. [a]Yields calculated over two steps. [b]Compounds accessed from corresponding hemiaminal ether building blocks. [c]Yields calculated over three steps.

7 Experimental

7.1 General Experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Fluorochem, Alfa Aesar and Acros. All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous diethyl ether, anhydrous ethanol, anhydrous methanol, and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. Anhydrous dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,2-dichloroethane (DCE) and anhydrous 1,4-dioxane were obtained from SureSeal bottles from Sigma−Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography was performed using silica gel 60 (35-70 μm particles) supplied by Merck. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Melting points (m.p.) were determined using Stuart melting point apparatus SMP3. X-ray measurements were carried out at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated Cu K_α radiation (λ = 1.54184 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT[167] and refined by a full matrix least squares technique based on F^2 using SHELXL2014.[168]

Proton (^{1}H) and carbon (^{13}C) NMR data was collected on a Bruker 300, 400 or 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br. (broad). Assignments were made using COSY, DEPT, HSQC, HMBC, NOESY and VT experiments.

7.2 General Procedures

General method A: Synthesis of enecarbamates *via* Shono oxidation and Brønsted acid-mediated elimination**:**

Compounds were prepared by a variation on the methods of Trindade *et al* and Tereshchenko *et al*.[41,54] An Electrasyn vial (10 or 20 mL) with a stir bar was charged with the Boc-protected amine in anhydrous methanol (10 or 20 mL) containing tetraethylammonium tosylate and was electrolysed with graphite electrodes at a constant current of 65 mA at 25 °C. After the passage of 2.5 $Fmol^{-1}$ of electricity, the mixture was concentrated *in vacuo*. The residue was taken up in toluene, NH_4Cl (20 mol%) was added and the mixture stirred at reflux for 1-4 h. Then, the mixture was allowed to cool to rt and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the corresponding enecarbamate as a mixture of rotamers.

General method B: Hydroamination of enecarbamates with amino esters**:**[42]

To a 7 mL vial were added [$Ir(dF(Me)ppy)_2(dtbbpy)PF_6$] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), amino ester hydrochloride (0.50 mmol), enecarbamate (0.25 mmol) and lithium hydroxide monohydrate (21.0 mg, 0.50 mmol). The vial was flushed with N_2 and toluene (5 mL) was then added and the resultant mixture was

stirred for 16 h under irradiation with a blue LED and fan cooling. The reaction was scaled out by repetition in additional vials as specified. The solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting amine as a mixture of rotamers.

General method C: Cbz/POC protection of amines:[60]

Benzyl or propargyl chloroformate (1.1 eq.) was slowly added to a mixture of amine (1.0 eq.) and $NaHCO_3$ (6.0 eq.) in DCM. The mixture was stirred for 16-96 h at room temperature, and then water was added (10 mL). The two layers were separated, and the organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting carbamate as a mixture of rotamers.

General method D: Tin-mediated cyclisation of protected amino esters:[60]

NaOH (1.1 eq.) was added to a solution of amino ester (1.0 eq.) in 1:1 MeOH:water (0.059 M) and stirred at 70 °C for 2 h or until complete by TLC and the solvent then evaporated under reduced pressure. To the resultant residue was added HCl (6 N) (0.089 M) and EtOAc (0.071 M) and the mixture stirred for 3 h or until complete by TLC and the solvent then evaporated under reduced pressure. To a suspension of the crude amino acid in toluene (0.075 M) was added *n*-Bu_2SnO (1.01 eq.) and the mixture refluxed under Dean-Stark for 16 h. The solvent was then evaporated under reduced pressure and the residue partitioned between DCM (10 mL) and water (10 mL). The organic layer was then washed with water (3 × 10 mL), dried ($MgSO_4$) and the solvent then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography to yield the resulting lactam as a mixture of rotamers.

General method E: Hydroamination of enecarbamates with benzylamines**:**

Compounds were prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF$_6$] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), 2-bromobenzylamine (186 mg, 1.00 mmol) and enecarbamate (0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. The reaction was scaled out by repetition in additional vials as specified. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the resulting amine as a mixture of rotamers.

General method F: Buchwald-Hartwig cyclisations of protected benzylamines**:**

Compounds were prepared by a variation on the method of Xia *et al*.[169] HCl (6 N) (0.089 M) was added to a solution of protected amine (1 eq.) in EtOAc (0.071 M) and stirred for 3 h or until complete by TLC. The solvent was then removed under reduced pressure to give the corresponding NH amine. $Pd_2(dba)_3$ (4 mol%) and BINAP (8 mol%) were dissolved in toluene and stirred at 110 °C for 30 min and then cooled to rt. This solution was then added to NaO*t*Bu (1.9 eq.) and the NH amine and the resulting mixture stirred at reflux for 16-96 h. The mixture was then allowed to cool to rt, filtered through celite, and washed with DCM (20 mL). The solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography to yield the corresponding bicyclic aniline as a mixture of rotamers.

General method G: Photochemical Paternò-Büchi annulations of enecarbamates and benzoylformates**:**

Compounds were prepared by a variation on the method of Rykaczewski *et al*.[156] To a vial were added enecarbamate or enamide (0.3 mmol), benzoylformate (0.2 mmol)

and MeCN (2 mL) and the solution was then degassed with N_2 for 5 min. 0.15 mL of the solution was then transferred to a fReactor, CSTR device and irradiated by a single 365 nm LED with a nominal radiant light output of 4.3 W and magnetically stirred for 1 h with fan cooling. The reaction mixture was then removed from the CSTR and flushed with 5 reaction volumes of MeCN to yield the crude product. The crude product was purified by flash column chromatography to yield the corresponding oxetane.

General method H: Amide couplings of carboxylic acid and amine *via* acid chloride formation**:**[160]

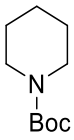
Oxalyl chloride (1.2 eq.) was added dropwise to a solution of carboxylic acid (1 eq. mmol) in DCM (1 M) with catalytic DMF and stirred at rt for 1 h. The solution was then concentrated under reduced pressure to give the crude acid chloride which was then dissolved in DCM (0.5 M). Amine (1.5 eq.) and Et_3N (2 eq.) were then added slowly at 0 °C and the resultant mixture stirred at rt for 16 h. The mixture was then concentrated under reduced pressure and the crude product purified as specified to yield the corresponding amide as a mixture of rotamers.

General method I: Rh-catalysed annulations of enecarbamates and hydroxamate esters:[162]

Enecarbamate (1.5 eq.) was added to a solution of $[Cp^*RhCl_2]_2$ (1 mol%), oven-dried CsOAc (0.3 eq.) and hydroxamate (1 eq.) in MeOH in a vial under a nitrogen atmosphere. The reaction was heated to 45 °C for 16 hours, after which time the solvent was removed *in vacuo*. The crude product was then purified by flash column chromatography to yield the corresponding amide as a mixture of rotamers.

7.3 Characterisation data

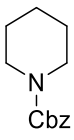
tert-Butyl piperidine-1-carboxylate 57[58]



57

Boc_2O (14 mL, 60 mmol) was added to piperidine (6.5 mL, 66 mmol) in DCM (210 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to yield carbamate **57** as a mixture of rotamers (11.0 g, 99%) as a colourless oil, ν_{max}/cm^{-1} 2976, 2934, 2855, 1687 (C=O), 1446, 1416, 1257, 1237, 1175, 1083 and 868; δ_H (400 MHz, $CDCl_3$) 3.38–3.31 (4H, m, 2-H_2, 6-H_2), 1.59–1.53 (2H, m, 4-H_2), 1.53–1.47 (4H, m, 3-H_2, 5-H_2), 1.45 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 155.1 (Boc C=O), 79.2 (Boc *C*Me_3), 44.8 (C-2, C-6), 28.6 (Boc C*Me*$_3$), 25.9 (C-4), 24.7 (C-3, C-5); HRMS found MNa^+, 208.1308. $C_{10}H_{19}NO_2Na$ requires 208.1308. Spectroscopic data are consistent with those reported in the literature.[61]

Benzyl piperidine-1-carboxylate 58[59]

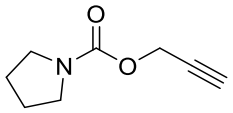


58

Benzyl chloroformate (4.5 mL, 31.7 mmol) was slowly added to a mixture of piperidine (3.0 mL, 30.0 mmol) and triethylamine (6.3 mL, 45.0 mmol) in DCM (24 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 48 h at room temperature, and then 1 M $HCl_{(aq)}$ was added (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The

organic layers were combined and washed with water (20 mL), sat. $NaHCO_{3(aq)}$ (20 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 90:10 hexane−EtOAc to yield carbamate **58** (4.67 g, 71%) as a colourless oil, R_f 0.52 (60:40 Hexane−EtOAc); ν_{max}/cm^{-1} 2935, 2854, 1692 (C=O), 1425, 1258, 1229, 1145, 1074, 1023 and 696; δ_H (400 MHz, $CDCl_3$) 7.45–7.27 (5H, m, Ph), 5.13 (2H, s, Cbz CH_2), 3.55–3.35 (4H, m, 2-H_2, 6-H_2), 1.68–1.41 (6H, m, 3-H_2, 4-H_2, 5-H_2); δ_C (100 MHz, $CDCl_3$) 155.5 (C=O), 137.2 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.9 (Ph), 67.0 (Cbz CH_2), 45.0 (C-2, C-6), 25.9 (C-4), 24.5 (C-3, C-5); HRMS found MNa^+, 242.1142. $C_{13}H_{17}NO_2Na$ requires 242.1152. Spectroscopic data are consistent with those reported in the literature.[62]

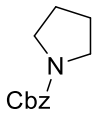
Prop-2-yn-1-yl pyrrolidine-1-carboxylate 59



59

Compound **59** was synthesised using general method C using propargyl chloroformate (0.9 mL, 7.0 mmol), pyrrolidine (0.7 mL, 8.4 mmol) and $NaHCO_3$ (3.53 g, 42.0 mmol) in DCM (9 mL) for 16 h to yield *carbamate* **59** as a 1:1 mixture of rotamers (1.05 g, 98%) as a yellow oil, ν_{max}/cm^{-1} 3291, 3240, 2854, 2878, 2125 (C≡C), 1693 (C=O), 1415, 1333, 1124, 1092 and 765; δ_H (500 MHz, $CDCl_3$) 4.70 (1H, d, *J* 2.4, OCH_2), 3.41 (2H, t, *J* 6.5, 2-H_2, 5-H_2), 3.37 (2H, t, *J* 6.6, 2-H_2, 5-H_2), 2.44 (1H, t, *J* 2.4, C≡CH), 1.92–1.81 (4H, m, 3-H_2, 4-H_2); δ_C (125 MHz, $CDCl_3$) 154.2 (C=O), 79.0 (*C*≡CH), 74.3 (C≡*C*H), 52.6 (OCH_2), 46.5 (C-2, C-5), 46.0 (C-2, C-5), 25.9 (C-3, C-4), 25.1 (C-3, C-4) (8 out of 12 signals present); HRMS found $2MNa^+$, 329.1470. $C_{16}H_{22}N_2O_4Na$ requires 329.1472.

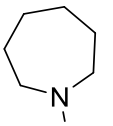
Benzyl pyrrolidine-1-carboxylate 60



60

Compound **60** was prepared by a variation on the method of Babich *et al*.[59] Benzyl chloroformate (6.0 mL, 42.5 mmol) was slowly added to a mixture of pyrrolidine (2.8 mL, 40.0 mmol) and triethylamine (8.4 mL, 60.0 mmol) in DCM (60 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 16 h at room temperature, and then 1 M $HCl_{(aq)}$ was added (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined and washed with water (20 mL), sat. $NaHCO_{3(aq)}$ (20 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield carbamate **60** (7.66 g, 94%) as a yellow oil, ν_{max}/cm^{-1} 2927, 2855, 1697 (C=O), 1448, 1415, 1357, 1105, 731 and 697; δ_H (500 MHz, $CDCl_3$) 7.41–7.27 (5H, m, Ph), 5.14 (2H, s, Cbz CH_2), 3.54–3.35 (4H, m, 2-H_2, 5-H_2), 1.92–1.81 (4H, m, 3-H_2, 4-H_2); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O), 137.3 (*ipso*-Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.0 (Ph), 66.7 (Cbz CH_2), 46.4 (C-2, C-5), 45.9 (C-2, C-5), 25.9 (C-3, C-4), 25.1 (C-3, C-4) (11 out of 16 signals present); HRMS found MNa^+, 228.0990. $C_{12}H_{15}NO_2Na$ requires 228.0995. Spectroscopic data are consistent with those reported in the literature.[63]

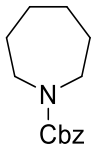
***tert*-Butyl azepane-1-carboxylate 61**



61

Compound **61** was prepared by a variation on the method of Abadie *et al*.[58] Boc_2O (4.6 mL, 20 mmol) was added to a solution of azepane (2.3 mL, 22 mmol) in DCM (70 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to yield carbamate **61** as a 1:1 mixture of rotamers (3.98 g, 100%) as a yellow oil; ν_{max}/cm^{-1} 2974, 2927, 2857, 1687 (C=O), 1413, 1160, 1115, 964 and 770; δ_H (400 MHz, $CDCl_3$) 3.37 (2H, app. t, *J* 6.1, 2-H_2, 7-H_2), 3.31 (2H, app. t, *J* 6.1, 2-H_2, 7-H_2), 1.71–1.58 (4H, br m, 3-H_2, 6-H_2), 1.57–1.48 (4H, br m, 4-H_2, 5-H_2), 1.45 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 155.8 (Boc C=O), 79.0 (Boc *C*Me_3), 47.1 (C-2, C-7), 46.7 (C-2, C-7), 28.7 (Boc C*Me*$_3$), 28.6 (Boc C*Me*$_3$), 27.6 (C-3, C-6), 27.0 (C-4, C-5), (8 out of 12 signals present); HRMS found MNa^+, 221.1461. $C_{11}H_{21}NO_2Na$ requires 221.1465. Spectroscopic data are consistent with those reported in the literature.[64]

Benzyl azepane-1-carboxylate 62

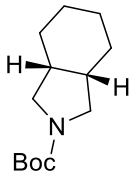


62

Compound **62** was prepared by a variation on the method of Babich *et al*.[59] Benzyl chloroformate (2.97 mL, 21.1 mmol) was slowly added to a mixture of azepane (2.25 mL, 20.0 mmol) and triethylamine (4.18 mL, 30.0 mmol) in DCM (16 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 64 h, and then 1 M $HCl_{(aq)}$ was added (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined and washed with water (20 mL), sat. $NaHCO_{3(aq)}$ (20 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 90:10 hexane−EtOAc to yield carbamate **62** as a 1:1 mixture of rotamers (3.28 g, 66%) as a colourless oil, R_f 0.54 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 2926, 2855, 1690

(C=O), 1475, 1453, 1419, 1257, 1199, 1175, 1074, 992, 767, 733 and 696; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.14 (2H, s, Cbz CH_2), 3.48–3.44 (2H, m, 2-H, 7-H), 3.44–3.40 (2H, m, 2-H, 7-H), 1.75–1.62 (4H, m, 3-H, 6-H), 1.58–1.49 (4H, m, 4-H, 5-H); δ_C (125 MHz, $CDCl_3$) 156.3 (C=O), 137.3 (*ipso*-Ph), 128.6 (Ph), 127.9 (Ph), 127.8 (Ph), 66.9 (Cbz CH_2), 47.2 (C-2, C-7), 46.7 (C-2, C-7), 28.7 (C-3, C-6), 28.5 (C-3, C-6), 27.5 (C-4, C-5), 27.1 (C-4, C-5); HRMS found MNa^+, 256.1312. $C_{14}H_{19}NO_2Na$ requires 256.1308. Spectroscopic data are consistent with those reported in the literature.[62]

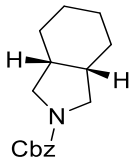
Cis-_tert_-butyl octahydro-2H-isoindole-2-carboxylate 63



63

Compound **63** was prepared by a variation on the method of Abadie *et al*.[58] Boc_2O (2.7 mL, 11.8 mmol) was added to a solution of *cis*-octahydro-1H-isoindole hydrochloride (1.59 g, 9.84 mmol) and Et_3N (2.7 mL, 19.7 mmol) in DCM (30 mL) and stirred at rt for 72 h. The solvent was then evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield slightly impure carbamate **63** as a 1:1 mixture of rotamers (2.17 g, ~97%) as a colourless oil, R_f 0.31 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2975, 2926, 2856, 1693 (C=O), 1392, 1304, 1136, 1092, 875 and 771; δ_H (400 MHz, $CDCl_3$) 3.36–3.25 (2H, m, 2-H, 9-H), 3.22 (1H, dd, *J* 10.6, 5.4, 2-H, 9-H), 3.14 (1H, dd, *J* 10.5, 5.7, 2-H, 9-H), 2.21–2.09 (2H, m, 3-H, 8-H), 1.59–1.42 (15H, m, Boc CMe_3, 4-H_2, 5-H_A, 6-H_A, 7-H_2), 1.38–1.39 (2H, m, 5-H_B, 6-H_B); δ_C (100 MHz, $CDCl_3$) 155.4 (Boc C=O), 80.0 (Boc *C*Me_3), 50.1 (C-2, C-9), 49.7 (C-2, C-9), 37.5 (C-3, C-8), 36.8 (C-3, C-8), 28.7 (Boc C*Me*$_3$), 26.0 (C-4, C-7), 23.02 (C-5, C-6), 22.96 (C-5, C-6) (10 out of 14 signals present); HRMS found MNa^+, 248.1618. $C_{13}H_{23}NO_2Na$ requires 248.1621.

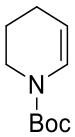
***Cis*-benzyl octahydro-2H-isoindole-2-carboxylate 64**



64

Compound **64** was prepared by a variation on the method of Babich *et al*.[59] Benzyl chloroformate (3.0 mL, 21.0 mmol) was slowly added to a mixture of of *cis*-octahydro-1H-isoindole hydrochloride (3.2 mL, 20.0 mmol) and triethylamine (16.6 mL, 46.0 mmol) in DCM (40 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 16 h at room temperature, and then 1 M $HCl_{(aq)}$ was added (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined and washed with water (20 mL), sat. $NaHCO_{3(aq)}$ (20 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield slightly impure carbamate **64** as a 1:1 mixture of rotamers (3.47 g, ~67%) as a brown oil; ν_{max}/cm^{-1} 2927, 2855, 1697 (C=O), 1415, 1357, 1105, 1091, 731 and 697; δ_H (500 MHz, $CDCl_3$) 7.42–7.31 (5H, m, Ph), 5.15 (1H, d, *J* 12.5, Cbz CH_2), 5.11 (1H, d, *J* 12.5, Cbz CH_2), 3.43–3.36 (2H, m, 2-H, 9-H), 3.30 (1H, dd, *J* 10.6, 5.5, 2-H, 9-H), 3.28 (1H, dd, *J* 10.5, 5.8, 2-H, 9-H), 2.23–2.13 (2H, m, 3-H, 8-H), 1.61–1.53 (2H, br m, 4-H_A, 7-H_A), 1.52–1.47 (2H, m, 5-H_A, 6-H_A), 1.47–1.40 (2H, br m, 4-H_B, 7-H_B), 1.38–1.32 (2H, m, 5-H_B, 6-H_B); δ_C (125 MHz, $CDCl_3$) 155.6 (Cbz C=O), 137.3 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.9 (Ph), 66.7 (CH_2 Cbz), 50.3 (C-2, C-9), 49.9 (C-2, C-9), 37.5 (C-3, C-8), 36.7 (C-3, C-8), 25.9 (C-4, C-7), 23.0 (C-5, C-6), 22.9 (C-5, C-6) (13 out of 20 signals present); HRMS found MNa^+, 282.1462. $C_{16}H_{21}NO_2Na$ requires 282.1465. Spectroscopic data are consistent with those reported in the literature.[66]

***tert*-Butyl 3,4-dihydropyridine-1(2H)-carboxylate 65**[55]



65

Method 1:

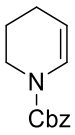
Compound **65** was synthesised using general method A using Boc protected amine **57** (1.02 g, 4.56 mmol), anhydrous methanol (10 mL), tetraethylammonium tosylate (83 mg, 0.28 mmol), toluene (10 mL) and NH_4Cl (57.8 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane–Et_2O to yield enecarbamate **65** as a 60:40 mixture of rotamers (464 mg, 47%) as a colourless oil, R_f 0.44 (80:20 hexane–Et_2O); ν_{max}/cm^{-1} 2976, 2934, 1688 (C=O), 1365, 1253, 1150, 990, 918, 876 and 729; δ_H (500 MHz, $CDCl_3$) 6.85 (0.4H, d, *J* 8.5, 2-H), 6.71 (0.6H, d, *J* 8.4, 2-H), 4.90 (0.4H, m, 3-H), 4.79 (0.6H, dt, *J* 8.1 and 3.8, 3-H), 3.63–3.43 (2H, m, 6-H_2), 2.09–1.95 (2H, m, 4-H_2), 1.86–1.72 (2H, m, 5-H_2), 1.48 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 152.9 (Boc C=O), 152.5 (Boc C=O), 125.8 (C-2), 125.4 (C-2), 105.8 (C-3), 105.3 (C-3), 80.6 (Boc *C*Me_3), 80.5 (Boc *C*Me_3), 42.7 (C-6), 41.6 (C-6), 28.5 (Boc C*Me*$_3$), 21.9, 21.6, 21.5 (C-4 and C-5) (15 out of 16 signals present); HRMS found $2MNa^+$, 389.2399. $C_{20}H_{34}N_2O_4Na$ requires 389.2411. Spectroscopic data are consistent with those reported in the literature.[54]

Method 2:

Super-Hydride® (4.6 mL of a 1 M solution in THF, 4.6 mmol) was added dropwise to a solution of the piperidone **73** (876 mg, 4.40 mmol) in toluene (10 mL) at –78 °C and stirred for 30 min at –78 °C. Then, DIPEA (4.3 mL, 27.1 mmol), DMAP (10.5 mg, 2 mol%) and TFAA (0.8 mL, 5.70 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (20 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 20 mL). The organic layers were combined and

washed with water (2 × 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 hexane−Et_2O to yield the enecarbamate **65** as a 60:40 mixture of rotamers (510 mg, 63%) as a yellow oil.

Benzyl 3,4-dihydropyridine-1(2H)-carboxylate 66[55]



66

Method 1:

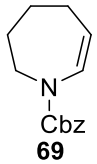
Compound **66** was synthesised using general method A using Cbz protected amine **58** (3 g, 13.7 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.84 mmol), toluene (20 mL) and NH_4Cl (147 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield enecarbamate **66** as a 60:40 mixture of rotamers (2.40 g, 81%) as a colourless oil, R_f 0.47 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2945, 1696 (C=O), 1412, 1341, 1257, 816 and 698; δ_H (400 MHz, $CDCl_3$) 7.42–7.28 (5H, m, Ph), 6.89 (0.4H, d, *J* 8.4, 2-H), 6.80 (0.6H, d, *J* 8.4, 2-H), 5.18 (2H, s, Cbz CH_2), 4.97 (0.4H, dt, *J* 8.1 and 4.1, 3-H), 4.86 (0.6H, dt, *J* 8.1 and 3.9, 3-H), 3.69–3.54 (2H, m, 6-H_2), 2.04 (2H, tdd, *J* 6.2, 3.8 and 2.0, 4-H_2), 1.87–1.78 (2H, m, 5-H_2); δ_C (100 MHz, $CDCl_3$) 153.7 (C=O), 153.3 (C=O), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 125.5 (C-2), 125.0 (C-2), 106.9 (C-3), 106.6 (C-3), 67.6 (Cbz CH_2), 67.5 (Cbz CH_2), 42.5 (C-6), 42.3 (C-6), 21.8, 21.6, 21.4 (C-4 and C-5) (17 out of 22 signals present); HRMS found MNa^+, 240.0988. $C_{13}H_{15}NO_2Na$ requires 240.0995. Spectroscopic data are consistent with those reported in the literature.[41]

Method 2:

Super-Hydride® (25 mL of a 1 M solution in THF, 25.3 mmol) was added dropwise to a solution of the piperidone **74** (5.66 g, 24.3 mmol) in toluene (49 mL) at –78 °C and

stirred for 30 min at –78 °C. Then, DIPEA (24.1 mL, 138 mmol), DMAP (59.3 mg, 2 mol%) and TFAA (4.0 mL, 29.2 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (100 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with water (2 × 100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 98:2 hexane−EtOAc to yield the enecarbamate **66** as a 60:40 mixture of rotamers (1.86 g, 35%) as a colourless oil (spectroscopic data as above).

Benzyl 2,3,4,5-tetrahydro-1H-azepine-1-carboxylate 69[55]



69

Method 1:

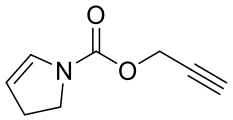
Compound **69** was synthesised using general method A using Cbz protected amine **62** (3 g, 12.9 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.84 mmol), toluene (20 mL) and NH_4Cl (161 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield enecarbamate **69** as an undetermined mixture of rotamers (661 mg, 22%) as a colourless oil, R_f 0.38 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 3034, 2930, 2860, 1699 (C=O), 1650, 1408, 1340, 1251, 1110, 978, 765, 724, 695; δ_H (400 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 6.65–6.46 (1H, m, 2-H), 5.17 (2H, s, Cbz CH_2), 5.13–4.95 (1H, m, 3-H), 3.76–3.65 (2H, m, 7-H_2), 2.24–2.12 (2H, m, 4-H_2), 1.87–1.67 (4H, m, 5-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 154.6 (C=O), 153.6 (C=O), 136.7 (*ipso*-Ph), 130.8 (C-2), 130.0 (C-2), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 116.0 (C-3), 115.9 (C-3), 67.6 (Cbz CH_2), 67.5 (Cbz CH_2), 47.8 (C-7), 28.2 (C-5 or C-6), 26.4 (C-4), 26.1 (C-4), 25.2 (C-5 or C-6) (16 out of 24 signals present); HRMS found MNa^+,

254.1151. $C_{14}H_{17}NO_2Na$ requires 254.1152. Spectroscopic data are consistent with those reported in the literature.[41]

Method 2:

Super-Hydride® (18.3 mL of a 1 M solution in THF, 18.3 mmol) was added dropwise to a solution of the piperidone **75** (4.36 g, 17.8 mmol) in toluene (35 mL) at –78 °C and stirred for 30 min at –78 °C. Then, DIPEA (17.5 mL, 101 mmol), DMAP (43.1 mg, 2 mol%) and TFAA (2.9 mL, 21.4 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (100 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with water (2 × 100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield the enecarbamate **69** as an undetermined mixture of rotamers (2.61 g, 63%) as a colourless oil.

Prop-2-yn-1-yl 2,3-dihydro-1H-pyrrole-1-carboxylate 67

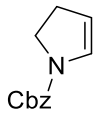


67

Compound **67** was synthesised using general method A using POC protected amine **59** (1 g, 6.53 mmol), anhydrous methanol (10 mL), tetraethylammonium tosylate (83 mg, 0.28 mmol), toluene (10 mL) and NH_4Cl (72 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield *enecarbamate* **67** as a 55:45 mixture of rotamers (441 mg, 45%) as a colourless oil, R_f 0.28 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 3293, 2949, 2864, 2127 (C≡C), 1698 (C=O), 1619 (C=O), 1416, 1333, 1119, 1089, 754 and 704; δ_H

(500 MHz, $CDCl_3$) 6.62–6.57 (0.45H, br m, 2-H), 6.55–6.49 (0.55H, br m, 2-H), 5.14–5.10 (0.45H, br m, 3-H), 5.09–5.05 (0.55H, br m, 3-H), 4.73 (2H, d, *J* 2.4, OCH_2), 3.82–3.73 (2H, br m, 5-H_2), 2.72–2.66 (0.9H, br m, 4-H_2), 2.66–2.61 (1.1H, br m, 4-H_2), 2.47 (1H, t, *J* 2.3, C≡CH); δ_C (125 MHz, $CDCl_3$) 152.1 (C=O), 151.3 (C=O), 129.6 (C-2), 128.9 (C-2), 109.5 (C-3), 109.4 (C-3), 78.4 (*C*≡CH), 74.8 (C≡*C*H), 53.0 (OCH_2), 52.9 (OCH_2), 45.4 (C-5), 45.2 (C-5), 29.9 (C-4), 28.8 (C-4) (14 out of 16 signals present); HRMS found MNa^+, 174.0521. $C_8H_9NO_2Na$ requires 174.0525.

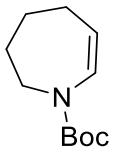
Benzyl 2,3-dihydro-1H-pyrrole-1-carboxylate 68



68

Compound **68** was synthesised using general method A using Cbz protected amine **60** (3 g, 14.6 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.84 mmol), toluene (20 mL) and NH_4Cl (161 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield slightly impure enecarbamate **68** as a 55:45 mixture of rotamers (252 mg, ~8%) as a colourless oil, R_f 0.41 (80:20 hexane−Et_2O); ν_{max}/cm^{-1} 2954, 1698 (C=O), 1415, 1337, 1122, 1088, 754 and 695; δ_H (500 MHz, $CDCl_3$) 7.40–7.33 (5H, m, Ph), 6.63 (0.45H, br m, 2-H), 6.54 (0.55H, br m, 2-H), 5.17 (2H, s , CH_2 Cbz), 5.09 (0.45H, br s, 3-H), 5.04 (0.55H, br s, 3-H), 3.83–3.74 (2H, br m, 5-H_2), 2.72–2.58 (2H, br m, 4-H_2); δ_C (125 MHz, $CDCl_3$) 153.0 (Cbz C=O), 152.3 (Cbz C=O), 136.8 (*ipso*-Ph), 136.7 (*ipso*-Ph), 129.9 (C-2), 129.2 (C-2), 128.7 (Ph), 128.6 (Ph), 128.21 (Ph), 128.16 (Ph), 128.1 (Ph), 128.0 (Ph), 108.9 (C-3), 108.8 (C-3), 67.2 (CH_2 Cbz), 67.0 (CH_2 Cbz), 45.4 (C-5), 45.2 (C-5), 29.9 (C-4), 28.8 (C-4); HRMS found MNa^+, 226.0830. $C_{12}H_{13}NO_2Na$ requires 226.0838. Spectroscopic data are consistent with those reported in the literature.[41]

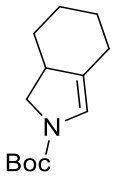
***tert*-Butyl 2,3,4,5-tetrahydro-1H-azepine-1-carboxylate 54**



54

Compound **54** was synthesised using general method A using Boc protected amine **61** (3.00 g, 15.1 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.42 mmol), toluene (20 mL) and NH_4Cl (161 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the enecarbamate **54** as an undetermined mixture of rotamers (2.05 g, 69%) as a colourless oil, R_f 0.69 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2976, 2930, 2863, 1698 (C=O), 1650, 1365, 1217, 1115, 1073, 1012, 858, 768 and 721; δ_H (400 MHz, $CDCl_3$) 6.60–6.37 (1H, m, 2-H), 5.07–4.86 (1H, m, 3-H), 3.69–3.58 (2H, m, 7-H_2), 2.17 (2H, app. ddd, *J* 11.6, 5.4, 1.5, 4-H_2), 1.82–1.63 (4H, m, 5-H_2, 6-H_2), 1.48 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 152.1 (Boc C=O), 130.8 (C-2), 114.2 (C-3), 80.4 (Boc *C*Me_3), 47.1 (C-7), 47.0 (C-7), 28.5 (Boc C*Me*$_3$), 28.2 (6), 26.4 (C-4), 25.4 (5) (10 out of 18 signals present); HRMS found MNa^+, 220.1304. $C_{11}H_{19}NO_2Na$ requires 220.1308. Spectroscopic data are consistent with those reported in the literature.[54]

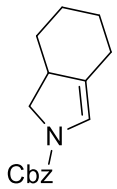
***tert*-Butyl 1,4,5,6,7,7a-hexahydro-2H-isoindole-2-carboxylate 70**



70

Compound **70** was synthesised using general method A using Boc protected amine **63** (2.00 g, 8.88 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (166 mg, 0.56 mmol), toluene (20 mL) and NH_4Cl (95.0 mg, 20 mol%). Reflux was carried out for 1 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield *enecarbamate* **70** as a 60:40 mixture of rotamers (1.45 g, 70%) as a pale yellow oil, R_f 0.68 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2858, 1687 (C=O), 1385, 1365, 1164, 1109, 892 and 773; δ_H (500 MHz, $CDCl_3$) 6.24 (0.4H, br s, 2-H), 6.12 (0.6H, br s, 2-H), 3.90 (0.6H, app. t, *J* 10.9, 9-H_A), 3.84 (0.4H, app. t, *J* 11.3, 9-H_A), 3.24 (0.6H, dd, *J* 11.4, 7.1, 9-H_B), 3.19 (0.4H, dd, *J* 11.3, 7.2, 9-H_B), 2.79–2.66 (1H, br m, 8-H), 2.38 (1H, app. t, *J* 15.3, 4-H_A), 2.00–1.87 (2H, m, 4-H_B, 7-H_A), 1.84–1.72 (2H, m, 5-H_A, 6-H_A), 1.46 (9H, s, Boc CMe_3), 1.31 (1H, app. qt, *J* 13.1, 3.0, 6-H_B), 1.22 (1H, app. qt, *J* 12.8, 3.2, 5-H_B), 1.16 (1H, app. dq, *J* 12.5, 3.1, 7-H_B); δ_C (125 MHz, $CDCl_3$) 152.3 (Boc C=O), 151.7 (Boc C=O), 125.5 (C-3), 125.4 (C-3), 120.5 (C-2), 120.4 (C-2), 79.8 (Boc *C*Me_3), 79.6 (Boc *C*Me_3), 52.2 (C-9), 51.7 (C-9), 43.3 (C-8), 42.2 (C-8), 34.6 (C-7), 28.6 (Boc C*Me*$_3$), 27.6 (C-5), 25.8 (C-4), 25.5 (C-6) (17 out of 22 signals present); HRMS found MNa^+, 246.1464. $C_{13}H_{21}NO_2Na$ requires 246.1465.

Benzyl 1,4,5,6,7,7a-hexahydro-2H-isoindole-2-carboxylate 71

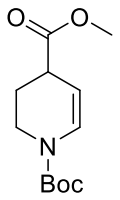


71

Compound **71** was synthesised using general method A using Boc protected amine **64** (2.73 g, 10.6 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (249 mg, 0.84 mmol), toluene (20 mL) and NH_4Cl (95.0 mg, 20 mol%). Reflux was carried out for 4 h. The crude product was purified by flash column chromatography

eluting with 95:5 hexane−EtOAc to yield slightly impure *enecarbamate* **71** as a 55:45 mixture of rotamers (816 mg, ~27%) as a yellow semi-solid, R_f 0.40 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2927, 2852, 1697 (C=O), 1421, 1089, 753, 734 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.35 (5H, m, Ph), 6.29 (0.45H, br s, 2-H), 6.21 (0.55H, br s, 2-H), 5.15 (2H, app. s, CH_2 Cbz), 3.97 (0.55H, app. t, *J* 10.9, 9-H_A), 3.94 (0.45H, app. t, *J* 10.8, 9-H_A), 3.34–3.28 (1H, m, 9-H_B), 2.81–2.70 (1H, br m, 8-H), 2.42 (0.45H, app. d, *J* 12.3, 4-H_A), 2.36 (0.55H, app. d, *J* 11.9, 4-H_A), 2.02–1.88 (2H, br m, 4-H_B, 7-H_A), 1.85–1.74 (2H, m, 5-H_A, 6-H_A), 1.37–1.11 (3H, br m, 5-H_B, 6-H_B, 7-H_B); δ_C (125 MHz, $CDCl_3$) 152.7 (Cbz C=O), 152.1 (Cbz C=O), 137.0 (*ipso*-Ph), 136.9 (*ipso*-Ph), 128.6 (Ph), 128.1 (Ph), 128.0 (Ph), 126.7 (C-3), 126.5 (C-3), 120.3 (C-2), 119.8 (C-2), 67.0 (CH_2 Cbz), 66.8 (CH_2 Cbz), 52.1 (C-9), 51.0 (C-9), 43.3 (C-8), 42.2 (C-8), 34.6 (C-7), 27.5 (C-5), 25.8 (C-4), 25.5 (C-6) (21 out of 28 signals present); HRMS found MNa^+, 280.1304. $C_{16}H_{19}NO_2Na$ requires 280.1309. Spectroscopic data are consistent with those reported in the literature.[42]

1-(*tert*-Butyl) 4-methyl 3,4-dihydropyridine-1,4(2H)-dicarboxylate 56

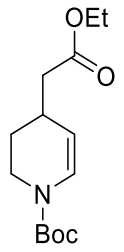


56

Compound **56** was synthesised using general method A using 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (2.00 g, 8.22 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (166 mg, 0.56 mmol), toluene (15 mL) and NH_4Cl (87.9 mg, 20 mol%). Reflux was carried out for 2 h. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield the enecarbamate **56** as a 60:40 mixture of rotamers (1.40 g, 70%) as a colourless oil, R_f 0.57 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 2976, 1735 (C=O), 1699 (C=O), 1650 (C=O), 1366, 1158, 1088, 1050 and 768; δ_H (500 MHz, $CDCl_3$) 6.98 (0.4H, d, *J* 7.7, 2-H), 6.85

(0.6H, d, *J* 8.0, 2-H), 5.01–4.94 (0.4H, br m, 3-H), 4.91–4.82 (0.6H, br m, 3-H), 3.70 (3H, s, Me), 3.67–3.51 (2H, m, 6-H_2), 3.17–3.08 (1H, br m, 4-H), 2.15–2.07 (1H, m, 5-H_A), 2.01–1.85 (1H, m, 5-H_B), 1.48 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 174.1 (C=O ester), 152.2 (Boc C=O), 127.2 (C-2), 126.9 (C-2), 101.9 (C-3), 101.5 (C-3), 81.2 (Boc *C*Me_3), 52.2 (Me), 40.5 (C-6), 39.6 (C-6), 37.6 (C-4), 37.3 (C-4), 28.4 (Boc C*Me*$_3$), 24.2 (C-5), 24.0 (C-5) (15 out of 20 signals present); HRMS found MNa^+, 264.1203. $C_{12}H_{19}NO_4Na$ requires 264.1206. Spectroscopic data are consistent with those reported in the literature.[54]

tert-Butyl 4-(2-ethoxy-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 72

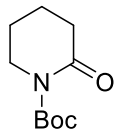


72

Compound **72** was synthesised using general method A using *tert*-butyl 4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (2.00 g, 7.36 mmol), anhydrous methanol (20 mL), tetraethylammonium tosylate (166 mg, 0.56 mmol), toluene (15 mL) and NH_4Cl (78.7 mg, 20 mol%). Reflux was carried out for 2 h. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the *enecarbamate* **72** as a 60:40 mixture of rotamers (1.18 g, 60%) as a colourless oil, R_f 0.53 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 2977, 2933, 1733 (C=O), 1699 (C=O), 1648 (C=O), 1408, 1365, 1238, 1153, 1114, 1028, 967, 862, 768 and 735; δ_H (400 MHz, $CDCl_3$) 6.86 (0.4H, d, *J* 7.9, 2-H), 6.73 (0.6H, d, *J* 8.0, 2-H), 4.77 (0.4H, d, *J* 6.2, 3-H), 4.68 (0.6H, d, *J* 6.2, 3-H), 4.15 (2H, q, *J* 7.1, ester OCH_2), 3.75–3.60 (1H, m, 6-H_A), 3.42 (1H, ddd, *J* 12.9, 9.4, 3.3, 6-H_B), 2.72–2.62 (1H, br m, 4-H), 2.39–2.21 (2H, m, ester CH_2), 2.03–1.89 (1H, m, 5-H_A), 1.56–1.50 (1H, m, 5-H_B), 1.48 (9H, s, Boc CMe_3), 1.26 (3H, t, *J* 7.1, Me); δ_C (100 MHz, $CDCl_3$) 172.4 (ester C=O), 151.5 (Boc C=O), 126.0 (C-

2), 125.7 (C-2), 108.5 (C-3), 108.0 (C-3), 80.9 (Boc *C*Me_3), 60.6 (OCH_2), 40.6 (ester CH_2), 39.9 (C-6), 29.1 (C-4), 28.5 (Boc C*Me*$_3$), 27.8 (C-5), 14.4 (Me) (14 out of 22 signals present); HRMS found MNa^+, 292.1520. $C_{14}H_{23}NO_4Na$ requires 292.1519.

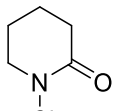
tert-Butyl 2-oxopiperidine-1-carboxylate 73[67]



73

Triethylamine (1.4 mL, 10.0 mmol), DMAP (1.22 g, 10 mmol) and Boc_2O (3.2 mL, 15.0 mmol) were added to a solution of δ-valerolactam (1.04 g, 10.0 mmol) in DCM (10 mL) at room temperature and the resulting mixture was stirred for 3.5 h at room temperature. The solvent was then evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 50:50 hexane−EtOAc to yield the piperidone **73** (964 mg, 46%) as a yellow semi-solid, R_f 0.27 (75:25 Et_2O−hexane); ν_{max}/cm^{-1} 2977, 1768, 1708 (C=O), 1288, 1246, 1136, 1091, 1057, 852 and 775; δ_H (400 MHz, $CDCl_3$) 3.64 (2H, ddd, *J* 6.3, 4.4, 1.4, 6-H_2), 2.55–2.41 (2H, m, 3-H_2), 1.87–1.74 (4H, m, 5-H_2, 4-H_2), 1.52 (9H, s, Boc CMe_3); δ_C (100 MHz, $CDCl_3$) 171.4 (lactam C=O), 152.9 (Boc C=O), 82.9 (Boc *C*Me_3), 46.4 (C-6), 35.0 (C-3), 28.2 (Boc C*Me*$_3$), 22.9 (C-4), 20.6 (C-5); HRMS found MNa^+, 220.1095. $C_{10}H_{18}NO_3$ requires 220.1100. Spectroscopic data are consistent with those reported in the literature.[67]

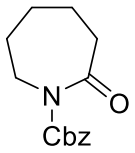
Benzyl 2-oxopiperidine-1-carboxylate 74[68]



74

A solution of *n*-BuLi (18.9 mL of a 1.6 M solution in hexanes, 30.3 mmol) was added dropwise to a solution of δ-valerolactam (2.00 g, 30.3 mmol) in THF (128 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and a solution of benzyl chloroformate (4.3 mL, 30.3 mmol) in THF (30 mL) was then added dropwise at –78 °C and the resulting mixture was stirred for 4 h. Sat. $NH_4Cl_{(aq)}$ (40 mL) was then added and the resulting mixture allowed to warm to room temperature and then diluted with Et_2O (100 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The organic layers were combined and washed with brine (100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 2:1 → 1:1 hexane−EtOAc) to yield the piperidone **74** (5.66 g, 80%) as a colourless oil, R_f 0.25 (6:4 hexane−EtOAc); ν_{max}/cm^{-1} 3033, 2951, 1771, 1709 (C=O), 1280, 1246, 1143, 1056, 738 and 698; δ_H (400 MHz, $CDCl_3$) 7.46–7.41 (2H, m, Ph), 7.40–7.28 (3H, m, Ph), 5.29 (2H, s, Cbz CH_2), 3.77–3.70 (2H, m, 6-H_2), 2.57–2.50 (2H, m, 3-H_2), 1.88–1.78 (4H, m, 5-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 171.3 (lactam C=O), 154.3 (Cbz C=O), 135.6 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 68.6 (Cbz CH_2), 46.7 (C-6), 35.0 (C-3), 22.8 (C-4), 20.6 (C-5); HRMS found MNa^+, 256.0946. $C_{13}H_{15}NO_3Na$ requires 256.0944. Spectroscopic data are consistent with those reported in the literature.[68]

Benzyl 2-oxoazepane-1-carboxylate 75



75

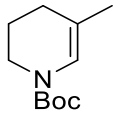
Method A:

Compound **75** was prepared by a variation on the method of Curti *et al*.[69] A solution of *n*-BuLi (21.5 mL of a 1.6 M solution in hexanes, 34.4 mmol) was added dropwise to a solution of caprolactam (3.00 g, 26.5 mmol) in THF (80 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and benzyl chloroformate (5.0 mL, 35.1 mmol) was then added dropwise at –78 °C and the resulting mixture was stirred for 1 h and then allowed to warm to rt. Sat. $NH_4Cl_{(aq)}$ (40 mL) was then added and then diluted with EtOAc (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with brine (3 × 50 mL), sat. $NaHCO_{3(aq)}$ (3 × 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 9:1 → 8:2 hexane−EtOAc) to yield the piperidone **75** (4.65 g, 71%) as a colourless oil, R_f 0.39 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 2931, 2858, 1769, 1704 (C=O), 1377, 1261, 1161, 735 and 696; δ_H (400 MHz, $CDCl_3$) 7.45–7.41 (2H, m, Ph), 7.39–7.28 (3H, m, Ph), 5.28 (2H, s, Cbz CH_2), 3.89–3.80 (2H, m, 7-H_2), 2.72–2.63 (2H, m, 3-H_2), 1.82–1.69 (6H, m, 4-H_2, 5-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 175.7 (lactam C=O), 154.4 (Cbz C=O), 135.7 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.0 (Ph), 68.7 (Cbz CH_2), 46.5 (C-7), 39.6 (C-3), 29.3 (C-4), 28.8 (C-6), 23.6 (C-5); HRMS found MNa^+, 270.1112. $C_{14}H_{17}NO_3Na$ requires 270.1101. Spectroscopic data are consistent with those reported in the literature.[170]

Method B:

Compound **75** was prepared by a variation on the method of Arizpe *et al*.[70] A solution of LHMDS (7.6 mL of a 1 M solution in hexanes, 7.6 mmol) was added dropwise to a solution of caprolactam (1.00 g, 7.62 mmol) in THF (30 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and benzyl chloroformate (1.1 mL, 7.62 mmol) was then added dropwise at –78 °C and the resulting mixture was slowly warmed to –40 °C and stirred for 3 h. Sat. $NH_4Cl_{(aq)}$ (30 mL) was then added and the resulting mixture allowed to warm to room temperature and then diluted with DCM (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 9:1 → 8:2 hexane−EtOAc) to yield the piperidone **75** (1.74 g, 92%) as a colourless oil.

tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 77[55,56]

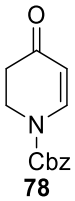


77

To a stirred solution of DIPA (1.5 mL, 11.0 mmol) in Et_2O (20 mL) was added *n*-BuLi (6.9 mL of a 1.6 M solution in hexanes, 11.0 mmol) dropwise at 0 °C to 5 °C under N_2. The solution was stirred for 15 min and then cooled to –78 °C whereupon addition of lactam **73** (2.00 g, 10.0 mmol) in Et_2O (20 mL) was performed by syringe addition. The solution was stirred at –78 °C for 1 h before iodomethane (0.93 mL, 15.0 mmol) was added dropwise at –50 °C. The solution was then slowly warmed to –20 °C and stirred for 30 min. Sat. $NH_4Cl_{(aq)}$ (20 mL) was then added and the layers separated. The aqueous layer was then extracted with Et_2O (3 × 20 mL), and the organics washed with sat. $NH_4Cl_{(aq)}$ (2 × 20 mL), dried ($MgSO_4$) and the solvent then evaporated under reduced pressure to give the crude product. The crude product was purified by flash

column chromatography eluting with 9:1 hexane−EtOAc to yield impure *lactam* (562 mg) as a yellow oil. Super-Hydride® (2.7 mL of a 1 M solution in THF, 2.67 mmol) was added dropwise to a solution of the lactam (541 mg, 2.54 mmol) in toluene (9.4 mL) at –78 °C and the mixture stirred for 30 min at –78 °C. Then, DIPEA (2.5 mL, 14.5 mmol), DMAP (6.2 mg, 2 mol%) and TFAA (0.42 mL, 3.05 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (10 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The organic layers were combined and washed with water (2 × 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield the enecarbamate **77** as a 60:40 mixture of rotamers (297 mg, 15% over two steps) as a yellow oil, R_f 0.46 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2975, 2928, 2877, 1695 (C=O), 1674 (C=O), 1452, 1393, 1253, 1154, 1110, 981 and 764; δ_H (500 MHz, $CDCl_3$) 6.59 (0.4H, br s, 2-H), 6.43 (0.6H, br s, 2-H), 3.46–3.34 (2H, m, 6-H_2), 1.91–1.84 (2H, m, 4-H_2), 1.77–1.69 (2H, br m, 5-H_2), 1.60 (3H, br s, Me), 1.41 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 152.9 (Boc C=O), 152.5 (Boc C=O), 120.5 (C-2), 120.2 (C-2), 114.7 (C-3), 114.2 (C-3), 80.4 (Boc *C*Me_3), 80.2 (Boc *C*Me_3), 42.1 (C-6), 41.0 (C-6), 28.5 (Boc C*Me*$_3$), 27.2 (C-4), 26.9 (C-4), 22.1 (C-5), 21.0 (C-5), 21.14 (Me), 21.09 (Me) (17 out of 18 signals present); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[56]

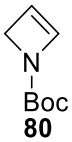
Benzyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate 78[71]



78

$NaBH_4$ (416 mg, 11 mmol) was added to a solution of 4-methoxypyridine (0.55 mL, 10 mmol) in MeOH (20 mL) at –78 °C and stirred for 15 min. Then, a solution of CbzCl (0.86 mL, 12 mmol) in diethyl ether (2 mL) was added dropwise over 30 min and then stirred at –78 °C for 1 h. Then, water (20 mL) was added and the mixture allowed to warm to rt. The two layers were then separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 80:20 hexane−Et_2O to yield the slightly impure enecarbamate **78** as a 55:45 mixture of rotamers (208 mg, ~9%) as a colourless oil, R_f 0.37 (1:1 hexane−Et_2O); ν_{max}/cm^{-1} 2942, 1705 (C=O), 1649 (C=O), 1338, 1213, 1104, 1048, 731 and 696; δ_H (500 MHz, $CDCl_3$) 7.38–7.36 (5H, m, Ph), 7.03 (0.45H, d, *J* 8.7, 2-H), 6.93 (0.55H, d, *J* 8.7, 2-H), 5.20 (2H, s, CH_2 Cbz), 5.03 (0.45H, d, *J* 8.7, 3-H), 4.92 (0.55H, d, *J* 8.7, 3-H), 3.75–3.68 (2H, m, 6-H_2), 1.98–1.89 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 198.8 (C=O), 153.6 (Cbz C=O), 153.0 (Cbz C=O), 137.0 (*ipso*-Ph), 136.1 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 128.1 (Ph), 128.0 (Ph), 127.5 (C-2), 127.1 (C-2), 106.0 (C-3), 105.5 (C-3), 68.1 (Cbz CH_2), 68.0 (Cbz CH_2), 40.23 (C-6), 40.17 (C-6), 30.9 (C-5) (20 out of 22 signals present); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[71]

tert-Butyl azete-1(2H)-carboxylate 80[72]

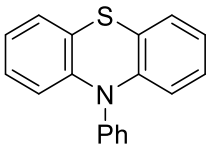


80

A solution of *t*-BuOK (686 mg, 6.11 mmol) in *t*-BuOH (20 mL) was added dropwise to a solution of tert-butyl 3-(tosyloxy)azetidine-1-carboxylate (2 g, 6.11 mmol), in *t*-BuOH (10 mL) and stirred at 80 °C for 16 h. The mixture was allowed to cool to rt and then, water (20 mL) was added. The aqueous layer was extracted with hexane (3 ×

20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 75:25 hexane−Et_2O to yield the enecarbamate **80** (404 mg, 41%) as a colourless oil, R_f 0.54 (1:1 hexane−Et_2O); ν_{max}/cm^{-1} 2978, 1700 (C=O), 1391, 1366, 1147 and 763; δ_H (500 MHz, $CDCl_3$) 6.56 (1H, app. s, 2-H), 5.53–5.52 (1H, br m, 3-H), 4.39 (2H, app. s, 4-H_2), 1.47 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 152.0 (Boc C=O), 138.8 (C-2), 111.9 (C-3), 80.3 (Boc *C*Me_3), 58.4 (C-4), 28.5 (Boc C*Me*$_3$); HRMS found $2MNa^+$, 333.1784. $C_{16}H_{26}N_2O_4Na$ requires 333.1785. Spectroscopic data are consistent with those reported in the literature.[72]

10-Phenyl-10H-phenothiazine (PTH) 84[171]



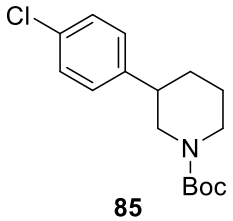
84

Method A:

To a 7 mL vial were added phenothiazine (500 mg, 2.50 mmol), NaO*t*-Bu (335 mg, 3.49 mmol), RuPhos (20 mg, 1.7 mol%) and RuPhos precatalyst (35 mg, 1.7 mol%). Then, 1,4-dioxane (2.5 mL) and chlorobenzene (356 µL, 3.53 mmol) were added under N_2 and the resulting mixture was heated at 110 °C for 16 h. The mixture was allowed to cool to room temperature and diluted with DCM (50 mL), washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to give PTH **84** (674 mg, 98%) as a white solid, R_f 0.54 (80:20 hexane−EtOAc); m.p. 91–92 °C, lit. 90–92 °C;[172] ν_{max}/cm^{-1} 3058, 3034, 2919, 2849, 1584, 1489, 1458, 1440, 1298, 1236, 740, 692 and 616; δ_H (500 MHz, $CDCl_3$) 7.60 (2H, t, *J* 7.7, Ph), 7.48 (1H, tt, *J* 7.5 and 1.2, Ph), 7.40

(2H, dd, *J* 7.7 and 1.3, Ph), 7.02 (2H, dd, *J* 7.3 and 1.9, Ar), 6.85 (2H, td, *J* 7.8 and 1.7, Ar), 6.81 (2H, td, *J* 7.3 and 1.5, Ar), 6.20 (2H, dd, *J* 8.0 and 1.4, Ar); δ_C (125 MHz, $CDCl_3$) 144.4 (*ipso*-Ar), 141.2 (*ipso*-Ph), 131.0 (Ph), 130.9 (Ph), 128.3 (Ph), 127.0 (Ar), 126.9 (Ar), 122.6 (Ar), 120.3 (*ipso*-Ar), 116.2 (Ar); HRMS found MK^+, 314.0604. $C_{18}H_{13}NSK$ requires 314.0401. Spectroscopic data are consistent with those reported in the literature.[171]

***tert*-Butyl 3-(4-chlorophenyl)piperidine-1-carboxylate 85**[73]

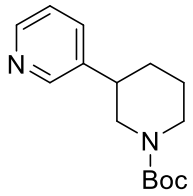


85

A 7 mL vial was charged with PTH (3 mg, 5 mol%), sodium formate (45 mg, 0.66 mmol), 1-chloro-4-iodobenzene (51 mg, 0.22 mmol) and enecarbamate **65** (100 mg, 0.55 mmol). Then, cyclohexanethiol (1.3 µL, 5 mol%) and a degassed solution of DMSO:water (20:1 v/v, 2.20 mL) were added under N_2. The resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, sat. $NaHCO_{3(aq)}$ (5 mL) was added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 95:50 → 90:10 hexane−EtOAc) to yield the β-arylated carbamate **85** as a mixture of rotamers (17 mg, 25%) as a colourless oil, R_f 0.31 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2975, 2932, 2856, 1686 (C=O), 1416, 1365, 1252, 1168, 1148, 1136, 1091, 822 and 523; δ_H (500 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.3, Ph), 7.18–7.14 (2H, m, Ph), 4.13 (2H, br s, 2-H_A, 6-H_A), 2.94–2.48 (3H, m, 3-H, 2-H_B, 6-H_B), 2.05–1.96 (1H, m, 4-H_A or 5-H_A), 1.79–1.70 (1H, m, 4-H_A or 5-H_A), 1.58–1.54 (2H, m, 4-H_B, 5-H_B), 1.46 (9H, s, Boc CMe_3); δ_C (125 MHz, $CDCl_3$) 155.0 (C=O), 142.1 (*ipso*-Ph), 132.4 (*ipso*-Ph), 128.8 (Ph), 128.6 (Ph), 79.7 (Boc *C*Me_3), 50.7 (C-2 or C-6), 44.4

(C-2 or C-6), 42.1 (C-3), 31.9 (C-4 or C-5), 28.6 (Boc C*Me*$_3$), 25.5 (C-4 or C-5); HRMS found MNa$^+$, 318.1228. $C_{16}H_{22}{}^{35}ClNO_2Na$ requires 318.1231. Spectroscopic data are consistent with those reported in the literature.[73]

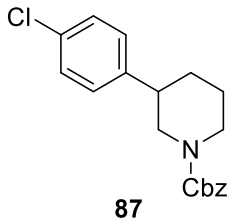
tert-Butyl 3-(pyridin-3-yl)piperidine-1-carboxylate 86[73]



86

A 7 mL vial was charged with PTH (3 mg, 5 mol%), sodium formate (45 mg, 0.66 mmol), 1-iodopyridine (45 mg, 0.22 mmol) and enecarbamate **65** (100 mg, 0.55 mmol). Then, cyclohexanethiol (1.3 μL, 5 mol%) and a degassed solution of DMSO:water (20:1 v/v, 2.20 mL) were added under N_2. The resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, sat. $NaHCO_{3(aq)}$ (5 mL) was added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 95:50 → 50:50 hexane−EtOAc) to yield the β-arylated carbamate **86** as a mixture of rotamers (12 mg, 21%) as a colourless oil, R_f 0.28 (EtOAc); ν_{max}/cm^{-1} 2975, 2931, 2857, 1685 (C=O), 1419, 1365, 1257, 1167, 1147 and 715; δ_H (500 MHz, $CDCl_3$) 8.57–8.40 (2H, m, Ar), 7.53 (1H, dt, *J* 7.9, 2.0, Ar), 7.24 (1H, dd, *J* 7.9, 4.8, Ar), 4.36–3.97 (2H, m, 2-H$_A$, 6-H$_A$), 2.92–2.60 (3H, m, 2-H$_B$, 6-H$_B$, 3-H), 2.09–1.96 (1H, m, 4-H$_A$), 1.80–1.74 (1H, m, 5-H$_A$), 1.69–1.56 (2H, m, 4-H$_B$, 5-H$_B$), 1.47 (9H, s, Boc CMe$_3$); δ_C (125 MHz, $CDCl_3$) 154.9 (C=O), 149.2 (*ipso*-Ar), 148.3 (Ar), 138.9 (*ipso*-Ar), 134.6 (Ar), 123.6 (Ar), 79.9 (Boc *C*Me$_3$), 50.2 (C-2 or C-6), 44.1 (C-2 or C-6), 40.2 (C-3), 31.6 (C-4 or C-5), 28.6 (Boc C*Me*$_3$), 25.4 (C-4 or C-5); HRMS found MH$^+$, 263.1754. $C_{15}H_{23}N_2O_2$ requires 263.1756. Spectroscopic data are consistent with those reported in the literature.[74]

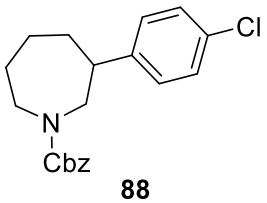
Benzyl 3-(4-chlorophenyl)piperidine-1-carboxylate 87



87

Compound **87** was prepared by a variation on the method of Boyington *et al*.[73] A 7 mL vial was charged with PTH (1.7 mg, 5 mol%), sodium formate (25 mg, 0.37 mmol), 1-chloro-4-iodobenzene (29 mg, 0.12 mmol) and enecarbamate **66** (67 mg, 0.31 mmol). Then, cyclohexanethiol (0.7 μL, 5 mol%) and a degassed solution of DMSO:water (20:1 v/v, 1.18 mL) were added under N_2. The resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, sat. $NaHCO_{3(aq)}$ (5 mL) was added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 95:50 → 90:10 hexane−EtOAc) to yield the *β-arylated-carbamate* **87** as a mixture of rotamers (7.5 mg, 25%) as a colourless oil, R_f 0.29 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 3032, 2933, 2855, 1693 (C=O), 1493, 1427, 1252, 1233, 1200, 1134, 1091, 825, 735 and 525; δ_H (400 MHz, $CDCl_3$) 7.45–7.29 (5H, m, Ar), 7.29–7.26 (2H, m, Ar), 7.14 (2H, br d, *J* 8.0, Ar), 5.22–5.05 (2H, s, Cbz CH_2), 4.41–4.10 (2H, m, 2-H_A, 6-H_A), 2.91–2.57 (3H, m, 3-H, 2-H_B, 6-H_B), 2.09–1.94 (1H, m, 4-H_A), 1.84–1.71 (1H, m, 5-H_A), 1.67–1.57 (2H, m, 4-H_B, 5-H_B); δ_C (100 MHz, $CDCl_3$) 155.4 (C=O), 141.8 (*ipso*-Ph), 140.0 (*ipso*-Ph), 132.5 (*ipso*-Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 67.3 (Cbz CH_2), 50.7 (C-2 or C-6), 44.5 (C-2 or C-6), 42.3 (C-3), 31.8 (C-4), 29.9 (C-5); HRMS found MNa^+, 352.1069. $C_{19}H_{20}{}^{35}ClNO_2Na$ requires 352.1075.

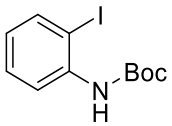
Benzyl 3-(4-chlorophenyl)azepane-1-carboxylate 88



88

Compound **88** was prepared by a variation on the method of Boyington *et al*.[73] A 7 mL vial was charged with PTH (6.8 mg, 5 mol%), sodium formate (102 mg, 1.50 mmol), 1-chloro-4-iodobenzene (119 mg, 0.50 mmol) and enecarbamate **69** (289 mg, 1.25 mmol). Then, cyclohexanethiol (2.9 µL, 5 mol%) and a degassed solution of DMSO:water (20:1 v/v, 4.8 mL) were added under N_2. The resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, sat. $NaHCO_{3(aq)}$ (5 mL) was added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 95:5 → 9:1 hexane−EtOAc) to yield the *β-arylated carbamate* **88** as a 1:1 mixture of rotamers (22.5 mg, 13%) as a colourless oil, R_f 0.34 (80:20 hexane–EtOAc); ν_{max}/cm^{-1} 2927, 2856, 1691 (C=O), 1420, 1272, 1212, 1176, 733 and 697; δ_H (400 MHz, d_6-acetone) 7.50–7.15 (9H, m, Ar), 5.25–5.03 (2H, m, Cbz CH_2), 3.91–3.69 (2H, m, 2-H_A, 7-H_A), 3.39 (0.5H, app. dt, *J* 14.0, 5.8, 7-H_B), 3.27 (0.5H, app. dt, *J* 14.0, 5.8, 7-H_B), 3.22 (0.5H, d, *J* 11.0, 2-H_B), 3.18 (0.5H, d, *J* 11.0, 2-H_B), 2.98–2.83 (1H, m, 3-H), 2.00–1.84 (3H, m, 4-H_A, 5-H_A, 6-H_A), 1.80–1.63 (2H, m, 4-H_B, 6-H_B), 1.49–1.36 (1H, m, 5-H_B); δ_C (100 MHz, d_6-acetone) 156.6 (C=O), 156.5 (C=O), 144.8 (*ipso*-Ar), 144.6 (*ipso*-Ar), 132.3 (*ipso*-Ar), 129.8 (Ar), 129.7 (Ar), 129.29 (Ar), 129.26 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 67.3 (CH_2 Cbz), 67.2 (CH_2 Cbz), 54.1 (C-2), 53.3 (C-2), 47.4 (C-3 or C-7), 47.2 (C-3 or C-7), 47.1 (C-3 or C-7), 46.8 (C-3 or C-7), 35.6 (C-4), 36.1 (C-4), 28.5 (C-6), 27.2 (C-6), 26.5 (C-5), 26.1 (C-5) (26 of 32 signals present); HRMS found MNa^+, 366.1225. $C_{20}H_{22}{}^{35}ClNO_2Na$ requires 366.1231.

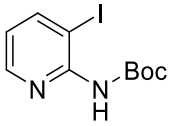
***tert*-Butyl (2-iodophenyl)carbamate 89**[75]



89

A solution of LHMDS (2 mL, 1N in THF, 2 mmol) was added dropwise to a solution of 2-iodoaniline (219 mg, 1 mmol) in THF (2 mL) at –78 °C under N_2. The mixture was allowed to warm to rt over 30 min and cooled to –78 °C. A solution of Boc_2O (0.25 mL, 1.1 mmol) in THF (2 mL) was then added dropwise and the mixture stirred at –78 °C for 1 h. Sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the resultant mixture warmed to rt. The mixture was extracted with EtOAc (100 mL), washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: 98:2 → 80:20 hexane−EtOAc to yield aniline **89** (196 mg, 61%) as a yellow oil, R_f 0.65 (80:20 hexane−EtOAc); ν_{max}/cm^{-1} 2926, 2855, 1960 (C=O), 1453, 1257, 1114 and 696; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, dd, *J* 8.3, 1.2, Ar), 7.74 (1H, dd, *J* 7.9, 1.5, Ar), 7.31 (1H, td, *J* 8.4, 1.4, Ar), 6.76 (1H, td, *J* 7.9, 1.6, Ar), 6.82 (1H, br s, *N*H), 1.53 (9H, s, *t*-Bu); δ_C (100 MHz, $CDCl_3$) 152.7 (C=O), 139.0 (Ar), 129.3 (Ar), 124.8 (Ar), 120.3 (Ar), 81.2 (*C*Me_3), 28.5 (C*Me*$_3$) (7 out of 9 signals present); HRMS found MNa^+, 341.9955. $C_{11}H_{14}INO_2Na$ requires 341.9961. Spectroscopic data are consistent with those reported in the literature.[75]

***tert*-Butyl (3-iodopyridin-2-yl)carbamate 90**

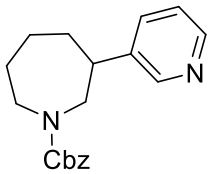


90

Compound **90** was prepared by a variation on the method of Guthrie *et al*.[75] A solution of LHMDS (1 mL, 1N in THF, 1 mmol) was added dropwise to a solution of 3-iodo-3-aminopyridine (110 mg, 0.5 mmol) in THF (1 mL) at –78 °C under N_2. The

mixture was allowed to warm to rt over 30 min and cooled to –78 °C. A solution of Boc_2O (0.13 mL, 0.55 mmol) in THF (1 mL) was then added dropwise and the mixture stirred at –78 °C for 1 h. Sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the resultant mixture warmed to rt. The mixture was extracted with EtOAc (100 mL), washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *aminopyridine* **90** (87 mg, 54%) as a white, amorphous solid, R_f 0.30 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 3182, 2975, 2928, 1720 (C=O), 1493, 1433, 1250, 1147, 1014 and 789; δ_H (400 MHz, $CDCl_3$) 8.42 (1H, dd, *J* 4.7, 1.6, Ar), 8.05 (1H, dd, *J* 7.8, 1.7, Ar), 7.16 (1H, br s, *N*H), 6.75 (1H, dd, *J* 7.8, 4.7, Ar), 1.55 (9H, s, *t*-Bu); δ_C (100 MHz, $CDCl_3$) 148.4 (Ar), 147.9 (Ar), 120.4 (Ar), 81.7 (*C*Me_3), 28.4 (C*Me*$_3$) (5 out of 8 signals present); HRMS found MNa^+, 342.9905. $C_{10}H_{13}IN_2O_2Na$ requires 342.9914.

Benzyl 3-(pyridin-3-yl)azepane-1-carboxylate 91

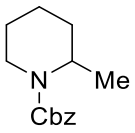


91

Compound **91** was prepared by a variation on the method of Boyington *et al*.[73] A 7 mL vial was charged with PTH (3 mg, 5 mol%), sodium formate (26 mg, 0.38 mmol), 3-iodopyridine (51 mg, 0.25 mmol) and enecarbamate **69** (146 mg, 0.63 mmol). Then, cyclohexanethiol (1.6 µL, 5 mol%) and a degassed solution of DMSO:water (20:1 v/v, 2.50 mL) were added under N_2. The resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, sat. $NaHCO_{3(aq)}$ (5 mL) was added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution:

9:1 → 1:1 hexane−EtOAc) to yield the *β-arylated carbamate* **91** as a 1:1 mixture of rotamers (18 mg, 23%) as a colourless oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 3032, 2927, 2858, 1692 (C=O), 1421, 1214, 1108 and 699; δ_H (500 MHz, $CDCl_3$) 8.53–8.38 (2H, m, Ar), 7.57 (0.5H, dd, *J* 7.9, Ar), 7.44–7.28 (5.5H, m, Ar), 7.23 (0.5H, dd, *J* 7.7, 4.9, Ar), 7.18 (0.5H, dd, *J* 7.7, 4.8, Ar), 5.23–5.11 (2H, m, Cbz CH_2), 3.97 (0.5H, dd, *J* 13.8, 4.2, 2-H_A), 3.92–3.82 (1H, m, 2-H_A, 7-H_A), 3.75 (0.5H, ddd, *J* 13.9, 8.0, 5.6, 7-H_A), 3.35 (0.5H, dt, *J* 14.1, 5.8, 7-H_B), 3.29 (0.5H, dt, *J* 13.8, 5.5, 7-H_B), 3.14 (0.5H, dd, *J* 10.4, 7.6, 2-H_B), 3.09 (0.5H, dd, *J* 10.8, 7.5, 2-H_B), 3.02–2.94 (0.5H, m, 3-H), 2.86 (0.5H, tt, *J* 11.0, 3.6, 3-H), 2.01–1.90 (2H, m, 4-H_A), 1.79–1.62 (3H, m, 5-H_A, 6-H_2), 1.53–1.43 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.4 (C=O), 156.2 (C=O), 149.01 (Ar), 148.98 (Ar), 139.9 (*ipso*-Ar), 139.8 (*ipso*-Ar), 137.0 (*ipso*-Ar), 136.9 (*ipso*-Ar), 134.9 (Ar), 134.5 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.10 (Ar), 128.05 (Ar), 127.91 (Ar), 127.85 (Ar), 67.3 (CH_2 Cbz), 67.2 (CH_2 Cbz), 53.6 (C-2), 52.7 (C-2), 47.0 (C-7), 46.8 (C-7), 44.7 (C-3), 44.1 (C-3), 35.3 (C-4), 34.7 (C-4), 28.1 (C-6), 27.8 (C-6), 25.9 (C-5), 25.5 (C-5) (33 of 34 signals present); HRMS found MH^+, 311.1747. $C_{19}H_{23}N_2O_2$ requires 311.1754.

Benzyl 2-methylpiperidine-1-carboxylate 108

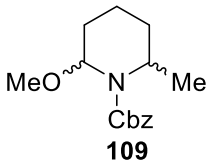


108

Compound **108** was prepared by a variation on the method of Babich *et al*.[59] Benzyl chloroformate (6 mL, 42.5 mmol) was slowly added to a mixture of 2-methylpiperidine (4.7 mL, 40.0 mmol) and triethylamine (8.4 mL, 60.0 mmol) in DCM (60 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 64 h at room temperature, and then 1 M $HCl_{(aq)}$ was added (40 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined and washed with water (50 mL), sat.

$NaHCO_{3(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give carbamate **108** as a 60:40 mixture of rotamers (8.82 g, 95%) as an orange oil, R_f 0.50 (60:40 hexane–EtOAc); ν_{max}/cm^{-1} 2935, 2860, 1688 (C=O), 1416, 1334, 1257, 1181, 1142, 1061, 909 and 893; δ_H (400 MHz, $CDCl_3$) 7.42–7.19 (5H, m, Ph), 5.13 (0.75H, s, Cbz CH_2), 5.13 (1.25H, s, Cbz CH_2), 4.47 (1H, m, 2-H), 4.01 (1H, m, 6-H_A), 2.90 (1H, dt, *J* 13.2 and 2.9, 6-H_B), 1.72–1.32 (6H, m, 3-H_2, 4-H_2, 5-H_2), 1.16 (3H, d, *J* 7.0, Me); δ_C (100 MHz, $CDCl_3$) 155.5 (C=O), 137.3 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.9 (Ph), 66.9 (Cbz CH_2), 46.3 (C-2), 39.1 (C-6), 30.2 (C-3), 25.8 (C-5), 18.7 (C-4), 16.0 (Me); HRMS found MNa^+, 256.1309. $C_{14}H_{19}NO_2Na$ requires 256.1308. Spectroscopic data are consistent with those reported in the literature.[173]

Benzyl 2-methoxy-6-methylpiperidine-1-carboxylate 109

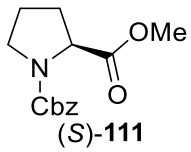


109

Compound **109** was prepared by a variation on the method of Trindade *et al*.[41] An Electrasyn vial (10 mL) with a stir bar was charged with Cbz protected amine **108** (1.03 g, 4.41 mmol), in anhydrous methanol (10 mL) containing tetraethylammonium tosylate (83 mg, 0.28 mmol) was electrolysed with graphite electrodes under a constant current of 65 mA at 25 °C. After the passage of 2.5 $Fmol^{-1}$ of electricity, the mixture was concentrated *in vacuo*. The residue was taken up in anhydrous DCM (20 mL) and H_2O (20 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (20 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give impure hemiaminal **109** as an undetermined mixture of diastereomers and rotamers (1.13 g, 98%) as a brown oil which was unstable to flash

column chromatography, ν_{max}/cm^{-1} 2942, 2828, 1695 (C=O), 1409, 1305, 1092, 1060, 1030, 736 and 697; δ_H (500 MHz, $CDCl_3$) for **109** 7.43–7.27 (5H, m, Ph), 5.60–5.28 (1H, m, H-6), 5.27–5.01 (2H, m, Cbz CH_2), 4.51–4.25 (0.8H, m, 2-H), 4.07–3.92 (0.2H, m, 2-H), 3.32–3.11 (3H, m, OMe), 2.05–1.78 (2H, m, 4-H_A, 3-H_A), 1.74–1.47 (3H, m, 3-H_B, 5-H_2), 1.46–1.38 (1H, m, 4-H_B), 1.37–1.22 (3H, m, Me); δ_C (125 MHz, $CDCl_3$) for **109** 156.7 (C=O), 155.8 (C=O), 136.7 (*ipso*-Ph), 128.7 (Ph), 128.63 (Ph), 128.61 (Ph), 128.3 (Ph), 128.21 (Ph), 128.17 (Ph), 127.9 (Ph), 86.5 (C-6), 86.2 (C-6), 82.3 (C-6), 67.6 (Cbz CH_2), 67.3 (Cbz CH_2), 57.2 (OMe), 57.0 (OMe), 55.3 (OMe), 55.1 (OMe), 48.0 (C-2), 46.7 (C-2), 30.5 (C-5), 30.2 (C-3), 20.0 (Me), 19.3 (Me), 13.6 (C-4); HRMS found MNa^+, 286.1407. $C_{15}H_{21}NO_3Na$ requires 286.1413. Spectroscopic data are consistent with those reported in the literature.[48]

1-Benzyl 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate (*S*)-111

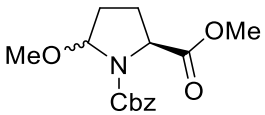


(*S*)-**111**

Compound *(S)*-**111** was prepared by a variation on the method of Babich *et al*.[59] Benzyl chloroformate (1.5 mL, 10.5 mmol) was slowly added to a mixture of L-Proline methyl ester hydrochloride (1.66 g, 10.0 mmol) and triethylamine (8.3 mL, 22.7 mmol) in DCM (20 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 64 h at room temperature, and then sat. $NH_4Cl_{(aq)}$ was added (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic layers were combined and washed with sat. $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 90:10 → 80:20 hexane−EtOAc) to yield *pyrrolidine* (*S*)-**111** as a 1:1 mixture of rotamers (1.79 g, 68%) as a yellow oil, R_f 0.29 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 2954, 2882, 1747 (C=O), 1704 (C=O), 1414,

1353, 1201, 1172, 1119, 1088 and 699; δ_H (400 MHz, $CDCl_3$) 7.40–7.26 (5H, m, Ph), 5.22–5.01 (2H, m, Cbz CH_2), 4.40 (0.5H, dd, *J* 8.6, 3.5, 2-H), 4.34 (0.5H, dd, *J* 8.6, 3.8, 2-H), 3.74 (1.5H, s, Me), 3.67–3.43 (2H, m, 5-H_2), 3.58 (1.5H, s, Me), 2.31–2.12 (1H, m, 3-H_A), 2.06–1.82 (3H, m, 3-H_B, 4-H_2); δ_C (100 MHz, $CDCl_3$) 173.4 (ester C=O), 173.3 (ester C=O), 155.0 (Cbz C=O), 154.4 (Cbz C=O), 136.84 (*ipso*-Ph), 136.75 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 67.2 (Cbz CH_2), 67.1 (Cbz CH_2), 59.3 (C-2), 59.0 (C-2), 52.4 (Me), 52.2 (Me), 47.1 (C-5), 46.6 (C-5), 31.1 (C-3), 30.1 (C-3), 24.5 (C-4), 23.7 (C-4) (23 of 24 signals present); HRMS found MNa^+, 286.1045. $C_{14}H_{17}NO_4Na$ requires 286.1050.

1-Benzyl 2-methyl (2*S*)-5-methoxypyrrolidine-1,2-dicarboxylate (*S*)-112

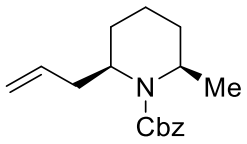


(*S*)-**112**

Compound *(S)*-**112** was prepared by a variation on the method of Trindade *et al*.[41] An Electrasyn vial (10 mL) with a stir bar was charged with Cbz protected amine (*S*)-**111** (1.05 g, 3.99 mmol), in anhydrous methanol (10 mL) containing tetraethylammonium tosylate (83 mg, 0.28 mmol) was electrolysed with graphite electrodes under a constant current of 65 mA at 25 °C. After the passage of 2.5 $Fmol^{-1}$ of electricity, the mixture was concentrated *in vacuo*. The residue was taken up in anhydrous DCM (20 mL) and H_2O (20 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (20 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−Et_2O to yield hemiaminal (*S*)-**112** as an undetermined mixture of diastereomers and rotamers (346 mg, 30%) as a colourless oil, R_f 0.61 (Et_2O); ν_{max}/cm^{-1} 2952, 2835, 1745 (C=O), 1709 (C=O), 1439, 1400, 1351, 1325, 1196, 1176, 1120, 1082, 1003, 774, 754 and 668; δ_H (500 MHz, $CDCl_3$) 7.41–

7.27 (5H, m, Ph), 5.41–4.96 (3H, m, Cbz CH_2, H-5), 4.47–4.33 (1H, m, 2-H), 3.79–3.29 (6H, m, Me, OMe), 2.52–2.27 (1H, m, 3-H_A), 2.07–1.75 (3H, m, 3-H_B, 4-H_2); δ_C (125 MHz, $CDCl_3$) 173.0 (ester C=O), 172.9 (ester C=O), 155.0 (Cbz C=O), 154.7 (Cbz C=O), 136.3 (*ipso*-Ph), 136.2 (*ipso*-Ph), 128.7 (Ph), 128.63 (Ph), 128.60 (Ph), 128.58 (Ph), 128.4 (Ph), 128.31 (Ph), 128.26 (Ph), 128.25 (Ph), 128.18 (Ph), 128.14 (Ph), 127.9 (Ph), 128.8 (Ph), 90.0 (C-5), 89.3 (C-5), 67.7 (Cbz CH_2), 67.4 (Cbz CH_2), 59.2 (C-2), 59.1 (C-2), 56.6 (OMe), 55.9 (OMe), 52.4 (Me), 52.2 (Me), 31.0 (C-5), 30.3 (C-5), 28.3 (C-3), 27.2 (C-3) (32 out of 60 signals present); HRMS found MNa^+, 316.1155. $C_{15}H_{19}NO_5Na$ requires 316.1155 and an impure mixture of hemiaminal (*S*)-**112** and starting material (*S*)-**111** as a colourless oil (559 mg). Spectroscopic data are consistent with those reported in the literature.[174]

Benzyl (2*R*,6*R*)-2-allyl-6-methylpiperidine-1-carboxylate *cis*-113

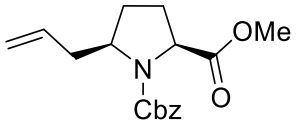


cis-**113**

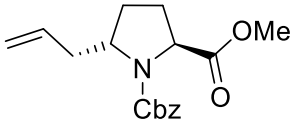
Compound *cis*-**113** was prepared by a variation on the method of David *et al*.[76] A solution of $TiCl_4$ (1.1 mL of a 1 M solution in DCM, 1.1 mmol) was added dropwise to a mixture of hemiaminal *cis*-**112** (269 mg, 1.0 mmol) and allyltrimethylsilane (0.79 mL, 5 mmol) in DCM (10 mL) at –78 °C and allowed to warm to room temperature, in the Dewar, for 16 h. Then sat. $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 20 mL). The organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product which contained a 75:25 mixture of diastereomeric products. The crude product was purified by flash column chromatography, eluting with 90:10 hexane−Et_2O to yield a single diastereomeric piperidine *cis*-**113** (112 mg, 41%) as a yellow oil, R_f 0.43 (60:40 hexane−Et_2O);

ν_{max}/cm^{-1} 2936, 2868, 1687 (C=O), 1406, 1342, 1311, 1270, 1070, 911, 770, 732 and 696; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.74 (1H, ddt, *J* 17.1, 10.1, and 7.1, allyl 2-H), 5.14 (2H, br s, Cbz CH_2), 5.07–4.97 (2H, m, allyl 3-H_2), 4.43–4.33 (1H, m, 2-H), 4.29–4.19 (1H, m, 6-H), 2.42–2.27 (2H, m, allyl 1-H_2), 1.77–1.59 (3H, m, 3-H_A, 4-H_A, 5-H_A), 1.59–1.38 (3H, m, 3-H_B, 4-H_B, 5-H_B), 1.21 (3H, d, *J* 7.0, Me); δ_C (125 MHz, $CDCl_3$) 155.9 (C=O), 137.2 (*ipso*-Ph), 136.4 (allyl C-2), 128.5 (Ph), 127.91 (Ph), 127.86 (Ph), 116.9 (allyl C-3), 66.9 (Cbz CH_2), 50.4 (C-6), 46.2 (C-2), 39.5 (allyl C-1), 30.2 (C-3), 26.8 (C-5), 20.7 (Me), 13.9 (C-4); HRMS found MNa^+, 296.1615. $C_{17}H_{23}NO_2Na$ requires 296.1621. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between Me and allyl CH_2. Spectroscopic data are consistent with those reported in the literature.[87]

1-Benzyl 2-methyl (2*S*,5*R*)-5-allylpyrrolidine-1,2-dicarboxylate *cis*-114 and 1-benzyl 2-methyl (2*S*,5*S*)-5-allylpyrrolidine-1,2-dicarboxylate *trans*-114



cis-**114**

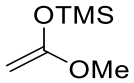


trans-**114**

Compound **114** was prepared by a variation on the method of Ludwig *et al*.[76] A solution of $TiCl_4$ (0.55 mL of a 1 M solution in DCM, 0.55 mmol) was added dropwise to a mixture of hemiaminal (*S*)-**112** (148 mg, 0.5 mmol) and allyltrimethylsilane (0.40 mL, 2.5 mmol) in DCM (5 mL) at –78 °C and allowed to warm to room temperature, in the Dewar, for 16 h. Then sat. $NaHCO_{3(aq)}$ (5 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The organic layers were combined and washed with brine (10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product which contained a 75:25 mixture of diastereomeric products. The crude product was purified by flash column chromatography (gradient elution: 90:10 → 80:20 hexane−EtOAc) to yield a

75:25 mixture of diastereomeric pyrrolidines *cis*-**114** and *trans*-**114** as a 55:45 mixture of rotamers (79 mg, 54%) as a colourless oil, R_f 0.60 (60:40 EtOAc−hexane); ν_{max}/cm^{-1} 3066, 3033, 2951, 1708 (C=O), 1437, 1405, 1349, 1274, 1197, 1172, 1003, 996, 915, 770, 748 and 697; δ_H (500 MHz, $CDCl_3$) 7.41–7.21 (5H, m, Ph), 5.90–5.61 (1H, m, allyl 2-H), 5.25–4.95 (4H, m, Cbz CH_2, allyl 3-H_2), 4.45–4.26 (1H, m, 2-H), 4.19–4.16 (0.13H, m, 5-H), 4.13–4.07 (0.12H, m, 5-H), 4.07–3.92 (0.75H, m, 5-H), 3.75 (1H, s, Me), 3.73 (0.35H, s, Me), 3.60 (1.25H, s, Me), 3.52 (0.4H, s, Me), 2.84–2.72 (0.4H, m, allyl 1-H_A), 2.71–2.54 (0.5H, m, allyl 1-H_A), 2.50–2.39 (0.1H, m, allyl 1-H_A), 2.30–2.10 (2H, m, 3-H_A, allyl 1-H_B), 2.09–1.87 (2H, m, 3-H_B, 4-H_A), 1.87–1.70 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 173.6 (ester C=O), 173.43 (ester C=O), 173.37 (ester C=O), 173.2 (ester C=O), 155.0 (Cbz C=O), 154.31 (Cbz C=O), 155.25 (Cbz C=O), 136.73 (*ipso*-Ph), 136.70 (*ipso*-Ph), 136.2 (allyl C-2), 136.1 (allyl C-2), 135.0 (allyl C-2), 134.8 (allyl C-2), 128.6 (Ph), 128.5 (Ph), 128.11 (Ph), 128.08 (Ph), 128.05 (Ph), 128.02 (Ph), 127.98 (Ph), 127.9 (Ph), 127.8 (Ph), 117.73 (allyl C-3), 117.65 (allyl C-3), 117.34 (allyl C-3), 117.30 (allyl C-3), 67.3 (Cbz CH_2), 67.2 (Cbz CH_2), 67.0 (Cbz CH_2), 66.9 (Cbz CH_2), 60.3 (C-5), 59.98 (C-5), 59.97 (C-5), 59.8 (C-5), 58.8 (C-2), 58.21 (C-2), 58.17 (C-2), 58.5 (C-2), 52.34 (Me), 52.31 (Me), 52.2 (Me), 52.1 (Me), 39.1 (allyl C-1), 39.0 (allyl C-1), 38.3 (allyl C-1), 38.1 (allyl C-1), 29.6 (C-3), 29.1 (C-3), 28.8 (C-3), 28.6 (C-3), 28.2 (C-4), 27.9 (C-4), 27.6 (C-4), 27.0 (C-4) (54 out of 68 signals present); HRMS found MNa^+, 326.1356. $C_{17}H_{21}NO_4Na$ requires 326.1363. Spectroscopic data are consistent with those reported in the literature.[89]

(1-Methoxyvinyloxy)trimethylsilane 115[92]



115

A solution of LHMDS (1 M in THF, 32.4 mL, 32.4 mmol) was diluted in anhydrous THF (20 mL) and cooled to –78 °C and a solution of methyl acetate (2.1 mL, 27.0 mmol) in

THF (12 mL) was added dropwise. After 30 min, TMSCl (4.1 mL, 32.4 mmol) was added and the resulting mixture was stirred for 1.5 h at –78 °C. The solvent was evaporated and the salts were precipitated with pentane. The solution was filtered through Celite and the solvent was evaporated. The crude product was purified by vacuum distillation (T = 25 °C) into a receiver flask at –78 °C to give impure silyl ketene acetal **115** (3.61 g) as a colourless oil, δ_H (500 MHz, $CDCl_3$) 3.55 (3H, s, Me), 3.22 (1H, d, *J* 2.8, CH), 3.11 (1H, d, *J* 2.8, CH), 0.23 (9H, s, $SiMe_3$); δ_C (125 MHz, $CDCl_3$) 162.2 (CH_2*C*), 60.0 (Me), 55.2 (CH_2), 2.6 ($SiMe_3$); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[92]

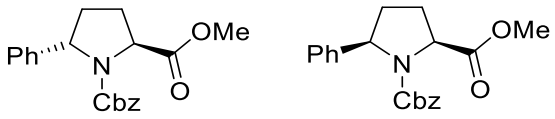
Benzyl (2*R*,6*R*)-2-(2-methoxy-2-oxoethyl)-6-methylpiperidine-1-carboxylate *cis*-116 and benzyl (2*S*,6*R*)-2-(2-methoxy-2-oxoethyl)-6-methylpiperidine-1-carboxylate *trans*-116

cis-**116** *trans*-**116**

Compound **116** was prepared by a variation on the method of Shono *et al*.[79] A solution of $TiCl_4$ (1.1 mL of a 1 M solution in DCM, 1.1 mmol) was added dropwise to the hemiaminal **109** (269 mg, 1.0 mmol) in DCM (10 mL) at –78 °C. Silyl ketene acetal **115** (440 mg, 3.0) was then added at –78 °C and the resulting mixture was allowed to warm to room temperature, in the Dewar, for 16 h. Then sat. $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 20 mL). The organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product which contained a 75:25 mixture of diastereomeric products. The crude product was purified by flash column chromatography (gradient elution: 90:10 → 80:20 hexane–Et_2O) to yield a 90:10 mixture of diastereomeric *esters cis*-**116** and *trans*-**116** (86 mg, 28%) as a colourless oil, R_f 0.17 (60:40 hexane–Et_2O); ν_{max}/cm^{-1}

2941, 2870, 1736 (C=O), 1687 (C=O), 1436, 1405, 1301, 1271, 1166, 1072, 964, 771, 736 and 697; δ_H (500 MHz, $CDCl_3$) 7.39–7.32 (4H, m, Ph), 7.31–7.26 (1H, m, Ph), 5.22–5.04 (2H, m, Cbz CH_2), 4.74–4.62 (0.9H, m, 6-H), 4.44–4.34 (0.9H, m, 2-H), 4.34–4.28 (0.1H, m, 6-H), 4.17–4.07 (0.1H, m, 2-H), 3.62 (3H, s, ester Me), 2.81 (0.1H, dd, *J* 15.2 and 5.2 ester CH_A), 2.65 (0.9H, dd, *J* 14.7 and 10.1 ester CH_A), 2.59–2.45 (1H, m, ester CH_B), 1.76–1.58 (4H, m, 3-H_A, 5-H_2, 4-H_A), 1.58–1.52 (1H, m, 3-H_B), 1.52–1.45 (1H, m, 4-H_B), 1.26 (0.3H, d, *J* 7.1, Me), 1.18 (2.7H, d, *J* 7.0, Me); δ_C (125 MHz, $CDCl_3$) 172.1 (ester C=O), 172.1 (ester C=O), 155.62 (Cbz C=O), 155.56 (Cbz C=O), 137.0 (*ipso*-Ph), 128.5 (Ph), 127.9 (Ph), 127.84 (Ph), 127.80 (Ph), 127.0 (Ph), 67.1 (Cbz CH_2), 66.8 (Cbz CH_2), 51.71 (ester Me), 51.65 (ester Me), 48.7 (6-H), 47.7 (2-H), 47.5 (6-H), 46.1 (2-H), 39.3 (ester CH_2), 39.2 (ester CH_2), 29.9 (C-3), 28.0 (C-5), 26.8 (C-3), 24.8 (C-5), 20.5 (Me), 20.4 (Me), 13.82 (C-4), 13.75 (C-4) (28 of 34 signals present); HRMS found MNa^+, 328.1516. $C_{17}H_{23}NO_4Na$ requires 328.1519.

1-Benzyl 2-methyl (2*S*,5*S*)-5-phenylpyrrolidine-1,2-dicarboxylate *trans*-117 and 1-benzyl 2-methyl (2*S*,5*R*)-5-phenylpyrrolidine-1,2-dicarboxylate *cis*-117

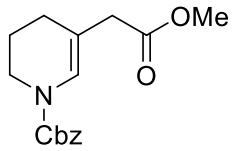


trans-**117** *cis*-**117**

Compound **117** was prepared by a variation on the method of Ludwig *et al*.[83] To a stirred solution of $CuBr{\cdot}Me_2S$ (411 mg, 0.5 mmol) in Et_2O (6 mL) was added dropwise a solution of PhLi (1.1 mL of a 1.9 M solution in dibutyl ether, 2.0 mmol) at –25 °C. After stirring for 30 min at –25 °C, the mixture was cooled to –78 °C and $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol) was added dropwise. After 5 min, a solution of hemiaminal (*S*)-**112** (139 mg, 0.47 mmol) in Et_2O (1 mL) was added dropwise and after 10 mins, the mixture was allowed to warm to room temperature. Then sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated and the aqueous layer was extracted with DCM (2 × 20 mL). The organic layers were combined and washed with $NaHCO_{3(aq)}$ (20

mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product which contained a 70:30 mixture of diastereomeric *carbamates trans*-**117** and *cis*-**117** as a 60:40 mixture of rotamers. The crude product was purified by flash column chromatography eluting with 90:10 hexane−Et_2O to yield the impure product which contained a 70:30 mixture of diastereomeric *carbamates trans*-**117** and *cis*-**117** as a 60:40 mixture of rotamers. The impure product was further purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield an impure 70:30 mixture of diastereomeric *carbamates trans*-**117** and *cis*-**117** as a 60:40 mixture of rotamers (116 mg, ~73%) as a colourless oil, R_f 0.34 (60:40 Et_2O−hexane); ν_{max}/cm^{-1} 3062, 3031, 2951, 1744 (C=O), 1700 (C=O), 1346, 1263, 1196, 1169, 1116, 1080 and 699; δ_H (500 MHz, $CDCl_3$) 7.65–7.58 (0.6H, m, Ph), 7.42–7.17 (7.8H, m, Ph), 6.95–6.88 (1.2H, m, Ph), 6.88–6.83 (0.4H, m, Ph), 5.32–4.94 (3H, m, 5-H, Cbz CH_2), 4.75 (0.4H, dd, *J* 9.1, 1.5, 2-H), 4.68 (0.3H, dd, *J* 9.1, 1.3, 2-H), 4.62 (0.2H, t, *J* 7.1, 2-H), 4.53 (0.1H, t, *J* 7.4, 2-H), 3.87 (0.6H, s, Me), 3.82 (1.2H, s, Me), 3.73 (0.3H, s, Me), 3.62 (0.9H, s, Me), 2.62–2.47 (0.7H, m, 4-H_A), 2.44–2.33 (1H, m, 4-H_A, 3-H_A), 2.31–2.24 (0.3H, m, 3-H_A), 2.19–2.11 (0.3H, m, 3-H_B), 2.07–1.98 (1H, m, 4-H_B, 3-H_B), 1.93–1.85 (0.7H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 173.4 (ester C=O), 173.2 (ester C=O), 173.0 (ester C=O), 155.4 (Cbz C=O), 155.0 (Cbz C=O), 154.6 (Cbz C=O), 154.3 (Cbz C=O), 143.7 (*ipso*-Ph), 143.3 (*ipso*-Ph), 142.9 (*ipso*-Ph), 142.5 (*ipso*-Ph), 136.50 (*ipso*-Ph), 136.47 (*ipso*-Ph), 136.4 (*ipso*-Ph), 136.2 (*ipso*-Ph), 129.5 (Ph), 128.59 (Ph), 128.56 (Ph), 128.48 (Ph), 128.45 (Ph), 128.2 (Ph), 128.11 (Ph), 128.10 (Ph), 128.05 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 127.3 (Ph), 127.2 (Ph), 127.1 (Ph), 127.00 (Ph), 127.96 (Ph), 126.31 (Ph), 126.25 (Ph), 67.3 (Cbz CH_2), 67.2 (Cbz CH_2), 67.1 (Cbz CH_2), 67.0 (Cbz CH_2), 63.1 (5-H), 62.9 (5-H), 61.9 (5-H), 61.5 (5-H), 60.9 (2-H), 60.6 (2-H), 60.3 (2-H), 60.1 (2-H), 52.42 (Me), 52.38 (Me), 52.2 (Me), 35.6 (C-4), 34.5 (C-4), 33.5 (C-4), 32.5 (C-4), 29.3 (C-3), 28.6 (C-3), 28.3 (C-3), 27.1 (C-3) (59 of 64 signals present); HRMS found MNa^+, 362.1360. $C_{20}H_{21}NO_4Na$ requires 362.1369. Spectroscopic data for *cis*-**117** are consistent with those reported in the literature.[93]

Benzyl 5-(2-methoxy-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 122[41,175]



122

Method A:

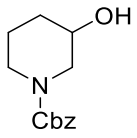
Into an oven-dried 7 mL Supelco vial fitted with a Teflon septum was added 2,6-lutidine (31.4 µL, 0.27 mmol), methyl bromoacetate (42.5 µL, 0.45 mmol), and enecarbamate **66** (30.0 mg, 0.138 mmol). The vial was then purged with nitrogen for 5 minutes, before the addition of a dry solvent solution of $Ir(ppy)_3$ (2 mg in 2 mL, prepared in an oven-dried vial under nitrogen flow). The vial was sealed and stirred for 3.5 hours under LED irradiation. After this period the reaction mixture was concentrated i*n vacuo* to yield the crude product. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield ester **122** as a 55:45 mixture of rotamers (16.8 mg, 42%) as a colourless oil, R_f 0.45 (60:40 hexane−EtOAc); ν_{max}/cm^{-1} 3033, 2951, 1736, 1698 (C=O), 1403, 1256, 1171, 1105, 1075, 760 and 698; δ_H (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ph), 6.85 (0.45H, br s, 2-H), 6.75 (0.55H, br s, 2-H), 5.17 (2H, s, Cbz CH_2), 3.67 (3H, s, Me), 3.62–3.55 (2H, m, 6-H), 3.01 (0.9H, br s, C*H*$_2$CO$_2$Me), 2.97 (1.1H, br s, C*H*$_2$CO$_2$Me), 2.10–2.04 (2H, m, 4-H), 1.89–1.79 (2H, m, 5-H); δ_C (125 MHz, $CDCl_3$) 172.2 (C=O ester), 153.6 (C=O Cbz), 153.1 (C=O Cbz), 136.44 (*ipso*-Ph), 136.40 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 124.0 (C-2), 123.5 (C-2), 112.2 (C-3), 111.7 (C-3), 67.7 (Cbz CH_2), 67.6 (Cbz CH_2), 51.98 (Me), 51.95 (Me), 41.9 (C-6), 41.8 (C-6), 40.7 (C*H*$_2$CO$_2$Me), 25.4 (C-4), 25.1 (C-4), 21.6 (C-5), 21.5 (C-5) (23 out of 28 signals present); HRMS found MNa^+, 312.1201. $C_{16}H_{19}NO_4Na$ requires 312.1192. Spectroscopic data are consistent with those reported in the literature.[41]

Method B:

DBU (1.24 g, 8.13 mmol) was added to a solution of ester **161** (2.13 g, 7.26 mmol) in THF (10 mL) and heated at reflux for 16 h. The solution was then concentrated *in*

vacuo and partitioned between water (20 mL) and EtOAc (50 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 90:10 hexane−EtOAc to yield carbamate **122** as a 55:45 mixture of rotamers (1.67 g, 79%) as a colourless oil.

Benzyl 3-hydroxypiperidine-1-carboxylate 159[105]

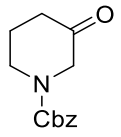


159

Benzyl chloroformate (4.68 mL, 33.0 mmol) was slowly added to a mixture of 3-hydroxypiperidine (3.03 g, 30.0 mmol) and triethylamine (4.59 mL, 33.0 mmol) in DCM (60 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 1.5 h at room temperature, and then 1 M $HCl_{(aq)}$ was added (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with sat. $NaHCO_{3(aq)}$ (20 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 50:50 hexane−EtOAc to yield alcohol **159** (7.04 g, 99%) as a colourless oil, R_f 0.37 (EtOAc); ν_{max}/cm^{-1} 3424 (OH), 2943, 2862, 1674 (C=O), 1431, 1263, 1227, 1145, 1068, 731 and 697; δ_H (400 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ph), 5.13 (2H, s, Cbz CH_2), 3.85–3.69 (2H, m, 3-H, 2-H_A), 3.65–3.53 (1H, m, 6-H_A), 3.31–3.11 (2H, m, 2-H_B, 6-H_B), 1.70 (1H, br s, OH), 1.96–1.84 (1H, m, 5-H_A), 1.84–1.74 (1H, m, 4-H_A), 1.61–1.40 (2H, m, 4-H_B, 5-H_B); δ_C (100 MHz, $CDCl_3$) 151.6 (C=O), 136.9 (*ipso*-Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 67.4 (Cbz CH_2), 66.2 (C-3), 50.9 (C-2), 44.3 (C-

6), 32.5 (C-5), 22.4 (C-4); HRMS found MNa^+, 258.1104. $C_{13}H_{17}NO_3Na$ requires 258.1106. Spectroscopic data are consistent with those reported in the literature.[105]

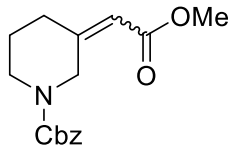
Benzyl 3-oxopiperidine-1-carboxylate 160



160

Compound **160** was prepared by a variation on the method of Pajouhesh *et al*.[106] DMP (41.1 g, 96.9 mmol) was added, in several portions, to a solution of alcohol **159** (20.7 g, 88.1 mmol) in DCM (450 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 72 h at room temperature. The resulting mixture was filtered and the filtrate was washed with brine (200 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. EtOAc (300 mL) was added, the resulting solid removed by filtration and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 2:1 hexane−EtOAc to yield ketone **160** (18.7 g, 91%) as a colourless oil, R_f 0.37 (EtOAc); ν_{max}/cm^{-1} 2955, 1692 (C=O), 1498, 1411, 1329, 1173 and 698; δ_H (400 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ph), 5.17 (2H, s, Cbz CH_2), 4.08 (2H, s, 2-H_2), 3.67 (2H, t, *J* 6.1, 6-H_2), 2.48 (2H, t, *J* 6.5, 4-H_2), 2.03 (2H, p, *J* 6.1, 5-H); δ_C (100 MHz, $CDCl_3$) 205.4 (C=O C-3), 155.4 (C=O Cbz), 136.4 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 67.7 (Cbz CH_2), 54.1 (C-2), 42.5 (C-6), 38.5 (C-4), 22.4 (C-5); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[176]

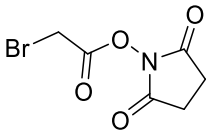
Benzyl 3-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate 161



161

Compound **161** was prepared by a variation on the method of Chang *et al*.[175] A solution of ketone **160** (18.6 g, 80.0 mmol) in DCM (43 mL) was added to a solution of methyl (triphenylphosphoranylidene)acetate (29.2 g, 87.2 mmol) in DCM (87 mL) and heated at reflux for 16 h. The solution was then concentrated *in vacuo* and partitioned between water (100 mL) and EtOAc (100 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined and washed with brine (200 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was then triturated with Et_2O (200 mL) and rinsed with ice-cold Et_2O (100 mL) to give a crude product. The crude product was purified by flash column chromatography (gradient elution: 8:2 → 2:1 hexane−Et_2O) to yield *ester* **161** as a 1:1 mixture of E:Z isomers and an undetermined mixture of rotamers (18.6 g, 80%) as a colourless oil, R_f 0.61, 0.55 (Et_2O); ν_{max}/cm^{-1} 3400, 2952, 1702 (C=O), 1417, 1256, 1162, 740 and 698; δ_H (500 MHz, $CDCl_3$) 7.41–7.27 (5H, m, Ph), 5.84–5.70 (0.5H, m, C*H*CO_2Me), 5.70–5.66 (0.5H, s, C*H*CO_2Me), 5.14 (1H, s, Cbz CH_2), 5.13 (1H, s, Cbz CH_2), 4.72 (1H, s, 2-H_2), 4.02 (1H, s, 2-H_2), 3.74–3.60 (3H, m, Me), 3.59–3.54 (2H, m, 6-H_2), 2.96 (1H, td, *J* 6.5, 1.4, 4-H_2), 2.36 (1H, td, *J* 5.0, 2.5, 4-H_2), 1.80–1.67 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 166.8 (C=O ester), 166.2 (C=O ester), 155.5 (C=O Cbz), 155.4 (C=O Cbz), 136.9 (*ipso*-Ph), 136.8 (*ipso*-Ph), 128.9 (Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (Ph), 127.8 (C-3), 115.6 (C-3, *C*HCO_2Me), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 51.3 (C-2, Me), 45.4 (C-2), 44.5 (C-6), 43.9 (C-6), 34.1 (C-4), 27.6 (C-4), 25.6 (C-5), 21.3 (C-5) (23 out of 28 signals present); HRMS found MNa^+, 312.1203. $C_{16}H_{19}NO_4Na$ requires 312.1212.

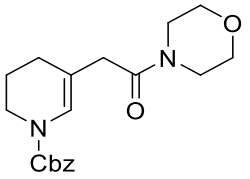
2,5-Dioxopyrrolidin-1-yl 2-bromoacetate 126



126

N-Hydroxysuccinimide (2.88 g, 25.0 mmol), bromoacetic acid (3.48 g, 25.0 mmol) and EDC hydrochloride (5.60 g, 30.0 mmol) were dissolved in DCM (20 mL) and stirred at rt for 72 h. Water (20 mL) was then added to the solution and the two layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic layers were combined and washed with 0.1 N HCl (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by recrystallisation (hexane-EtOAc) to yield activated ester **126** (2.82 g, 48%) as a white crystalline solid, m.p. 112–114 °C, lit. 115-116 °C;[177] ν_{max}/cm^{-1} 3020, 2971, 1838, 1736, 1732 (C=O), 1204, 1086, 1062, 1046, 891, 821 and 641; δ_H (500 MHz, $CDCl_3$) 4.37 (2H, s, CH_2Br), 2.84 (4H, s, 3-H, 4-H); δ_C (125 MHz, $CDCl_3$) 168.5 (C=O amide), 163.3 (C=O amide), 38.0 (CH_2Br), 25.7 (C-3, C-4); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[178]

Benzyl 5-(2-morpholino-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 162

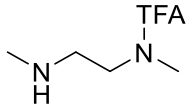


162

Compound **162** was prepared by a variation on the method of Trindade *et al*.[41] Into an oven-dried 7mL Supelco vial fitted with a Teflon septum was weighed Na_2HPO_4 (29 mg, 0.27 mmol), succinimidyl bromoacetate **126** (60 mg, 0.39 mmol), and

enecarbamate **66** (30 mg, 0.138 mmol). The vial was then purged with nitrogen for 5 minutes, before the addition of a dry MeCN solution of $Ir(ppy)_3$ (2 mg in 2 mL, prepared in an oven-dried vial under nitrogen flow). The vial was sealed, and the slurry was stirred for 5 hours under blue LED irradiation (32 W blue LED Kessil H150). After this period, morpholine (24 µL, 0.28 mmol) was added neat and the reaction mixture stirred for 16 h in the dark. The reaction mixture was then diluted with dichloromethane and filtered. The inorganic precipitate was washed thoroughly with dichloromethane and the combined filtrates concentrated *in vacuo* to yield the crude product. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amide* **162** as a 55:45 mixture of rotamers (55 mg, 19%) as a colourless oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 2927, 2859, 1700 (C=O), 1643, 1407, 1259, 1114, 761 and 699; δ_H (500 MHz, $CDCl_3$) 7.39–7.27 (5H, m, Ph), 6.80 (0.45H, br s, 2-H), 6.66 (0.55H, br s, 2-H), 5.15 (2H, s, Cbz CH_2), 3.67–3.53 (8H, m, 6-H_2, NC$H_2$$CH_2O$, OCH_2), 3.50–3.39 (2H, m, NC$H_2$$CH_2O$), 3.05 (0.9H, br s, C$H_2$$CO_2Me$), 3.01 (1.1H, br s, C$H_2$$CO_2Me$), 2.09–2.22 (2H, m, 4-$H_2$), 1.89–1.78 (2H, m, 5-$H_2$); δ_C (125 MHz, $CDCl_3$) 169.3 (C=O amide), 153.6 (C=O Cbz), 153.0 (C=O Cbz), 136.33 (*ipso*-Ph), 136.26 (*ipso*-Ph), 128.63 (Ph), 128.55 (Ph), 128.39 (Ph), 128.35 (Ph), 128.3 (Ph), 128.1 (Ph), 123.1 (C-2), 122.5 (C-2), 113.2 (C-3), 112.7 (C-3), 67.7 (Cbz CH_2), 67.5 (Cbz CH_2), 67.0 (OCH_2), 66.9 (OCH_2), 66.8 (OCH_2), 66.7 (OCH_2), 46.40 (N*C*H_2CH_2O), 46.35 (N*C*H_2CH_2O), 42.1 (N*C*H_2CH_2O), 42.0 (N*C*H_2CH_2O), 41.9 (C-6), 41.8 (C-6), 40.3 (C$H_2$$CO_2Me$), 40.0 (C$H_2$$CO_2Me$), 25.6 (C-4), 25.0 (C-4), 21.6 (C-5), 21.5 (C-5) (33 out of 60 signals present); HRMS found MH^+, 345.1810. $C_{19}H_{25}N_2O_4$ requires 345.1809.

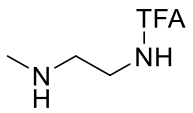
2,2,2-Trifluoro-*N*-methyl-*N*-(2-(methylamino)ethyl)acetamide 165[108]



165

Ethyl trifluoroacetate (1.2 mL, 10.0 mmol) was slowly added to a solution of *N*,*N*'-dimethylethylenediamine (1.1 mL, 10.0 mmol) in THF (40 mL) at 0 °C. The solution was then allowed to warm to rt and stirred for 16 h. The solvent was then evaporated under reduced pressure to yield *amide* **165** as a 2:1 mixture of rotamers (1.73 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 2800, 2486, 1671 (C=O), 1466, 1418, 1197, 1172, 1121, 829, 798 and 719; δ_H (400 MHz, $CDCl_3$) 3.56 (1.3H, t, *J* 6.7, C*H*$_2$NCOCF$_3$), 3.51 (0.7H, t, *J* 6.7, C*H*$_2$NCOCF$_3$), 3.20–3.14 (2H, m, *Me*NCOCF$_3$), 3.06 (1H, s, *Me*NCOCF$_3$), 2.84 (2H, t, *J* 6.4, C*H*$_2$NH), 2.46 (3H, s, *Me*NH), 1.85 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 157.2 (C=O), 120.9 (q, *J* 289.3, CF_3), 49.9, 49.2, 48.6 (CH_2), 36.6, 36.4, 35.8, 35.7 (Me) (9 out of 12 signals present); δ_F (376 MHz, $CDCl_3$) –68.6 (1F, s, CF_3), –69.8 (2F, s, CF_3); HRMS found MH^+, 185.0895. $C_6H_{12}F_3N_2O$ requires 185.0901.

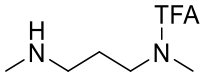
2,2,2-Trifluoro-N-(2-(methylamino)ethyl)acetamide 168[108]



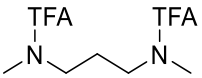
168

Ethyl trifluoroacetate (1.2 mL, 10.0 mmol) was slowly added to a solution of 2-methylaminoethylamine (0.9 mL, 10.0 mmol) in THF (40 mL) at 0 °C and stirred at 0 °C for 10 mins. The solvent was then evaporated under reduced pressure to yield *amide* **168** (1.70 g, 100%) as a yellow semi–solid, ν_{max}/cm^{-1} 3305, 2949, 2855, 2809, 1701 (C=O), 1592, 1188, 1142, 857 and 721; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, br s, NH), 3.39 (2H, t, *J* 5.8, C*H*$_2$NCOCF$_3$), 2.77 (2H, t, *J* 5.7, C*H*$_2$NH), 2.40 (3H, s, Me), 1.20 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 157.5 (q, *J* 36.9, C=O), 116.0 (q, *J* 287.6, CF_3), 49.6 (*C*H$_2$NCOCF$_3$), 38.9 (*C*H$_2$NH), 35.8 (Me); δ_F (376 MHz, $CDCl_3$) –76.0 (s, CF_3); HRMS found MH^+, 171.0739. $C_5H_{10}F_3N_2O$ requires 171.0740.

2,2,2-Trifluoro-*N*-methyl-*N*-(3-(methylamino)propyl)acetamide 170 and *N*,*N*'-(propane-1,3-diyl)bis(2,2,2-trifluoro-N-methylacetamide) 389[31]



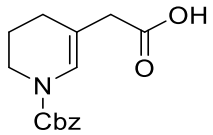
170



389

Ethyl trifluoroacetate (1.2 mL, 10.0 mmol) was slowly added to a solution of *N,N*'-dimethyl-1,3-propanediamine (1.3 mL, 10.0 mmol) in THF (40 mL) at 0 °C. The solution was then allowed to warm to room temperature and stirred for 1 h at room temperature. The solvent was then evaporated under reduced pressure to yield *amides* **170** (as a 2:1 mixture of rotamers) and **389** as a 9:1 mixture (1.87 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 3331, 2952, 2802, 2486, 1672 (C=O), 1470, 1425, 1199, 1177, 1128, 832, 799 and 720; δ_H for **170** (500 MHz, $CDCl_3$) 3.54–3.46 (2H, m, C*H*$_2$NCOCF$_3$), 3.14–3.11 (2H, m, *Me*NCOCF$_3$), 3.04–3.02 (1H, m, *Me*NCOCF$_3$), 2.60 (2H, dt, *J* 11.7, 6.9, C*H*$_2$NH), 2.43 (3H, s, *Me*NH), 2.25 (1H, br s, NH), 1.82–1.75 (2H, m, C*H*$_2$CH$_2$N); δ_C for **39** (125 MHz, $CDCl_3$) 157.1 (q, *J* 35.6, C=O), 116.7 (q, *J* 287.8, CF$_3$), 116.6 (q, *J* 287.8, CF$_3$), 49.1 (*C*H$_2$NH), 48.8 (*C*H$_2$NH), 48.0 (q, *J* 3.1, *C*H$_2$NCOCF$_3$), 47.5 (*C*H$_2$NCOCF$_3$), 36.60 (*Me*NH), 36.57 (*Me*NH), 35.4 (*Me*NCOCF$_3$), 35.01 (*Me*NCOCF$_3$), 28.7 (*C*H$_2$CH$_2$N), 26.8 (*C*H$_2$CH$_2$N) (13 out of 14 signals present); δ_F for **170** (376 MHz, $CDCl_3$) –68.9 (1F, s, CF$_3$), –69.9 (2F, s, CF$_3$); HRMS found MH^+, 199.1050. $C_7H_{14}F_3N_2O$ requires 199.1053.

2-(1-((Benzyloxy)carbonyl)-1,4,5,6-tetrahydropyridin-3-yl)acetic acid 171

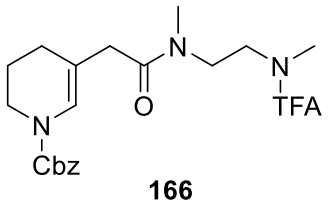


171

Ester **122** (5.09 g, 17.5 mmol) and LiOH (845 mg, 35.0 mmol) were stirred in THF (20 mL) and water (20 mL) at rt for 48 h. After this period the reaction mixture was

concentrated i*n vacuo* and the residue was dissolved in water (50 mL). The solution was then washed with DCM (2 × 20 mL). To the aqueous layer, citric acid (1 N) was added, until a pH of 5 was reached, and then extracted with DCM (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield *carboxylic acid* **171** as a 55:45 mixture of rotamers (3.43 g, 71%) as a colourless oil, ν_{max}/cm^{-1} 3033 (OH), 2951, 1698 (C=O), 1402, 1257, 1170, 1106, 759, 725 and 697; δ_H (400 MHz, $CDCl_3$) 10.49 (1H, br s, OH), 7.42–7.27 (5H, m, Ph), 6.89 (0.45H, br s, 2-H), 6.78 (0.55H, br s, 2-H), 5.18 (2H, s, Cbz CH_2), 3.66–3.52 (2H, m, 6-H), 3.02 (2H, d, *J* 12.4, C*H*$_2$CO$_2$Me), 2.16–2.03 (2H, m, 4-H), 1.92–1.77 (2H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 172.8 (C=O acid), 153.6 (C=O Cbz), 153.2 (C=O Cbz), 136.33 (*ipso*-Ph), 136.28 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 124.3 (C-2), 123.8 (C-2), 111.6 (C-3), 111.2 (C-3), 67.8 (Cbz CH_2), 67.7 (Cbz CH_2), 41.9 (C-6), 41.8 (C-6), 40.5 (C*H*$_2$CO$_2$Me), 25.3 (C-4), 25.1 (C-4), 21.6 (C-5), 21.5 (C-5) (21 out of 26 signals present); HRMS found MNa^+, 298.1047. $C_{15}H_{17}NO_4Na$ requires 298.1056.

Benzyl 5-(2-(methyl(2-(2,2,2-trifluoro-N-methylacetamido)ethyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 166

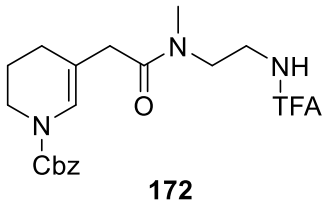


166

Carboxylic acid **171** (169 mg, 0.554 mmol), amine **165** (99 mg, 0.554 mmol), and EDC·HCl (129 mg, 0.665 mmol) were dissolved in DCM (5 mL) and stirred at rt for 16 h. The solution was then concentrated *in vacuo* and the residue was dissolved in DCM (20 mL) and washed with water (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude product. The crude product was purified by flash column chromatography (gradient elution: 2:1 → 1:2 hexane−EtOAc) to yield *amide* **166** as a 55:45 mixture of rotamers (116 mg, 47%) as a colourless oil, R_f 0.29 (EtOAc); ν_{max}/cm^{-1} 2945, 1691 (C=O), 1645 (C=O), 1406, 1255, 1189, 1145, 757 and 699; δ_H (500 MHz, $CDCl_3$) 7.38–7.27 (5H, m, Ph), 6.77 (0.45H, br s, 2-H), 6.66 (0.55H,

br s, 2-H), 5.18–5.11 (2H, m, Cbz CH_2), 3.62–3.44 (6H, m, 6-H_2, 10-H_2, 11-H_2), 3.19–3.10 (2.3H, m, 12-Me), 3.08–2.92 (5.7H, m, 7-H_2, 9-Me, 12-Me), 2.08–1.98 (2H, m, 4-H_2), 1.87–1.76 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 171.43 (C-9 C=O), 171.37 (C-9 C=O), 156.7 (q, *J* 35.9, C-13 C=O), 153.5 (C=O Cbz), 153.0 (C=O Cbz), 136.39 (*ipso*-Ph), 136.25 (*ipso*-Ph), 128.56 (Ph), 128.55 (Ph), 128.3 (Ph), 128.2 (Ph), 128.0 (Ph), 123.3 (C-2), 122.7 (C-2), 116.5 (q, *J* 287.9, C-14 CF_3), 116.4 (q, C-14 CF_3), 113.0 (C-3), 112.6 (C-3), 67.6 (Cbz CH_2), 67.4 (Cbz CH_2), 46.5 (12-Me), 46.4 (12-Me), 44.4 (9-Me), 44.3 (9-Me), 41.9 (C-6), 41.8 (C-6), 41.9 (C-7), 41.8 (C-7), 36.2 (9-Me), 36.0 (9-Me), 35.3 (12-Me), 35.2 (12-Me), 25.4 (C-4), 25.0 (C-4), 21.53 (C-5), 21.47 (C-5) (36 out of 38 signals present); δ_F (376 MHz, $CDCl_3$) –68.68 (0.25F, s, CF_3), –68.70 (0.3F, s, CF_3), –68.8 (0.05F, s, CF_3), –68.9 (0.05F, s, CF_3), –69.9 (2F, s, CF_3), –70.00 (0.15F, s, CF_3), –70.03 (0.20F, s, CF_3); HRMS found MH^+, 442.1952. $C_{21}H_{27}F_3N_3O_4$ requires 442.1953.

Benzyl 5-(2-(methyl(2-(2,2,2-trifluoroacetamido)ethyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 172

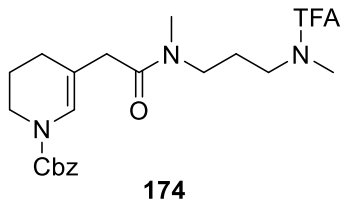


172

Carboxylic acid **171** (612 mg, 2.22 mmol), amine **168** (378 mg, 2.22 mmol), and EDC·HCl (1.27 g, 6.66 mmol) were dissolved in DCM (10 mL) and stirred at rt for 16 h. The solution was then concentrated *in vacuo* and the residue was dissolved in DCM (20 mL) and washed with water (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude product. The crude product was purified by flash column chromatography (gradient elution: 1:1 hexane−EtOAc → EtOAc) to yield *amide* **172** as a 55:45 mixture of rotamers (717 mg, 76%) as a colourless oil, R_f 0.24 (EtOAc); ν_{max}/cm^{-1} 3279, 3057, 2943, 2859, 1701 (C=O), 1633 (C=O), 1407, 1264, 1163, 731 and 699; δ_H (400 MHz, $CDCl_3$) 8.13 (0.55H, br m, *N*H), 7.89 (0.45H, br m, *N*H), 7.41–7.28 (5H, m, Ph), 6.75 (0.55H, br s, 2-H), 6.67 (0.45H, br s, 2-H), 5.17 (2H, s, Cbz CH_2), 3.66–3.55 (4H, m, 6-H_2, 10-H_2), 3.55–3.43 (2H, m, 11-H_2), 3.11–3.01 (5H,

m, Me, 7-H_2), 2.06–1.99 (2H, m, 4-H_2), 1.90–1.79 (2H, m, 5-H_2); δ_C (100 MHz, $CDCl_3$) 173.5 (C-9 C=O), 173.1 (C-9 C=O), 159.0 (C-13 C=O), 153.8 (C=O Cbz), 136.4 (*ipso*-Ph), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 123.04 (C-2), 123.00 (C-2), 112.6 (C-3), 112.1 (C-3), 67.7 (Cbz CH_2), 47.0 (C-10), 42.0 (C-6), 41.9 (C-6), 40.6 (C-7), 40.3 (C-7), 40.1 (C-11), 39.9 (C-11), 37.1 (9-Me), 36.6 (9-Me), 25.4 (C-4), 25.1 (C-4), 21.6 (C-5), 21.5 (C-5) (27 out of 36 signals present); δ_F (376 MHz, $CDCl_3$) –76.0 (0.55F, s, CF_3), –76.1 (0.45F, s, CF_3); HRMS found MNa^+, 450.1614. $C_{20}H_{24}F_3N_3O_4Na$ requires 450.1617.

Benzyl 5-(2-(methyl(3-(2,2,2-trifluoro-*N*-methylacetamido)propyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 174

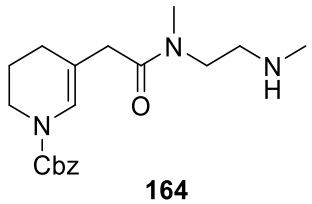


174

Carboxylic acid **171** (192 mg, 0.47 mmol), amine **170** (93 mg, 0.47 mmol), and EDC·HCl (108 mg, 0.56 mmol) were dissolved in DCM (5 mL) and stirred at rt for 16 h. The solution was then concentrated *in vacuo* and the residue was dissolved in DCM (20 mL) and washed with water (20 mL). The organic layer was the dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude product. The crude product was purified by flash column chromatography (gradient elution: 1:1 hexane−EtOAc → EtOAc) to yield *amide* **174** as a 55:45 mixture of two rotamers by ^{1}H NMR spectroscopy and as a undetermined mixture of up to 8 rotamers by ^{13}C NMR spectroscopy (81 mg, 38%) as a colourless oil, R_f 0.21 (EtOAc); ν_{max}/cm^{-1} 2935, 1631 (C=O), 1638 (C=O), 1404, 1256, 1188, 1140, 757 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.26 (5H, m, Ph), 6.77 (0.45H, br s, 2-H), 6.64 (0.55H, br s, 2-H), 5.14 (2H, s, Cbz CH_2), 3.62–3.53 (2H, m, 6-H_2), 3.44–3.23 (4H, m, 10-H_2, 12-H_2), 3.13–2.83 (8H, m, Me, 7-H_2), 2.10–1.97 (2H, m, 4-H_2), 1.89–1.73 (4H, m, 5-H_2, 11-H_2); δ_C (125 MHz, $CDCl_3$) 170.01 (C-9 C=O), 170.96 (C-9 C=O), 170.9 (C-9 C=O), 170.8 (C-9 C=O), 170.4 (C-9 C=O), 170.3 (C-9 C=O), 156.9 (q, *J* 35.6, C-13 C=O), 153.5 (C=O Cbz), 153.0 (C=O Cbz), 136.37 (*ipso*-Ph), 136.35 (*ipso*-Ph),

128.6 (Ph), 128.3 (Ph), 128.19 (Ph), 128.17 (Ph), 128.0 (Ph), 123.2 (C-2), 123.1 (C-2), 122.9 (C-2), 122.7 (C-2), 122.6 (C-2), 122.5 (C-2), 116.6 (q, *J* 287.9 CF_3), 116.5 (q, *J* 287.9 CF_3), 116.4 (q, *J* 287.9 CF_3), 113.2 (C-3), 113.0 (C-3), 112.8 (C-3), 112.6 (C-3), 67.6 (Cbz CH_2), 67.5 (Cbz CH_2), 67.44 (Cbz CH_2), 67.40 (Cbz CH_2), 47.5 (C-10/C-12), 47.4 (C-10/C-12), 47.34 (C-10/C-12), 47.27 (C-10/C-12), 47.1 (C-10/C-12), 47.0 (C-10/C-12), 45.39 (C-10/C-12), 45.35 (C-10/C-12), 45.2 (C-10/C-12), 45.1 (C-10/C-12), 41.9 (C-6), 41.8 (C-6), 40.6 (C-7), 40.5 (C-7), 40.3 (C-7), 40.2 (C-7), 40.1 (C-7), 40.0 (C-7), 35.8 (Me), 35.7 (Me), 35.5 (Me), 35.0 (Me), 34.49 (Me), 34.46 (Me), 33.3 (Me), 26.3 (C-4/C-11), 26.2 (C-4/C-11), 25.7 (C-4/C-11), 25.6 (C-4/C-11), 25.49 (C-4/C-11), 25.45 (C-4/C-11), 25.4 (C-4/C-11), 25.11 (C-4/C-11), 25.07 (C-4/C-11), 25.0 (C-4/C-11), 24.3 (C-4/C-11), 24.2 (C-4/C-11), 21.6 (C-5) 21.5 (C-5) (72 out of 160 signals present); δ_F (376 MHz, $CDCl_3$) –68.7 (0.15F, s, CF_3), 68.76 (0.4F, s, CF_3), 68.78 (0.45F, s, CF_3), –69.8 (2F, s, CF_3); HRMS found MH^+, 456.2104. $C_{22}H_{29}F_3N_3O_4$ requires 456.2110.

Benzyl 5-(2-(methyl(2-(methylamino)ethyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 164

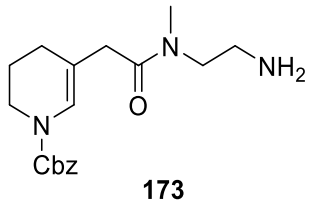


164

A solution of K_2CO_3 (40 mg, 0.29 mmol) in water (0.5 mL) was added to a solution of *N*-TFA amide **166** (116 mg, 0.26 mmol) in MeOH (1 mL) and stirred at rt for 16 h and then concentrated *in vacuo*. The residue was partitioned between DCM (20 mL) and brine (20 mL) and the two layers were separated. The aqueous layer was extracted with DCM (20 mL) and the organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: 95:5 → 90:10 DCM: Methanolic ammonia (7N) to yield *amine* **164** as a 55:45 mixture of rotamers (71 mg, 78%) as a colourless oil, R_f 0.40 (90:10 DCM:methanolic ammonia (7N)); ν_{max}/cm^{-1} 3434, 3052, 2946, 1698 (C=O), 1633 (C=O), 1447, 1262, 730 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.27 (5H, m,

Ph), 6.77 (0.45H, br s, 2-H), 6.66 (0.55H, br s, 2-H), 5.14 (2H, s, Cbz CH_2), 3.61–3.53 (2H, m, 6-H_2), 3.50–3.34 (2H, m, 10-H_2), 3.12–3.01 (2H, m, 7-H_2), 2.99 (1.7H, s, 9-Me), 2.93–2.87 (1.3H, m, 9-Me), 2.71 (2H, dt, *J* 15.9 and 6.7, 11-H_2), 2.47–2.31 (3H, m, 12-*Me*), 2.09–1.99 (2H, m, 4-H_2), 1.88–1.76 (2H, m, 5-H_2), 1.26 (1H, br s, NH); δ_C (125 MHz, $CDCl_3$) 170.1 (C-9 C=O), 153.5 (C=O Cbz), 153.0 (C=O Cbz), 136.4 (*ipso*-Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 123.0 (C-2), 122.9 (C-2), 122.5 (C-2), 122.4 (C-2), 113.8 (C-3), 113.4 (C-3), 113.3 (C-3), 113.0 (C-3), 67.5 (Cbz CH_2), 67.4 (Cbz CH_2), 50.0 (C-11), 49.9 (C-11), 49.8 (C-11), 49.4 (C-11), 47.80 (C-10), 47.78 (C-10), 42.0 (C-6), 41.82 (C-6), 41.79 (C-6), 40.7 (C-7), 40.4 (C-7), 40.1 (C-7), 39.9 (C-7), 36.67 (Me), 36.65 (Me), 36.42 (Me), 36.38 (Me), 36.3 (Me), 33.7 (Me-12), 33.6 (Me-12), 25.5 (C-4), 25.2 (C-4), 25.1 (C-4), 21.6 (C-5), 21.5 (C-5) (42 out of 68 signals present); HRMS found MH^+, 346.2125. $C_{19}H_{28}N_3O_3$ requires 346.213.

Benzyl 5-(2-((2-aminoethyl)(methyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 173

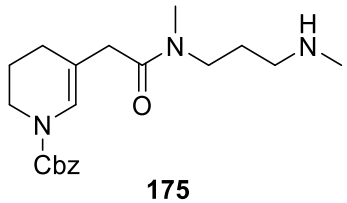


173

A solution of K_2CO_3 (166 mg, 1.20 mmol) in water (1.3 mL) was added to a solution of *N*-TFA amide **172** (468 mg, 1.09 mmol) in MeOH (3.3 mL) and stirred at rt for 16 h and then concentrated *in vacuo*. The residue was partitioned between DCM (20 mL) and brine (20 mL) and the two layers were separated. The aqueous layer was extracted with DCM (20 mL) and the organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: 98:2 → 97:3 DCM:methanolic ammonia (7N) to yield *amine* **173** as a 55:45 mixture of rotamers (197 mg, 55%) as a colourless oil, R_f 0.48 (90:10 DCM:methanolic ammonia (7N)); ν_{max}/cm^{-1} 3307, 3052, 2936, 1697 (C=O), 1671 (C=O), 1404, 1258, 1171, 1107, 730 and 697; δ_H (400 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ph), 6.78 (0.45H, br s, 2-H), 6.67 (0.55H, br s, 2-H), 5.16 (2H,

s, Cbz CH_2), 3.62–3.55 (2H, m, 6-H_2), 3.46–3.30 (2H, m, 10-H_2), 3.16–2.98 (4H, m, 11-H_2, Me), 2.95–2.76 (3H, m, 7-H_2, Me), 2.10–2.03 (2H, m, 4-H_2), 1.90–1.81 (2H, m, 5-H_2), 1.26 (2H, br s, NH); δ_C (100 MHz, $CDCl_3$) 171.2 (C-9 C=O), 153.6 (C=O Cbz), 153.1 (C=O Cbz), 136.5 (*ipso*-Ph), 128.6 (Ph), 128.34 (Ph), 128.26 (Ph), 128.1 (Ph), 123.1 (C-2), 122.5 (C-2), 113.4 (C-3), 112.9 (C-3), 67.6 (Cbz CH_2), 67.5 (Cbz CH_2), 53.0 (C-10), 52.9 (C-10), 51.2 (C-10), 51.1 (C-10), 42.1 (C-6), 41.9 (C-6), 40.8 (C-7/C-11), 40.5 (C-7/C-11), 40.4 (C-7/C-11), 40.2 (C-7/C-11), 40.1 (C-7/C-11), 39.9 (C-7/C-11), 33.63 (Me), 33.61 (Me), 36.4 (Me), 36.3 (Me), 25.7 (C-4), 25.2 (C-4), 21.7 (C-5), 21.6 (C-5) (34 out of 64 signals present); HRMS found MH^+, 332.1967. $C_{18}H_{26}N_3O_3$ requires 332.1974.

Benzyl 5-(2-(methyl(3-(methylamino)propyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 175

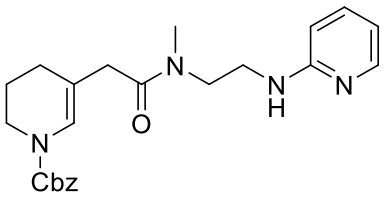


175

A solution of K_2CO_3 (52 mg, 0.38 mmol) in water (1 mL) was added to a solution of *N*-TFA amide **174** (157 mg, 0.34 mmol) in MeOH (2.4 mL) and stirred at rt for 16 h and then concentrated *in vacuo*. The residue was partitioned between DCM (20 mL) and brine (20 mL) and the two layers were separated. The aqueous layer was extracted with DCM (20 mL) and the organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: 97:3 → 90:10 DCM: Methanolic ammonia (7N) to yield *amine* **175** as a 55:45 mixture of rotamers (102 mg, 83%) as a colourless oil, R_f 0.26 (90:10 DCM:Methanolic ammonia (7N)); ν_{max}/cm^{-1} 2934, 2798, 1698 (C=O), 1634 (C=O), 1403, 1257, 1072, 760 and 699; δ_H (500 MHz, $CDCl_3$) 7.36–7.25 (5H, m, Ph), 6.76 (0.45H, br s, 2-H), 6.65 (0.55H, br s, 2-H), 5.13 (2H, s, Cbz CH_2), 3.60–3.51 (2H, m, 6-H_2), 3.42–3.29 (2H, m, 10-H_2), 3.09–2.97 (2H, m, 7-H_2), 2.96–2.83 (3H, m, 9-Me), 2.56–2.44 (2H, m, 12-H_2), 2.40–2.31 (3H, m, 13-*Me*), 2.07–1.99 (2H, m, 4-H_2),

1.86–1.75 (2H, m, 5-H_2), 1.73–1.60 (2H, m, 11-H_2), 1.50 (1H, br s, NH); δ_C (125 MHz, $CDCl_3$) 170.7 (C-9 C=O), 170.6 (C-9 C=O), 153.5 (C=O Cbz), 153.0 (C=O Cbz), 136.4 (*ipso*-Ph), 128.5 (Ph), 128.14 (Ph), 128.13 (Ph), 128.10 (Ph), 127.98 (Ph), 127.95 (Ph), 123.0 (C-2), 122.8 (C-2), 122.42 (C-2), 122.37 (C-2), 114.0 (C-3), 113.5 (C-3), 113.3 (C-3), 112.9 (C-3), 67.47 (Cbz CH_2), 67.45 (Cbz CH_2), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 48.82 (C-12), 48.77 (C-12), 47.93 (C-10), 47.86 (C-10), 45.5 (C-10), 45.4 (C-10), 41.9 (C-6), 41.8 (C-6), 40.6 (C-7), 40.4 (C-7), 40.0 (C-7), 39.8 (C-7), 36.6 (Me-13), 36.5 (Me-13), 36.42 (Me-13), 36.39 (Me-13), 35.6 (Me-9), 35.5 (Me-9), 33.3 (Me-9), 28.7 (C-11), 28.6 (C-11), 27.2 (C-11), 25.4 (C-4), 25.1 (C-4), 25.0 (C-4), 21.58 (C-5), 21.55 (C-5), 21.50 (C-5) 21.48 (C-5) (52 out of 72 signals present); HRMS found MH^+, 360.2299. $C_{20}H_{30}N_3O_3$ requires 360.2287.

Benzyl 5-(2-(methyl(2-(pyridin-2-ylamino)ethyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 176

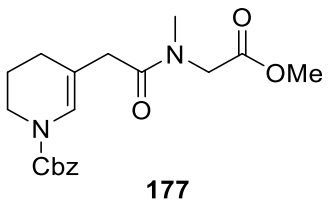


176

Compound **176** was prepared by a variation on the method of Wagaw *et al*.[111] 2-Bromopyridine (14.3 µL, 0.15 mmol), amine **173** (50.0 mg, 0.15 mmol), $Pd_2(dba)_3$ (2.8 mg, 2 mol%), BINAP (3.7 mg, 4 mol%), NaO*t*Bu (20.2 mg, 0.21 mmol) and toluene (1.4 mL) were added to an oven-dried flask and purged with N_2 for 5 min. The mixture was then heated at 70 °C for 16 h and then cooled to rt. Et_2O (10 mL) was then added and the organic layer washed with brine (3 × 10 mL, dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with EtOAc to yield slightly impure *amine* **176** which was then purified *via* preparative HPLC eluting with gradient elution: 5:95 →

30:70 → 55:45 → 95:5 MeCN–H_2O to give as a 55:45 mixture of rotamers (14.9 mg, 11%) as a colourless oil, R_f 0.17 (EtOAc); ν_{max}/cm^{-1} 2926 (NH), 2856, 1697 (C=O), 1665 (C=O), 1411, 1259, 1135, 737 and 699; δ_H (400 MHz, $CDCl_3$) 8.02 (0.45H, br d, *J* 4.4, Ar), 7.92 (0.55H, br d, *J* 4.0, Ar), 7.47–7.28 (6H, m, Ar, Ph), 7.15–6.97 (1H, br m, NH), 6.76 (0.45H, s, 2-H), 6.65 (0.55H, s, 2-H), 6.50 (1H, app. t, *J* 7.8, Ar), 6.47–6.38 (1H, m, Ar), 5.19 (2H, s, Cbz CH_2), 3.83–3.73 (2H, m, 11-H_2), 3.53–3.41 (4H, m, 6-H_2, 10-H_2), 3.01 (1.35H, br s, Me), 2.99 (1.65H, br s, Me), 2.81 (0.9H, br s, 7-H_2), 2.76 (1.1H, br s, 7-H_2), 1.91–1.82 (2H, br m, 4-H_2), 1.70–1.58 (2H, br m, 5-H_2); δ_C (100 MHz, $CDCl_3$) 171.6 (C=O C-8), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 124.2 (C-2), 123.6 (C-2), 117.0 (C-3), 112.8 (Ar), 112.2 (Ar), 106.3 (Ar), 67.8 (Cbz CH_2), 67.6 (Cbz CH_2), 48.6 (C-11), 43.6 (C-7), 41.8 (C-11), 41.7 (C-11), 39.5 (C-6), 36.6 (Me), 25.0 (C-4), 24.8 (C-4), 21.4 (C-5), 21.3 (C-5) (22 out of 42 signals present); HRMS found MH^+, 409.2233. $C_{23}H_{29}N_4O_3$ requires 409.2234.

Benzyl 5-(2-((2-methoxy-2-oxoethyl)(methyl)amino)-2-oxoethyl)-3,4-dihydropyridine-1(2H)-carboxylate 177

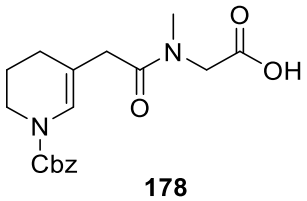


177

Carboxylic acid **171** (1.03 g, 3.74 mmol), sarcosine methyl ester hydrochloride (522 mg, 3.74 mmol), and EDC·HCl (2.15 g, 11.2 mmol) were dissolved in DCM (10 mL) and stirred at rt for 48 h. The solution was then concentrated *in vacuo* and the residue was dissolved in DCM (20 mL) and washed with water (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude product. The crude product was purified by flash column chromatography (gradient elution: 2:1 hexane−EtOAc → EtOAc) to yield *amide* **177** as a 40:35:15:10 mixture of rotamers (645 mg, 48%) as a pale yellow oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 2950, 1747 (C=O), 1698 (C=O), 1646 (C=O), 1401, 1257, 1203, 1171, 1104, 974, 760, 736 and 697; δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 6.84 (0.35H, br s, 2-H), 6.76 (0.1H, br s, 2-H), 6.73

(0.4H, br s, 2-H), 6.66 (0.15H, br s, 2-H), 5.17 (2H, s, Cbz CH_2), 4.10 (0.75H, br s, 10-H_2), 4.09 (0.85H, br s, 10-H_2), 4.07 (0.2H, br s, 10-H_2), 4.04 (0.2H, br s, 10-H_2), 3.72 (1.1H, br s, OMe), 3.70 (1.3H, br s, OMe), 3.67 (0.6 H, br s, OMe), 3.63–3.53 (2H, m, 6-H_2), 3.13 (0.7H, br s, 7-H_2), 3.11–3.05 (3.2H, m, 9-Me, 7-H_2), 3.03 (0.2H, br s, 7-H_2), 2.98 (0.2H, br s, 7-H_2), 2.96 (0.7H, br s, 9-Me), 2.11–2.02 (2H, m, 4-H_2), 1.90–1.79 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 171.6 (C-9 C=O), 171.5 (C-9 C=O), 171.0 (C-9 C=O), 169.9 (ester C=O), 169.8 (ester C=O), 169.6 (ester C=O), 169.5 (ester C=O), 153.6 (Cbz C=O), 153.5 (Cbz C=O), 153.13 (Cbz C=O), 153.05 (Cbz C=O), 136.50 (*ipso*-Ph), 136.47 (*ipso*-Ph), 136.4 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.31 (Ph), 128.28 (Ph), 128.26 (Ph), 128.2 (Ph), 128.1 (Ph), 123.3 (C-2), 122.9 (C-2), 113.3 (C-3), 113.1 (C-3), 112.73 (C-3), 112.67 (C-3), 67.63 (Cbz CH_2), 67.61 (Cbz CH_2), 67.53 (Cbz CH_2), 67.51 (Cbz CH_2), 52.4 (OMe), 52.3 (OMe), 52.23 (OMe), 52.21 (OMe), 51.8 (C-10), 49.7 (C-10), 49.6 (C-10), 42.1 (C-6), 42.0 (C-6), 41.9 (C-6), 41.8 (C-6), 40.9 (C-7), 40.6 (C-7), 40.4 (C-7), 40.1 (C-7), 37.1 (9-Me), 37.0 (9-Me), 35.3 (9-Me), 25.4 (C-4), 25.1 (C-4), 24.9 (C-4), 24.7 (C-4), 21.7 (C-5), 21.6 (C-5) 21.54 (C-5), 21.47 (C-5) (57 out of 68 signals present); HRMS found MNa^+, 383.1599. $C_{19}H_{24}N_2O_5Na$ requires 383.1583.

_N_-(2-(1-((Benzyloxy)carbonyl)-1,4,5,6-tetrahydropyridin-3-yl)acetyl)-_N_-methylglycine 178

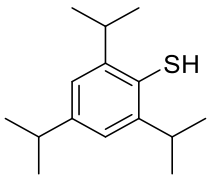


178

Ester **177** (534 mg, 1.48 mmol) and LiOH (70.9 mg, 2.96 mmol) were stirred in THF (5 mL) and water (5 mL) at rt for 48 h. After this period the reaction mixture was concentrated i*n vacuo* and the residue was dissolved in water (20 mL). The solution was then washed with DCM (2 × 10 mL). To the aqueous layer, citric acid (1 N) was added, until a pH of 5 was reached, and then extracted with DCM (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield *carboxylic acid* **178** as a 35:35:15:15 mixture of rotamers

(327 mg, 64%) as a white, amorphous solid, ν_{max}/cm^{-1} 3415 (COOH), 2933, 1700 (C=O), 1673, 1610, 1406, 1260, 1203, 1174, 1109 and 699; δ_H (500 MHz, $CDCl_3$) 10.83 (1H, br s, OH), 7.38–7.25 (5H, m, Ph), 6.82 (0.35H, br s, 2-H), 6.79 (0.15H, br s, 2-H), 6.70 (0.35H, br s, 2-H), 6.66 (0.15H, br s, 2-H), 5.17–5.11 (2H, m, Cbz CH_2), 4.11–4.06 (1.4H, m, 10-H_2), 4.04 (0.3H, br s, 10-H_2), 4.00 (0.3H, br s, 10-H_2), 3.54 (2H, app. dt, *J* 11.7, 7.9, 6-H_2), 3.11 (0.7H, br s, 7-H_2), 3.09–3.02 (3.2H, m, Me, 7-H_2), 2.99 (0.3H, br s, 7-H_2), 2.93 (0.8H, s, Me), 2.01 (2H, app. dt, *J* 12.6, 6.0, 4-H_2), 1.85–1.72 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 172.3 (C-9 C=O), 172.2 (C-9 C=O), 172.1 (acid C=O), 171.89 (acid C=O), 171.86 (C-9 C=O), 171.8 (C-9 C=O), 171.3 (acid C=O), 171.0 (acid C=O), 153.62 (Cbz C=O), 153.58 (Cbz C=O), 153.11 (Cbz C=O), 153.06 (Cbz C=O), 136.22 (*ipso*-Ph), 136.17 (*ipso*-Ph), 136.14 (*ipso*-Ph), 136.10 (*ipso*-Ph), 128.5 (Ph), 128.2 (Ph), 128.1 (Ph), 128.0 (Ph), 123.3 (C-2), 123.2 (C-2), 122.84 (C-2), 122.81 (C-2), 113.4 (C-3), 112.9 (C-3), 112.7 (C-3), 112.5 (C-3), 67.55 (Cbz CH_2), 67.50 (Cbz CH_2), 51.58 (C-10), 51.55 (C-10), 49.6 (C-10), 49.5 (C-10), 41.9 (C-6), 41.8 (C-6), 41.7 (C-6), 41.6 (C-6), 40.3 (C-7), 40.2 (C-7), 40.0 (C-7), 39.8 (C-7), 37.0 (9-Me), 36.9 (9-Me), 35.3 (9-Me), 25.0 (C-4), 24.8 (C-4), 24.62 (C-4), 24.57 (C-4), 21.4 (C-5) 21.3 (C-5), 21.2 (C-5) (52 out of 64 signals present); HRMS found MH^+, 347.1616. $C_{18}H_{23}N_2O_5$ requires 347.1601.

2,4,6-Triisopropylbenzenethiol 132[179]

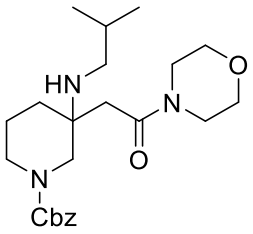


132

A solution of 2,4,6-triisopropylbenzene-1-sulfonyl chloride (6.06 g, 20.0 mmol) in THF (25 mL) was added dropwise to a solution of $LiAlH_4$ (16.7 mL of a 2.4 M solution in THF, 40.0 mmol) at 0 °C. An extra portion of $LiAlH_4$ (16.7 mL of a 2.4 M solution in THF, 40.0 mmol) was then added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 16 h. The reaction mixture was cooled

to 0 °C and diluted with THF (40 mL). Then, water (3 mL), 10% w/w NaOH solution (5 mL), and water (10 mL) were added dropwise and the mixture allowed to stir at 0 °C for 10 min. $MgSO_4$ was then added and the mixture was allowed to stir at room temperature for 30 min. The white solids were then removed *via* vacuum filtration with THF and Et_2O rinsing. The solvent was then evaporated under reduced pressure to give a yellow semi-solid which was purified by vacuum distillation to give thiol **132** (2.01 g, 43%) as a pale yellow oil, ν_{max}/cm^{-1} 2958, 2928, 2868, 1429, 1382, 1316, 1102, 1061, 875 and 743; δ_H (500 MHz, $CDCl_3$) 7.01 (2H, s, Ph), 3.51 (2H, septet, *J* 6.8, C*H*Me_2), 3.07 (1H, s, SH), 2.87 (1H, septet, *J* 6.9, C*H*Me_2), 1.27 (12H, d, *J* 6.9, CH*Me*$_2$), 1.25 (6H, d, *J* 6.9, CH*Me*$_2$); δ_C (125 MHz, $CDCl_3$) 148.3 (*ipso*-Ph), 147.2 (*ipso*-Ph), 124.4 (*ipso*-Ph), 121.5 (Ph), 34.3 (*C*HMe_2), 31.9 (*C*HMe_2), 24.2 (CH*Me*$_2$), 23.4 (CH*Me*$_2$); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[180]

Benzyl 3-(isobutylamino)-3-(2-morpholino-2-oxoethyl)piperidine-1-carboxylate 180

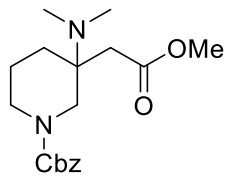


180

Compound **180** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (3.2 mg, 2 mol%), TRIP thiol (19 mg, 50 mol%) and enecarbamate **162** (55 mg, 0.16 mmol). Toluene (3.2 mL) and isobutylamine (80 µL, 0.80 mmol) was then added under N_2 and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by strong cation exchange chromatography (1 g benzene sulfonic acid bonded resin H^+ form pre equilibrated with 3 × column volumes of DCM. Sample loaded in DCM (ca. 2ml) and washed with 10 × column volumes of methanol.

Impure compound was eluted with 10 × column volumes of methanolic ammonia (7N) and further purified by flash column chromatography (gradient elution: 98:2 → 95:5 methanolic ammonia (7N) to yield *amine* **180** as a mixture of rotamers (13 mg, 19%) as a yellow oil, R_f 0.16 (95:5 DCM–methanolic ammonia (7N)); ν_{max}/cm^{-1} 2952, 2925, 1603 (C=O), 1634, 1431, 1271, 1238, 1115 and 699; δ_H (500 MHz, d_4-MeOD) 7.41–7.28 (5H, m, Ph), 5.15 (2H, s, Cbz CH_2), 3.71–3.33 (12H, m, 2-H_2, 6-H_2, NC$H_2$$CH_2O, OCH_2$), 2.60–2.40 (2H, m, C$H_2$$CO_2$Me), 2.40–2.24 (2H, m, N$CH_2$), 1.80–1.69 (3H, m, 4-$H_2$, 5-$H_A$), 1.68–1.58 (1H, m, C$H$$Me_2$), 1.58–1.49 (1H, m, 5-$H_B$), 0.98–0.82 (6H, m, Me); δ_C (125 MHz, d_4-MeOD) 171.5 (C=O amide), 157.3 (C=O Cbz), 138.2 (*ipso*-Ph), 129.6 (Ph), 129.1 (Ph), 128.8 (Ph), 68.3 (Cbz CH_2), 67.7 (OC$H_2$$CH_2$N), 56.1 (C-3), 55.7 (C-3), 52.4 (NCH_2), 52.1 (NCH_2), 50.0 (NHCH_2), 47.3 (NHCH_2), 45.5 (NHCH_2), 42.9 (NHCH_2), 34.8 (*C*$H_2$$CO_2$Me), 34.2 (C-4), 27.7 (*C*HMe_2), 22.4 (C-5), 22.0 (C-5), 21.2 (CH*Me*$_2$), 21.0 (CH*Me*$_2$) (23 out of 72 signals present); HRMS found MH^+, 418.2715. $C_{23}H_{36}N_3O_4$ requires 418.2706.

Benzyl 3-(dimethylamino)-3-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate 182

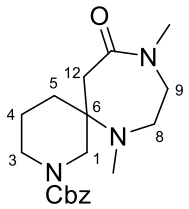


182

Compound **182** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (5.1 mg, 2 mol%), TRIP thiol (30 mg, 50 mol%) and enecarbamate **122** (83 mg, 0.29 mmol). Toluene (4 mL) and dimethylamine (1 mL, 5.6N in EtOH) was then added under N_2 and the resultant mixture was stirred for 48 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by strong cation exchange chromatography (1 g benzene sulfonic acid bonded resin H^+ form pre equilibrated with 3 × column volumes of DCM. Sample loaded in DCM (ca. 2ml) and washed with 10 × column volumes of methanol.

Impure compound was eluted with 10 × column volumes of methanolic ammonia (7N) and further purified by flash column chromatography (gradient elution: 9:1 hexane–EtOAc → EtOAc to yield *amine* **182** as a 55:45 mixture of rotamers (15 mg, 15%) as an orange oil, R_f 0.37 (EtOAc); ν_{max}/cm^{-1} 2949, 2924, 2855, 2785, 1730 (C=O), 1697 (C=O), 1434, 1233, 1145, 762 and 698; δ_H (500 MHz, d_4-MeOD) 7.41–7.25 (5H, m, Ph), 5.11 (2H, s, Cbz CH_2), 3.89 (1H, d, *J* 13.8, 2-H_A), 3.74 (1H, dt, *J* 9.3, 4.1, 6-H_A), 3.67–3.95 (3H, m, OMe), 3.28–3.05 (2H, m, 2-H_B, 6-H_B), 2.48–2.31 (2H, m, C*H*$_2$CO$_2$Me), 2.28 (3.3H, br s, NMe), 2.21 (2.7H, br s, NMe), 1.97–1.87 (1H, m, 4-H_A), 1.80–1.66 (2H, m, 4-H_B, 5-H_A), 1.52–1.43 (1H, m, 5-H_B); δ_C (125 MHz, d_4-MeOD) 171.2 (C=O ester), 157.3 (C=O Cbz), 138.3 (*ipso*-Ph), 138.0 (*ipso*-Ph), 129.5 (Ph), 129.23 (Ph), 129.20 (Ph), 129.08 (Ph), 129.05 (Ph), 128.8 (Ph), 68.4 (Cbz CH_2), 68.3 (Cbz CH_2), 58.9 (C-3), 58.8 (C-3), 52.1 (OMe), 51.1 (C-2), 45.2 (C-6), 38.3 (NMe_2), 35.7 (C*H*$_2$CO$_2$Me), 35.4 (C*H*$_2$CO$_2$Me), 32.9 (C-4), 32.8 (C-4), 21.8 (C-5), 21.6 (C-5) (24 out of 30 signals present); HRMS found MH^+, 335.1968. $C_{18}H_{27}N_2O_4$ requires 335.1965.

Benzyl 7,10-dimethyl-11-oxo-2,7,10-triazaspiro[5.6]dodecane-2-carboxylate 189

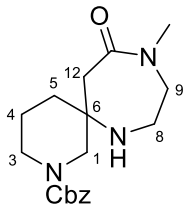


189

Compound **189** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (4.2 mg, 2 mol%), TRIP thiol (25 mg, 50 mol%) and amine **164** (70 mg, 0.20 mmol). Toluene (4.2 mL) was then added under N_2 and the resultant mixture was stirred for 72 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 98:2 DCM−MeOH to yield *spirocycle* **189** as a mixture of rotamers (40

mg, 57%) as a yellow oil, R_f 0.40 (90:10 DCM−MeOH); ν_{max}/cm^{-1} 3412, 2927, 2859, 1693 (C=O), 1630 (C=O), 1439, 1271, 1242 and 700; δ_H (500 MHz, $CDCl_3$) 7.40–7.23 (5H, m, Ph), 5.09 (2H, s, Cbz CH_2), 3.75–3.50 (2H, m, 1-H/8-H/9-H), 3.49–3.30 (2H, m, 3-H_2), 3.29–3.20 (1H, m, 1-H/8-H/9-H), 3.19–3.02 (2H, m, 1-H/8-H/9-H), 3.01–2.83 (4H, m, 10-Me, 1-H/8-H/9-H), 2.79–2.65 (1H, m, 12-H_A), 2.65–2.47 (1H, m, 12-H_B), 2.45–2.31 (3H, m, 7-Me), 1.82–1.50 (4H, m, 4-H_2, 5-H_2); δ_C (125 MHz, $CDCl_3$) 172.2 (C=O C-11), 172.1 (C=O C-11), 155.7 (C=O Cbz), 155.4 (C=O Cbz), 136.9 (*ipso*-Ph), 136.7 (*ipso*-Ph), 128.6 (Ph), 128.13 (Ph), 128.05 (Ph), 127.9 (Ph), 67.3 (Cbz CH_2), 54.4 (C-6), 51.3 (C-1/C-8), 51.1 (C-1/C-8), 50.8 (C-1/C-8), 46.8 (C-9), 46.4 (C-9), 44.2 (C-3), 40.2 (C-12), 39.4 (C-12), 36.2 (Me), 36.0 (Me), 35.7 (Me), 32.0 (C-4/C-5), 21.1 (C-4/C-5), 20.8 (C-4/C-5) (26 out of 34 signals present); HRMS found MH^+, 346.2118. $C_{14}H_{28}NO_2$ requires 346.2130.

Benzyl 10-methyl-11-oxo-2,7,10-triazaspiro[5.6]dodecane-2-carboxylate 190

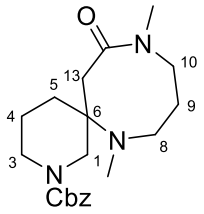


190

Compound **190** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (5.1 mg, 2 mol%), TRIP thiol (30 mg, 50 mol%) and amine **173** (82.8 mg, 0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 72 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 98:2 DCM−Methanolic ammonia (7N) to yield *spirocycle* **190** (17.2 mg, 21%) as a mixture of rotamers as a colourless oil, R_f 0.57 (90:10 DCM− Methanolic ammonia (7N)); ν_{max}/cm^{-1} 2932, 1697 (C=O), 1640 C=O), 1437, 1406, 1262, 761 and

698; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.12 (2H, s, Cbz CH_2), 3.99–3.66 (2H, m, 1-H/3-H/8-H/9-H), 3.60–3.22 (2H, m, 1-H/3-H/8-H/9-H), 3.15–2.70 (7H, m, Me, 1-H/3-H/8-H/9-H), 2.86–2.48 (1H, m, 12-H_2), 1.85–1.51 (4H, m, 4-H_2, 5-H_2), 1.31–1.11 (2H, m, NH_2); δ_C (125 MHz, $CDCl_3$) 172.0 (C=O C-11), 155.8 (C=O Cbz), 136.8 (*ipso*-Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (Ph), 67.4 (Cbz CH_2), 53.5 (C-1/C-3/C-8/C-9), 52.2 (C-1/C-3/C-8/C-9), 50.6 (C-6), 48.2 (C-12), 44.4 (C-1/C-3/C-8/C-9), 42.6 (C-1/C-3/C-8/C-9), 36.1 (Me), 33.2 (C-4/C-5), 21.2 (C-4/C-5), 20.8 (C-4/C-5) (17 out of 32 signals present); HRMS found MH^+, 332.1977. $C_{18}H_{26}N_3O_3$ requires 332.1974.

Benzyl 7,11-dimethyl-12-oxo-2,7,11-triazaspiro[5.7]tridecane-2-carboxylate 192

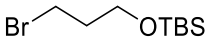


192

Compound **192** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (5mg, 2 mol%), TRIP thiol (30 mg, 50 mol%) and amine **175** (90.2 mg, 0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 72 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 DCM:Methanolic ammonia (7N) to yield a mixture of starting amine **175** and spirocycle **192** (19.6 mg). To this mixture in DCM (2 mL) was added Boc_2O (12.5 µL, 0.06 mmol) and stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 98:2 DCM:Methanolic ammonia (7N) to yield *spirocycle* **192** as a mixture of rotamers (5.2 mg, 6%) as a colourless oil, R_f 0.39 (95:5 DCM:methanolic ammonia (7N)); ν_{max}/cm^{-1} 2931, 1694 (C=O), 1643 (C=O),

1405, 1258, 1148 and 600; δ_H (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ph), 5.22–5.02 (2H, m, Cbz CH_2), 4.19–3.79 (1H, m, 1-H/3-H/8-H/10-H), 3.74–3.46 (1H, m, 1-H/3-H/8-H/10-H), 3.45–3.07 (4H, m, 1-H/3-H/8-H/10-H), 3.06–2.94 (2H, m, 1-H/3-H/8-H/10-H), 2.94–2.68 (4H, m, *N*-Me), 2.57–2.00 (4H, m, *N*-Me, 13-H_2), 1.95–1.65 (4H, m, 4-H_2, 5-H_2), 1.47–1.34 (2H, m, 9-H_2); δ_C (125 MHz, $CDCl_3$) 171.4 (C=O C-12), 170.4 (C=O C-12), 155.9 (C=O Cbz), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.3 (Ph), 128.1 (Ph), 128.0 (Ph), 127.6 (Ph), 67.2 (Cbz CH_2), 59.1 (C-6), 50.1 (C-3), 46.9 (C-1/C-3/C-8/C-10), 46.4 (C-1/C-3/C-8/C-10), 44.4 (C-1/C-3/C-8/C-10), 42.1 (C-1/C-3/C-8/C-10), 34.4 (Me), 33.6 (Me), 31.8 (C-13), 25.5 (C-4/C-5/9), 21.7 (C-4/C-5/C-9), 20.9 (C-4/C-5/C-9), 20.5 (C-4/C-5/C-9) (24 out of 36 signals present); HRMS found MH^+, 360.2280. $C_{20}H_{30}N_3O_3$ requires 360.2282.

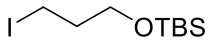
(3-Bromopropoxy)(*tert*-butyl)dimethylsilane 200[112]



200

Imidazole (5.45 g, 80.0 mmol) added to a solution of 3-bromopropanol (4.52 mL, 50.0 mmol) in DCM (50 mL) at rt. TBSCl (9.04 g, 60.0 mmol) was then added portion wise and stirred at rt for 16 h. Sat. $NaHCO_{3(aq)}$ (50 mL) was then added and the organics extracted with Et_2O (2 × 100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 95:5 hexane−EtOAc to yield TBS-protected alcohol **200** (12.4 g, 98%) as a colourless oil, R_f 0.57 (95:5 hexane-EtOAc); ν_{max}/cm^{-1} 2954, 2929, 2857, 1254, 1099, 1061, 951, 941, 892, 774 and 663; δ_H (400 MHz, $CDCl_3$) 3.73 (2H, t, *J* 5.7, CH_2OTBS), 3.52 (2H, t, *J* 5.7, CH_2Br), 2.03 (2H, p, *J* 5.7, CH_2CH_2Br), 0.90 (9H, s, $SiCMe_3$), 0.07 (6H, s, $SiMe_2$); δ_C (100 MHz, $CDCl_3$) 60.6 (CH_2OTBS), 35.7 (CH_2CH_2Br), 30.8 (CH_2Br), 26.1 ($SiCMe_3$), 18.5 ($SiCMe_3$), –5.2 ($SiMe_2$); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[112]

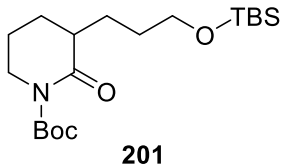
(3-Iodopropoxy)(*tert*-butyl)dimethylsilane 202[113]



202

NaI (8.40 g, 56.1 mmol) was added to alkyl bromide **200** (4.74 g, 22.7 mmol) in anhydrous acetone (15 mL) and heated at 60 °C for 20 min. Then the mixture was diluted with Et_2O (50 mL) and the solid removed *via* filtration. The solvent was then evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 4:1 hexane−EtOAc to yield alkyl iodide **202** (5.34 g, 78%) as a pale yellow oil, R_f 0.60 (2:1 hexane-EtOAc); ν_{max}/cm^{-1} 2953, 2928, 2856, 1471, 1254, 1097, 1052, 830 and 773; δ_H (400 MHz, $CDCl_3$) 3.67 (2H, t, *J* 5.7, CH_2OTBS), 3.27 (2H, t, *J* 5.7, CH_2I), 1.99 (2H, p, *J* 5.7, CH_2CH_2I), 0.90 (9H, s, $SiCMe_3$), 0.07 (6H, s, $SiMe_2$); δ_C (100 MHz, $CDCl_3$) 62.5 (CH_2OTBS), 36.3 (CH_2CH_2I), 26.1 ($SiCMe_3$), 18.5 (CH_2I), 3.9 ($SiCMe_3$), –5.2 ($SiMe_2$); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[113]

***tert*-Butyl 3-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-oxopiperidine-1-carboxylate 201**

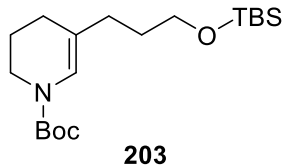


201

To a stirred solution of lactam **73** (49.6 mg, 0.50 mmol) in THF (1 mL) was added *n*-BuLi (0.63 mL of a 1.6 M solution in hexanes, 1.0 mmol) dropwise at –78 °C under N_2. The solution was stirred at –78 °C for 5 min and then allowed to warm to 0 °C over 30 min. Alkyl iodide **202** (150 mg, 0.5 mmol) in THF (1 mL) was then added at –78 °C and stirred for 1 h. Boc_2O (0.17 mL, 0.75 mmol) was then added at –78 °C and the

solution allowed to warm to rt over 16 h. Sat. $NHCO_{2(aq)}$ (5 mL) was then added and the layers separated. The aqueous layer was then extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$) and the solvent then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography eluting with 90:10 hexane−EtOAc to yield *lactam* **201** (39.1 mg, 21%) as a colourless oil, R_f 0.43 (8:2 hexane-EtOAc); ν_{max}/cm^{-1} 2952, 2930, 2857, 1770 (C=O), 1713 (C=O), 1290, 1250, 1147, 1094, 833 and 773; δ_H (500 MHz, $CDCl_3$) 3.73 (1H, ddd, *J* 12.7, 7.5, 5.0, 6-H_A), 3.66–3.54 (3H, m, 6-H_B, 9-H_2), 2.40 (1H, app. dtd, *J* 10.6, 7.0, 5.4, 3-H), 2.05–1.97 (1H, m, 4-H_A), 1.95–1.88 (1H, m, 7-H_A), 1.88–1.82 (1H, m, 5-H_A), 1.82–1.73 (1H, m, 5-H_B), 1.64–1.54 (2H, m, 8-H_2), 1.53–1.44 (12H, m, 4-H_B, 7-H_B, CMe_3), 0.87 (9H, s, $SiCMe_3$), 0.03 (6H, s, $SiMe_2$); δ_C (125 MHz, $CDCl_3$) 174.4 (C=O C-2), 153.2 (C=O Boc), 82.8 ($C(Me)_3$), 63.6 (C-9), 45.7 (C-6), 43.7 (C-3), 30.4 (C-8), 28.2 (CMe_3), 27.7 (C-7), 26.2 (C-4), 26.1 ($SiCMe_3$), 21.8 (C-5), 18.5 ($SiCMe_3$), –5.2 ($SiMe_2$); HRMS found MNa^+, 389.2386. $C_{19}H_{37}NO_4SiNa$ requires 394.2384.

tert-Butyl 5-(3-((tert-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2H)-carboxylate 203

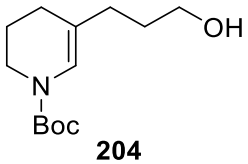


203

Compound **203** was prepared by a variation on the method of Yu *et al.*[55] Super-Hydride® (10.5 mL of a 1 M solution in THF, 10.5 mmol) was added dropwise to a solution of the lactam **201** (3.72 g, 10.0 mmol) in toluene (37 mL) at –78 °C and stirred for 30 min at –78 °C. Then, DIPEA (9.9 mL, 57.0 mmol), DMAP (24.4 mg, 2 mol%) and TFAA (1.7 mL, 12.0 mmol) were added and the resultant mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. Then, water (10 mL) was added and the two layers were separated and the aqueous layer was

extracted with DCM (2 × 10 mL). The organic layers were combined and washed with water (2 × 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with 95:5 hexane−EtOAc to yield *enecarbamate* **203** as a 60:40 mixture of rotamers (1.12 g, 32%) as a yellow oil, R_f 0.46 (8:2 hexane-EtOAc); ν_{max}/cm^{-1} 2930, 2858, 1698 (C=O), 1347, 1252, 1155, 1096, 833 and 774; δ_H (500 MHz, $CDCl_3$) 6.70–6.65 (0.4H, br m, 2-H), 6.55–6.48 (0.6H, br m, 2-H), 3.63–3.57 (2H, br m, 9-H_2), 3.52–3.24 (2H, br m, 6-H_2), 2.05–1.98 (2H, m, 7-H_2), 1.96 (2H, t, *J* 6.0, 4-H_2), 1.84–1.74 (2H, br m, 5-H_2), 1.61 (1H, app. p, *J* 7.8, 8-H_2), 1.48 (9H, s, CMe_3), 0.91–0.84 (9H, br m, $SiCMe_3$), 0.06–0.02 (6H, br m, $SiMe_2$); δ_C (125 MHz, $CDCl_3$) 153.0 (C=O Boc), 152.5 (C=O Boc), 120.7 (C-2), 120.2 (C-2), 118.1 (C-3), 117.4 (C-3), 80.4 (*C*$(Me)_3$), 80.2 (*C*$(Me)_3$), 63.1 (C-9), 62.7 (C-9), 42.3 (C-6), 41.3 (C-6), 31.8 (C-7), 31.7 (C-7), 31.3 (C-8), 31.1 (C-8), 28.5 (C*Me*$_3$), 26.1 (Si*CMe*$_3$), 25.2 (C-4), 25.1 (C-4), 22.1 (C-5), 21.9 (C-5), 18.5 (Si*C*Me_3), –5.1 ($SiMe_2$) (21 out of 28 signals present); HRMS found MNa^+, 378.2433. $C_{19}H_{37}NO_3SiNa$ requires 378.2434.

tert-Butyl 5-(3-hydroxypropyl)-3,4-dihydropyridine-1(2H)-carboxylate 204

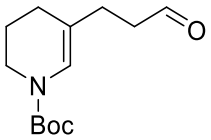


204

Compound **204** was prepared by a variation on the method of McLaughlin *et al*.[114] TBAF (5.1 mL of a 1M solution in THF, 5.1 mmol) was added dropwise to a suspension of TBS protected alcohol **203** (1.12 g, 3.15 mmol) in THF (20 mL) and the mixture stirred at rt for 16 h. Et_2O (30 mL) was then added and the mixture was washed with water (2 × 30 mL) and brine (30 mL) and then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield

slightly impure alcohol **204** as a 55:45 mixture of rotamers (588 mg, 77%) as a yellow oil, R_f 0.29 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3436 (OH), 2932, 2871, 1693 (C=O), 1392, 1365, 1254, 1153, 1077, 1041, 973, 766 and 734; δ_H (500 MHz, $CDCl_3$) 6.71 (0.45H, s, 2-H), 6.55 (0.55H, s, 2-H), 3.68–3.61 (2H, m, 9-H_2), 3.50 (1.1H, t, *J* 5.6, 6-H_2), 3.46 (0.9H, t, *J* 5.5, 6-H_2), 2.09–2.03 (2H, m, 7-H_2), 1.97 (2H, t, *J* 6.0, 4-H_2), 1.84–1.77 (2H, m, 5-H_2), 1.68 (2H, p, *J* 6.5, 8-H_2), 1.60 (1H, br s, OH), 1.48 (9H, s, C(Me)$_3$); δ_C (125 MHz, $CDCl_3$) 156.0 (C=O Boc), 152.5 (C=O Boc), 120.9 (C-2), 120.5 (C-2), 117.7 (C-3), 117.2 (C-3), 80.5 (*C*(Me)$_3$), 80.4 (*C*(Me)$_3$), 62.83 (C-9), 62.77 (C-9), 42.3 (C-6), 41.1 (C-6), 31.9 (C-7), 31.8 (C-7), 31.0 (C-8), 30.8 (C-8), 28.53 (C(*Me*)$_3$), 28.46 (C(*Me*)$_3$), 25.2 (C-4), 25.0 (C-4), 22.0 (C-5), 21.9 (C-5); HRMS found MNa^+, 264.1566. $C_{13}H_{23}NO_3Na$ requires 264.1570. Spectroscopic data are consistent with those reported in the literature.[115]

***tert*-Butyl 5-(3-oxopropyl)-3,4-dihydropyridine-1(2H)-carboxylate 206**

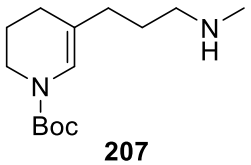


206

Compound **206** was prepared by a variation on the method of Pajouhesh *et al*.[106] DMP (459 mg, 0.880 mmol) was added, in several portions, to a solution of alcohol **204** (212 mg, 0.880 mmol) in DCM (4.9 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 16 h at room temperature. The resulting mixture was filtered and the filtrate was washed with brine (20mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. EtOAc (30 mL) was added, the resulting solid removed by filtration and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield slightly impure *aldehyde* **206** as a 55:45 mixture of rotamers (108 mg, 41%) as a colourless oil, R_f 0.50 (1:1

hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2931, 1603 (C=O), 1396, 1366, 1165, 766 and 750; δ_H (400 MHz, $CDCl_3$) 9.78 (1H, br s, CHO), 6.72 (0.45H, s, 2-H), 6.56 (0.55H, s, 2-H), 3.54–3.40 (2H, m, 6-H_2), 2.48–2.50 (2H, m, 8-H_2), 2.33 (2H, t, *J* 7.4, 7-H_2), 1.95 (2H, t, *J* 6.1, 4-H_2), 1.86–1.74 (2H, m, 5-H_2), 1.48 (9H, s, C(Me)$_3$); δ_C (100 MHz, $CDCl_3$) 202.5 (C=O C-9), 202.4 (C=O C-9), 152.9 (C=O Boc), 152.4 (C=O Boc), 121.6 (C-2), 121.1 (C-2), 116.0 (C-3), 115.4 (C-3), 80.7 (*C*(Me)$_3$), 80.5 (*C*(Me)$_3$), 42.4 (C-8), 42.3 (C-8), 42.2 (C-6), 41.2 (C-6), 28.6 (C(*Me*)$_3$), 28.5 (C(*Me*)$_3$), 28.02 (C-7), 27.95 (C-7), 25.2 (C-4), 25.1 (C-4), 21.9 (C-5), 21.7 (C-5); HRMS found MNa^+, 262.1410. $C_{13}H_{21}NO_3Na$ requires 262.1414.

tert-Butyl 5-(3-(methylamino)propyl)-3,4-dihydropyridine-1(2H)-carboxylate 207

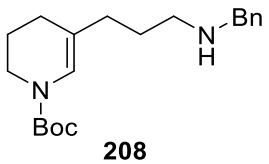


207

Compound **207** was prepared by a variation on the method of Kumpaty *et al*.[116] Ti(Oi-Pr)$_4$ (0.16 mL, 0.418 mmol) was added dropwise to a solution of $MeNH_2$ (0.63 mL of a 2 M solution in MeOH). A solution of aldehyde **206** (100 mg, 0.418 mmol) in MeOH (1 mL) was then added and the mixture stirred at rt for 5 h. $NaBH_4$ (15.8 mg, 0.418 mmol) was then added and the mixture stirred for 16 h. Water was then added (1 mL per 5 mmol aldehyde) and the inorganic precipitate filtered and washed with Et_2O (20 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL) then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 95:5 DCM: methanolic ammonia (7N) yield slightly impure *amine* **207** as a 55:45 mixture of rotamers (47.8 mg, 45%) as a colourless oil, R_f 0.12 (95:5 DCM: methanolic ammonia (7N)); ν_{max}/cm^{-1} 2935 (NH), 2864, 2774, 1692 (C=O), 1365, 1318, 1158, 1108 and 765; δ_H (500 MHz, $CDCl_3$) 6.65 (0.45H, s, 2-H), 6.50 (0.55H, s, 2-H), 3.47 (1.1H, t, *J* 5.6, 6-H_2), 3.43 (0.9H, t, *J* 5.4, 6-H_2), 2.53 (2H, app. q, *J*

8.0, 9-H_2), 2.42–2.37 (3H, m, Me), 2.02–1.96 (2H, m, 7-H_2), 1.96–1.91 (2H, m, 4-H_2), 1.81–1.72 (2H, m, 5-H_2), 1.57 (2H, p, *J* 7.5, 8-H_2), 1.46 (9H, s, $C(Me)_3$), 1.42 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 152.9 (C=O Boc), 152.4 (C=O Boc), 120.6 (C-2), 120.3 (C-2), 117.9 (C-3), 117.5 (C-3), 80.4 ($C(Me)_3$), 80.2 ($C(Me)_3$), 51.9 (C-9), 42.3 (C-6), 41.3 (C-6), 36.60 (Me), 36.57 (Me), 33.3 (C-7), 33.2 (C-7), 28.6 ($C(Me)_3$), 28.5 ($C(Me)_3$), 28.3 (C-8), 28.0 (C-8), 25.1 (C-4), 24.9 (C-4), 22.0 (C-5), 21.9 (C-5) (23 out of 24 signals present); HRMS found MH^+, 255.2066. $C_{14}H_{27}N_2O_2$ requires 255.2067.

tert-Butyl 5-(3-(benzylamino)propyl)-3,4-dihydropyridine-1(2H)-carboxylate 208

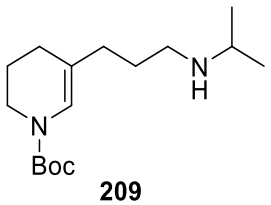


208

Compound **208** was prepared by a variation on the method of Kumpaty *et al*.[116] Ti(Oi-Pr)$_4$ (0.44 mL, 1.13 mmol) was added dropwise to a solution of benzylamine (0.37 mL, 3.39 mmol) in MeOH (2 mL). A solution of aldehyde **206** (271 mg, 1.13 mmol) in MeOH (1 mL) was then added and the mixture stirred at rt for 5 h. $NaBH_4$ (42.7 mg, 1.13 mmol) was then added and the mixture stirred for 16 h. Water was then added (1 mL per 5 mmol aldehyde) and the inorganic precipitate filtered and washed with Et_2O (20 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL) then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 98:2 DCM: methanolic ammonia (7N) yield *amine* **208** as a 55:45 mixture of rotamers (78.9 mg, 21%) as a colourless oil, R_f 0.23 (98:2 DCM: methanolic ammonia (7N)); ν_{max}/cm^{-1} 3062, 2974 (NH), 2839, 1696 (C=O), 1392, 1365, 1316, 1254, 1157, 1112, 984, 735 and 699; δ_H (500 MHz, $CDCl_3$) 7.35–7.29 (4H, m, Ph), 7.27–7.22 (1H, m, Ph), 6.68 (0.45H, s, 2-H), 6.52 (0.55H, s, 2-H), 3.79 (1.1H, s, 11-H_2), 3.78 (0.9H, s, 11-H_2), 3.48 (1.1H, t, *J* 5.5, 6-H_2), 3.45 (0.9H, t, *J* 5.6, 6-H_2), 2.63

(2H, t, *J* 6.8, 9-H_2), 2.01 (2H, t, *J* 7.3, 7-H_2), 1.95 (2H, t, *J* 5.8, 4-H_2), 1.82–1.72 (2H, m, 5-H_2), 1.63 (2H, p, *J* 7.4, 8-H_2), 1.54 (1H, br s, NH), 1.48 (9H, s, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 153.0 (C=O Boc), 152.5 (C=O Boc), 140.5 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 127.1 (Ph), 127.0 (Ph), 120.7 (C-2), 120.4 (C-2), 118.0 (C-3), 117.5 (C-3), 80.4 ($C(Me)_3$), 80.3 ($C(Me)_3$), 54.2 (C-11), 54.1 (C-11), 49.2 (C-9), 42.3 (C-6), 41.3 (C-6), 33.31 (C-7), 33.27 (C-7), 28.54 ($C(Me)_3$), 28.47 (C-8), 28.3 (C-8), 25.2 (C-4), 25.0 (C-4), 22.0 (C-5), 21.9 (C-5) (27 out of 32 signals present); HRMS found MH^+, 331.2390. $C_{20}H_{31}N_2O_2$ requires 331.2380.

tert-Butyl 5-(3-(isopropylamino)propyl)-3,4-dihydropyridine-1(2H)-carboxylate 209

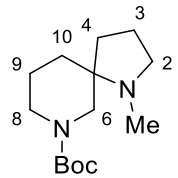


209

Compound **209** was prepared by a variation on the method of Kumpaty *et al*.[116] Ti(Oi-Pr)$_4$ (0.44 mL, 1.13 mmol) was added dropwise to a solution of isopropylamine (0.29 mL, 3.39 mmol) in MeOH (2 mL). A solution of aldehyde **206** (271 mg, 1.13 mmol) in MeOH (1 mL) was then added and the mixture stirred at rt for 5 h. $NaBH_4$ (42.7 mg, 1.13 mmol) was then added and the mixture stirred for 16 h. Water was then added (1 mL per 5 mmol aldehyde) and the inorganic precipitate filtered and washed with Et_2O (20 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL) then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 95:5 DCM: methanolic ammonia (7N) yield slightly impure *amine* **209** as a 55:45 mixture of rotamers (122 mg, 38%) as a colourless oil, R_f 0.42 (95:5 DCM: methanolic ammonia (7N)); ν_{max}/cm^{-1} 2965, 2930 (NH), 2869, 1695 (C=O), 1670, 1391, 1364, 1315, 1253, 1154, 1108, 984 and 763; δ_H (500 MHz, $CDCl_3$)

6.62 (0.45H, s, 2-H), 6.46 (0.55H, s, 2-H), 3.43 (1.1H, t, *J* 5.5, 6-H_2), 3.39 (0.9H, t, *J* 5.3, 6-H_2), 2.72 (1H, p, *J* 6.2, 11-H), 2.51 (2H, app. q, *J* 7.4, 9-H_2), 1.98–1.92 (2H, m, 7-H_2), 1.92–1.87 (2H, m, 4-H_2), 1.76–1.68 (2H, m, 5-H_2), 1.52 (2H, p, *J* 7.5, 8-H_2), 1.43 (9H, s, $C(Me)_3$), 1.38 (1H, br s, NH), 1.00–0.96 (6H, m, 12-H_6); δ_C (125 MHz, $CDCl_3$) 152.8 (C=O Boc), 152.3 (C=O Boc), 120.5 (C-2), 120.2 (C-2), 117.8 (C-3), 117.3 (C-3), 80.3 ($C(Me)_3$), 80.1 ($C(Me)_3$), 48.8 (C-11), 48.7 (C-11), 49.22 (C-9), 47.16 (C-9), 42.2 (C-6), 41.2 (C-6), 33.3 (C-7), 28.6 (C-8), 28.5 (C-8), 28.4 ($C(Me)_3$), 25.0 (C-4), 24.8 (C-4), 23.0 (C-12), 21.9 (C-5), 21.8 (C-5) (23 out of 26 signals present); HRMS found MNa^+, 305.2202. $C_{16}H_{30}N_2O_2Na$ requires 305.2199.

tert-Butyl 1-methyl-1,7-diazaspiro[4.5]decane-7-carboxylate 210

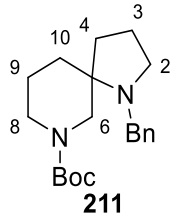


210

Compound **210** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (2.6 mg, 2 mol%), TRIP thiol (15 mg, 50 mol%) and enecarbamate **207** (32.6 mg, 0.128 mmol). Toluene (2.5 mL) was then added under N_2 and the resultant mixture was stirred for 48 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 98:2 DCM: methanolic ammonia (7N) to yield *[6,5] spirocycle* **210** as 60:40 mixture of rotamers (20.1 mg, 62%) as a yellow oil, R_f 0.42 (95:5 DCM: methanolic ammonia (7N)); ν_{max}/cm^{-1} 2930, 2867, 1690 (C=O), 1422, 1366, 1157 and 764; δ_H (500 MHz, $CDCl_3$) 4.22–4.07 (0.6H, br m, 8-H_A), 4.05–3.94 (0.4H, br m, 8-H_A), 3.87–3.76 (0.4H, br m, 6-H_A), 3.74–3.62 (0.6H, br m, 6-H_A), 2.92–2.72 (2H, br m, 2-H_2), 2.70–2.44 (2H, br m, 6-H_B, 8-H_B), 2.36 (3H, s, Me), 1.89–1.72 (3H, m, 3-H_A, 9-H_2), 1.68–1.48 (5H, m, 3-H_B, 4-H_2, 10-H_2), 1.45–1.43 (9H, br m,

$C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 79.5 ($C(Me)_3$), 61.5 (C-5), 49.1 (C-6), 46.8 (C-6), 44.7 (C-8), 43.7 (C-8), 34.5 (Me), 33.8 (Me), 33.2 (C-3), 31.5 (C-4), 28.6 ($C(Me)_3$), 23.9 (C-10), 23.4 (C-10), 21.4 (C-9) (15 out of 24 signals present); Expected mass not observed in HRMS.

***tert*-Butyl 1-benzyl-1,7-diazaspiro[4.5]decane-7-carboxylate 211**

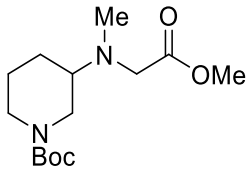


211

Compound **211** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [$Ir(dF(Me)ppy)_2(dtbbpy)PF_6$] (2.6 mg, 2 mol%), TRIP thiol (14 mg, 50 mol%) and enecarbamate **208** (41.3 mg, 0.125 mmol). Toluene (2.5 mL) was then added under N_2 and the resultant mixture was stirred for 48 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 99:1 DCM: methanolic ammonia (7N) to yield *[6,5] spirocycle* **211** as an undetermined mixture of rotamers (12.0 mg, 29%) as a yellow oil, R_f 0.67 (98:2 DCM: methanolic ammonia (7N)); ν_{max}/cm^{-1} 2971, 2931, 2866, 1687 (C=O), 1422, 1368, 1248, 1154, 841 and 650; δ_H (500 MHz, $CDCl_3$) 7.38–7.27 (4H, m, Ph), 7.25–7.19 (1H, m, Ph), 4.24–3.85 (2H, br, 6-H_A, 8-H_A), 3.85–3.73 (1H, br m, Bn CH_2), 3.61 (1H, d, *J* 11.9, Bn CH_2), 2.91–2.48 (4H, br m, 2-H_2, 6-H_B, 8-H_B), 1.79–1.52 (8H, br m, 3-H_2, 4-H_2, 9-H_2, 10-H_2), 1.48–1.43 (9H, br m, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Boc), 128.7 (Ph), 128.4 (Ph), 128.3 (Ph), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 126.9 (Ph), 79.5 ($C(Me)_3$), 62.2 (C-5), 52.8 (Bn CH_2), 52.7 (Bn CH_2), 51.5 (C-2), 49.4 (C-6), 44.7 (C-8), 43.8 (C-8), 34.1 (C-3), 33.4 (C-4), 32.8 (C-4), 28.6 ($C(Me)_3$), 24.0 (C-10),

23.7 (C-10), 21.3 (C-9) (23 out of 32 signals present); HRMS found MH^+, 331.2380. $C_{20}H_{31}N_2O_2$ requires 331.2380.

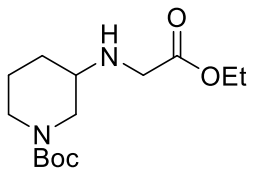
tert-Butyl 3-((2-methoxy-2-oxoethyl)(methyl)amino)piperidine-1-carboxylate 228



228

Compound **228** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF$_6$] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), sarcosine methyl ester hydrochloride (70.0 mg, 0.50 mmol), enecarbamate **65** (45.8 mg, 0.25 mmol) and lithium hydroxide monohydrate (21.0 mg, 0.50 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 72 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **228** as a 1:1 mixture of rotamers (3.0 mg, 4%) as a colourless oil, R_f 0.40 (EtOAc); ν_{max}/cm^{-1} 2931, 2860, 1738 (C=O), 1689 (C=O), 1421, 1392, 1264, 1241, 1174, 1152, 844 and 767; δ_H (500 MHz, $CDCl_3$) 4.30–3.98 (1H, br m, 2-H$_A$), 3.97–3.86 (1H, br m, 6-H$_A$), 3.71 (3H, s, 11-Me), 3.42 (1H, d, *J* 17.2, 8-H$_2$), 3.26 (1H, d, *J* 16.9, 8-H$_2$), 2.75–2.51 (3H, br m, 3-H, 2-H$_B$, 6-H$_B$), 2.45 (3H, s, 7-Me), 1.99–1.91 (1H, br m, 4-H$_A$), 1.76–1.67 (1H, br m, 5-H$_A$), 1.45 (9H, s, C(Me)$_3$), 1.43–1.31 (2H, br m, 4-H$_B$, 5-H$_B$); δ_C (125 MHz, $CDCl_3$) 172.05 (C=O C-9), 155.0 (C=O Boc), 79.7 (*C*(Me)$_3$), 58.9 (C-3), 55.2 (C-8), 51.7 (C-11), 39.6 (C-7), 29.9 (C-4), 28.6 (C(*Me*)$_3$), 24.4 (C-5) (10 out of 12 signals present); HRMS found MH^+, 287.1966. $C_{14}H_{27}N_2O_4$ requires 287.1965.

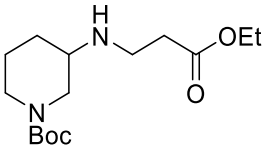
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate 231**



231

Compound **231** was synthesised using general method B using enecarbamate **65** (45.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **231** as a 1:1 mixture of rotamers (59.0 mg, 82%) as a yellow oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 2967, 2932, 2859, 1738 (C=O), 1688 (C=O), 1420, 1365, 1238, 1153, 1026, 844 and 768; δ_H (500 MHz, $CDCl_3$) 4.16 (2H, q, *J* 7.1, 11-H_2), 4.07–3.78 (1H, m, 2-H_A), 3.74 (1H, app. dt, *J* 13.1, 4.2, 6-H_A), 3.43 (1H, d, *J* 17.3, 8-H_A), 3.39 (1H, d, *J* 17.3, 8-H_B), 2.91–2.79 (1H, m, 6-H_B), 2.78–2.56 (1H, m, 2-H_B), 2.56–2.46 (1H, m, 3-H), 1.92–1.84 (1H, m, 4-H_A), 1.73 (1H, br s, NH), 1.70–1.62 (1H, m, 5-H_A), 1.46–1.37 (10H, m, 5-H_B, $C(Me)_3$), 1.33–1.27 (1H, m, 4-H_B), 1.25 (3H, t, *J* 7.1, 12-H_3); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O C-9), 154.9 (C=O Boc), 79.6 ($C(Me)_3$), 61.0 (C-11), 53.6 (C-3), 49.4 (C-2), 48.7 (C-2), 48.5 (C-8), 44.7 (C-6), 43.9 (C-6), 31.4 (C-4), 28.5 ($C(Me)_3$), 23.8 (C-5), 23.4 (C-5), 14.3 (C-12) (15 out of 24 signals present); HRMS found MH^+, 287.1965. $C_{14}H_{27}N_2O_4$ requires 287.1965. Spectroscopic data are consistent with those reported in the literature.[60]

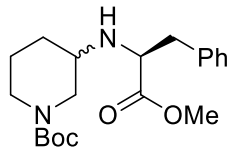
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate 232**



232

Compound **232** was synthesised using general method B using enecarbamate **65** (45.8 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **232** as a 1:1 mixture of rotamers (59.8 mg, 80%) as a yellow oil, R_f 0.11 (EtOAc); ν_{max}/cm^{-1} 2976, 2932, 2856, 1731 (C=O), 1687 (C=O), 1466, 1392, 1238, 1150 and 767; δ_H (500 MHz, $CDCl_3$) 4.11 (2H, q, *J* 7.1, 12-H_2), 4.07–3.80 (1H, m, 2-H_A), 3.79–3.75 (0.5H, m, 6-H_A), 3.75–3.72 (0.5H, m, 6-H_A), 2.96–2.77 (3H, m, 6-H_B, 8-H_2), 2.76–2.49 (2H, m, 2-H_B, 3-H), 2.45 (2H, app. dd, *J* 14.6, 8.2, 9-H_2), 1.92–1.83 (1H, m, 4-H_A), 1.69–1.60 (1H, m, 5-H_A), 1.49–1.35 (11H, m, NH, 5-H_B, C$(Me)_3$), 1.29–1.16 (4H, m, 4-H_B, 13-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-10), 155.0 (C=O Boc), 79.5 (*C*$(Me)_3$), 60.5 (C-11), 53.7 (C-3), 49.5 (C-2), 49.1 (C-2), 44.7 (C-6), 43.9 (C-6), 42.4 (C-8), 35.2 (C-9), 31.6 (C-4), 28.5 (C(*Me*)$_3$), 23.9 (C-5), 23.5 (C-5), 14.3 (C-13) (16 out of 26 signals present); HRMS found MH^+, 301.2131. $C_{15}H_{29}N_2O_4$ requires 301.2122. Spectroscopic data are consistent with those reported in the literature.[60]

tert-Butyl 3-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate _(S)_-233

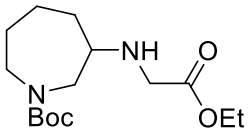


(S)-**233**

Compound *(S)*-**233** was synthesised using general method B using enecarbamate **65** (45.8 mg, 0.25 mmol) and L-phenylalanine methyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amino ester (S)*-**233** as an unresolved mixture of rotamers and diastereomers (139 mg, 51%) as a yellow oil, R_f 0.64 (EtOAc); ν_{max}/cm^{-1} 2975, 2931, 2857, 1736 (C=O), 1688 (C=O), 1422, 1365, 1261, 1239, 1172, 1151, 766 and 700; δ_H (500 MHz, $CDCl_3$) 7.30–7.26 (2H, m, Ph), 7.24–7.20

(1H, m, Ph), 7.18–7.14 (2H, m, Ph), 3.94–3.68 (2H, m, 2-H_A, 6-H_A), 3.69–3.58 (4H, m, OMe, 8-H), 2.97–2.86 (2H, m, 9-H_2), 2.80 (1H, ddd, *J* 13.5, 12.1, 6.7, 6-H_B), 2.66 (0.5H, dd, *J* 12.6, 9.1, 2-H_B), 2.57–2.46 (1H, m, 3-H, 2-H_B), 2.45–2.36 (0.5H, m, 3-H), 1.85–1.74 (1H, m, 4-H_A), 1.68–1.60 (1H, m, 5-H_A), 1.56 (1H, br s, NH), 1.44 (9H, m, C(Me)$_3$), 1.42–1.30 (1H, m, 5-H_B), 1.30–1.21 (0.5H, m, 4-H_B), 1.16 (0.5H, ddd, *J* 13.1, 12.1, 3.8, 4-H_B); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O CO_2Me), 175.3 (C=O CO_2Me), 155.0 (C=O Boc), 137.4 (*ipso*-Ph), 137.3 (*ipso*-Ph), 130.4 (Ph), 129.3 (Ph), 128.6 (Ph), 128.5 (Ph), 126.8 (Ph), 79.6 (*C*(Me)$_3$), 79.1 (*C*(Me)$_3$), 60.4 (C-8), 52.7 (C-3), 51.9 (OMe), 51.8 (OMe), 49.4 (C-2), 48.6 (C-2), 44.6 (C-6), 43.8 (C-6), 40.3 (C-9), 40.1 (C-9), 32.1 (C-4), 30.7 (C-4), 28.58 (C(*Me*)$_3$), 28.57 (C(*Me*)$_3$), 23.8 (C-5), 23.4 (C-5) (28 out of 32 signals present); HRMS found MNa^+, 385.2103. $C_{20}H_{30}N_2O_4Na$ requires 385.2098.

tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate 234

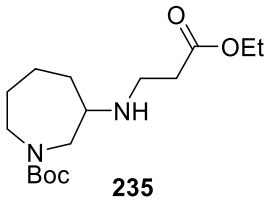


234

Compound **234** was synthesised using general method B using enecarbamate **54** (49.3 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **234** as a 60:40 mixture of rotamers (68.2 mg, 42%) as a yellow oil, R_f 0.25 (EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2864, 1738 (C=O), 1687 (C=O), 1365, 1298, 1162, 842 and 771; δ_H (500 MHz, $CDCl_3$) 4.20 (1.2H, q, *J* 7.1, 12-H_2), 4.17 (0.8H, q, *J* 7.1, 12-H_2), 3.76 (0.4H, dd, *J* 14.0, 3.9, 2-H_A), 3.70–3.62 (1.2H, m, 2-H_A, 7-H_A), 3.55–3.49 (0.4H, m, 7-H_B), 3.48 (0.8H, m, 9-H_2), 3.45 (1.2H, m, 9-H_2), 3.22–3.09 (1H, m, 7-H_A, 7-H_B), 2.89 (0.4H, dd, *J* 14.0, 8.5, 2-H_B), 2.84–2.72 (1H, m, 2-H_B, 3-H), 2.66–2.58 (0.6H, m, 3-H), 1.90–1.79 (1.6H, m, 4-H_A, 6-H_A), 1.79–1.42 (1.4H, m, 5-H_A, 6-H_A) 1.64 (1H, br s, NH), 1.61–1.55 (1H, m, 6-H_B), 1.47

(5.4H, s, $C(Me)_3$), 1.45 (3.6H, s, $C(Me)_3$), 1.41–1.31 (2H, m, 4-H_B, 5-H_B), 1.27 (1.8H, t, *J* 7.0, 13-H_3), 1.26 (1.2H, t, *J* 7.0, 13-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-10), 156.0 (C=O Boc), 155.7 (C=O Boc), 79.6 (*C*$(Me)_3$), 79.4 (*C*$(Me)_3$), 61.0 (C-12), 60.9 (C-12), 58.5 (C-3), 58.0 (C-3), 50.7 (C-2), 50.2 (C-2), 49.2 (C-9), 48.9 (C-9), 47.9 (C-7), 46.8 (C-7), 35.3 (C-4), 34.3 (C-4), 28.6 (C(*Me*)$_3$), 27.9 (C-6), 27.5 (C-6), 22.8 (C-5), 22.7 (C-5), 14.4 (C-13), 14.3 (C-13) (24 out of 26 signals present); HRMS found MH^+, 301.2133. $C_{15}H_{29}N_2O_4$ requires 301.2122. Spectroscopic data are consistent with those reported in the literature.[181]

tert-Butyl 3-((3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate 235

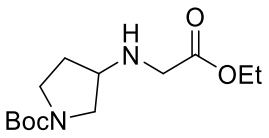


235

Compound **235** was synthesised using general method B using enecarbamate **54** (49.3 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **235** as a 55:45 mixture of rotamers (56.6 mg, 36%) as a yellow oil, R_f 0.11 (EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2859, 1732 (C=O), 1689 (C=O), 1468, 1413, 1365, 1299, 1164 and 772; δ_H (500 MHz, $CDCl_3$) 4.14 (1.1H, q, *J* 7.0, 13-H_2), 4.12 (0.9 H, q, *J* 7.0, 13-H_2), 3.80 (0.45H, dd, *J* 13.7, 4.0, 2-H_A), 3.73 (0.55H, dd, *J* 13.8, 3.1, 2-H_A), 3.69 (0.55H, ddd, *J* 14.5, 8.3, 3.0, 7-H_A), 3.50 (0.45H, ddd, *J* 14.5, 8.3, 3.0, 7-H_A), 3.20–3.09 (1H, m, 7-H_B), 2.94 (1.1H, t, *J* 6.0, 9-H_2), 2.93 (0.9H, t, *J* 6.0, 9-H_2), 2.85 (0.45H, dd, *J* 13.7, 8.6, 2-H_B), 2.81–2.72 (1H, m, 2-H_B, 3-H), 2.72–2.65 (0.55H, m, 3-H), 2.48 (2H, t, *J* 5.9, 10-H_2), 1.89–1.78 (1.55H, m, 4-H_A, 6-H_A), 1.78–1.69 (1.45H, m, 5-H_A, 6-H_A) 1.62–1.51 (2H, m, NH, 6-H_B), 1.47 (4.95H, s, $C(Me)_3$), 1.45 (4.05H, s, $C(Me)_3$), 1.41–1.29 (2H, m, 4-H_B, 5-H_B), 1.26 (1.65H, t, *J* 7.1,

14-H_3), 1.25 (1.35H, t, *J* 7.1, 14-H_3); δ_C (125 MHz, $CDCl_3$) 173.0 (C=O C-11), 172.8 (C=O C-11), 156.0 (C=O Boc), 155.7 (C=O Boc), 79.5 (*C*$(Me)_3$),79.3 (*C*$(Me)_3$), 60.6 (C-13), 60.5 (C-13), 58.4 (C-3), 57.9 (C-3), 51.2 (C-2), 50.7 (C-2), 48.0 (C-7), 46.9 (C-7), 42.9 (C-9), 35.31 (C-10), 35.27 (C-10), 35.2 (C-4), 34.2 (C-4), 28.7 (C(*Me*)$_3$), 28.6 (C(*Me*)$_3$), 28.0 (C-6), 27.6 (C-6), 22.9 (C-5), 22.8 (C-5), 14.4 (C-14) (21 out of 28 signals present); HRMS found MNa^+, 337.2099. $C_{16}H_{30}N_2O_4Na$ requires 337.2098.

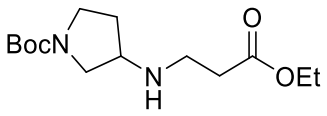
tert-Butyl 3-((2-ethoxy-2-oxoethyl)amino)pyrrolidine-1-carboxylate 236



236

Compound **236** was synthesised using general method B using enecarbamate **81** (42.3 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield amino ester **236** as a 1:1 mixture of rotamers (77.2 mg, 57%) as a yellow oil, R_f 0.27 (EtOAc); ν_{max}/cm^{-1} 2976, 2934, 2879, 1738 (C=O), 1693 (C=O), 1404, 1168, 1114 and 772; δ_H (500 MHz, $CDCl_3$) 4.19 (2H, q, *J* 7.1, 10-H_2), 3.54–3.42 (2H, m, 2-H_A, 5-H_A), 3.42–3.38 (2H, m, 7-H_2), 3.38–3.33 (1H, m, 5-H_B), 3.32–3.28 (1H, m, 3-H), 3.15 (0.5H, dd, *J* 10.9, 4.3, 2-H_B), 3.08 (0.5H, dd, *J* 10.8, 5.0, 2-H_B), 2.01 (1H, app. td, *J* 12.9, 6.2, 4-H_A), 1.73 (1H, app. dd, *J* 11.7, 5.4, 4-H_B), 1.66 (1H, br s, NH), 1.45 (9H, s, C$(Me)_3$), 1.28 (3H, t, *J* 7.1, 11-H_3); δ_C (125 MHz, $CDCl_3$) 172.5 (C=O C-8), 154.8 (C=O Boc), 154.7 (C=O Boc), 79.3 (*C*$(Me)_3$), 61.1 (C-10), 57.4 (C-3), 56.6 (C-3), 52.0 (C-2), 51.4 (C-2), 49.4 (C-7), 49.3 (C-7), 44.5 (C-5), 44.1 (C-5), 32.1 (C-4), 31.4 (C-4), 28.7 (C(*Me*)$_3$), 14.4 (C-11) (17 out of 22 signals present); HRMS found MH^+, 273.1809. $C_{13}H_{25}N_2O_4$ requires 273.1809. Spectroscopic data are consistent with those reported in the literature.[181]

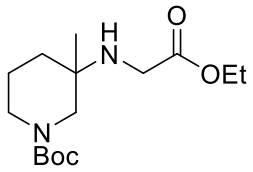
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate 237**



237

Compound **237** was synthesised using general method B using enecarbamate **81** (42.3 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester* **237** as a 1:1 mixture of rotamers (89.5 mg, 63%) as a yellow oil, R_f 0.10 (EtOAc); ν_{max}/cm^{-1} 2976, 2932, 2873, 1733 (C=O), 1692 (C=O), 1405, 1167 and 771; δ_H (500 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.1, 11-H_2), 3.56 (0.5H, dd, *J* 10.7, 6.1, 2-H_A), 3.52 (0.5H, dd, *J* 11.2, 4.8, 2-H_A), 3.50–3.38 (1H, m, 5-H_A), 3.38–3.31 (1H, m, 5-H_B), 3.31–3.26 (1H, m, 3-H), 3.10 (0.5H, dd, *J* 10.7, 5.0, 2-H_B), 3.02 (0.5H, dd, *J* 10.6, 5.7, 2-H_B), 2.93–2.82 (2H, m, 7-H_2), 2.50 (2H, t, *J* 6.4, 8-H_2), 2.04 (1H, app. td, *J* 13.0, 5.9, 4-H_A), 1.73 (1H, app. d5, *J* 15.2, 7.3, 4-H_B), 1.49 (1H, br s, NH), 1.45 (9H, s, C$(Me)_3$), 1.26 (3H, t, *J* 7.1, 12-H_3); δ_C (125 MHz, $CDCl_3$) 172.8 (C=O C-9), 154.8 (C=O Boc), 79.3 (*C*$(Me)_3$), 60.7 (C-11), 57.8 (C-3), 57.0 (C-3), 52.1 (C-2), 51.7 (C-2), 44.6 (C-5), 44.2 (C-5), 43.5 (C-7), 35.0 (C-8), 32.2 (C-4), 31.5 (C-4), 28.7 (C(*Me*)$_3$), 14.4 (C-12) (16 out of 24 signals present); HRMS found MH^+, 287.1969. $C_{14}H_{27}N_2O_4$ requires 287.1965.

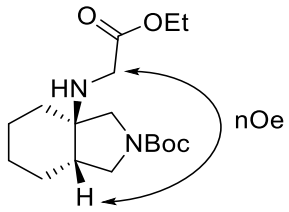
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 238**



238

Compound **238** was synthesised using general method B using enecarbamate **65** (45.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in duplicate and the contents of the two vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *amino ester* **238** as an undetermined mixture of rotamers (69.3 mg, 46%) as a yellow oil, R_f 0.33 (EtOAc); ν_{max}/cm^{-1} 2974, 2933, 2862, 1740 (C=O), 1692 (C=O), 1424, 1366, 1276, 1165 and 765; δ_H (500 MHz, $CDCl_3$) 4.18 (2H, q, *J* 6.9, 11-H_2), 3.59–3.50 (1H, m, 6-H_A), 3.48–3.32 (3H, m, 2-H_A, 8-H_2), 3.18–3.09 (1H, m, 6-H_B), 3.00 (1H, d, *J* 13.0, 2-H_B), 1.68–1.58 (3H, m, NH, 4-H_B, 5-H_B), 1.54–1.46 (2H, m, 4-H_B, 5-H_B), 1.45 (9H, s, $C(Me)_3$), 1.27 (3H, t, *J* 7.1, 12-H_3), 1.03 (3H, s, 13-Me); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O C-9), 155.1 (C=O Boc), 79.7 ($C(Me)_3$), 61.0 (C-11), 51.2 (C-2), 44.2 (C-8), 43.6 (C-6), 36.3 (C-4), 28.6 ($C(Me)_3$), 23.0 (Me-13), 21.6 (C-5), 14.4 (C-12) (12 out of 13 signals present); HRMS found MH^+, 301.2206. $C_{15}H_{29}N_2O_4$ requires 301.2207.

tert-Butyl 3a-((2-ethoxy-2-oxoethyl)amino)octahydro-2H-isoindole-2-carboxylate _cis_-239

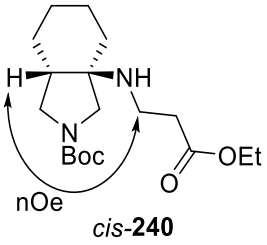


cis-**239**

Compound *cis*-**239** was synthesised using general method B using enecarbamate **70** (55.8 mg, 0.25 mmol) and glycine ethyl ester hydrochloride (70.0 mg, 0.50 mmol). Reaction was performed in triplicate and the contents of the three vials combined before work-up. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *amino ester cis*-**239** as a 1:1 mixture of rotamers (138 mg, 56%) as a yellow oil, R_f 0.34 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2929, 2857, 1738 (C=O), 1694 (C=O), 1392, 1365, 1172, 1097, 881 and 772; δ_H (500

MHz, $CDCl_3$) 4.19 (1H, q, *J* 7.1, 14-H_2), 4.18 (1H, q, *J* 7.1, 14-H_2), 3.54–3.46 (1H, m, 9-H_A), 3.40 (1H, d, *J* 16.9, 11-H_A), 3.35–3.28 (1.5H, m, 2-H_A, 11-H_B), 3.27–3.21 (1H, m, 2-H_A, 9-H_B), 3.19–3.12 (1H, m, 2,-H_B, 9-H_B), 3.09 (0.5H, d, *J* 10.8, 2-H_B), 1.98 (1H, app. q, *J* 6.8, 8-H), 1.80 (1H, br s, NH), 1.68 (1H, app. dt, *J* 12.7, 8.5, 4-H_A), 1.61–1.49 (4H, m, 5-H_2, 6-H_2), 1.45 (4.5H, s, C(Me)$_3$), 1.45 (4.5H, s, C(Me)$_3$), 1.40–1.31 (3H, m, 4-H_B, 7-H_2), 1.27 (1.5H, t, *J* 7.1, 15-H_3), 1.27 (1.5H, t, *J* 7.1, 15-H_3); δ_C (125 MHz, $CDCl_3$) 172.9 (C=O C-12), 172.8 (C=O C-12), 155.4 (C=O Boc), 155.3 (C=O Boc), 79.34 (*C*(Me)$_3$), 79.32 (*C*(Me)$_3$), 61.2 (C-14), 60.5 (C-3), 59.9 (C-3), 54.6 (C-2), 53.4 (C-2), 49.7 (C-9), 48.9 (C-9), 44.8 (C-11), 44.7 (C-11), 42.5 (C-8), 41.2 (C-8), 29.71 (C-4), 29.68 (C-4), 28.7 (C(*Me*)$_3$), 25.7 (C-7), 25.1 (C-7), 22.5, 22.2, 22.02, 21.96 (C-5, C-6), 14.3 (C-15) (27 out of 30 signals present); HRMS found MNa^+, 349.2098. $C_{17}H_{30}N_2O_4Na$ requires 349.2098. The stereochemistry was assigned through positive NOESY interaction between 8-H and 11-H_2.

tert-Butyl 3a-((3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate _cis_-240

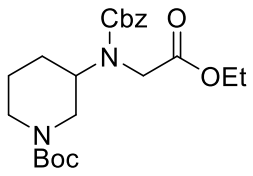


cis-**240**

Compound *cis*-**240** was synthesised using general method B using enecarbamate **70** (55.8 mg, 0.25 mmol) and ethyl 3-aminopropionate hydrochloride (75.0 mg, 0.50 mmol). The crude product was purified by flash column chromatography eluting with EtOAc to yield *amino ester cis*-**240** as a 1:1 mixture of rotamers (37.9 mg, 45%) as a yellow oil, R_f 0.20 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2858, 1733 (C=O), 1694 (C=O), 1042, 1366, 1174, 1155, 1101, 844 and 769; δ_H (500 MHz, $CDCl_3$) 4.13 (1H, q, *J* 7.1, 15-H_2), 4.12 (1H, q, *J* 7.1, 15-H_2), 3.50–3.41 (1H, m, 9-H_A), 3.32 (0.5H, d, *J* 10.8, 2-H_A), 3.26–3.20 (1H, m, 2-H_A, 9-H_B), 3.19–3.08 (1.5H, m, 2-H_B, 9-H_B), 2.86 (1H, dt, *J*

11.4, 5.3, 11-H_A), 2.69 (1H, dt, *J* 11.4, 5.3, 11-H_B), 2.45 (2H, app. td, *J* 6.3, 4.1, 12-H_2), 1.98 (1H, app. dd, *J* 12.7, 6.3, 8-H), 1.67–1.56 (2H, m, 4-H_A, 7-H_A), 1.56–1.47 (3H, m, NH, 5-H/6-H), 1.46–1.42 (9H, m, 5-H/6-H, C(Me)$_3$), 1.40–1.30 (3H, m, 5-H/6-H, 7-H_B), 1.25 (1.5H, t, *J* 7.1, 16-H_3), 1.25 (1.5H, t, *J* 7.1, 16-H_3); δ_C (125 MHz, $CDCl_3$) 172.99 (C=O C-13), 172.95 (C=O C-13), 155.39 (C=O Boc), 155.38 (C=O Boc), 79.22 (*C*(Me)$_3$), 79.19 (*C*(Me)$_3$), 60.6 (C-15), 60.5 (C-15), 60.4 (C-3), 59.8 (C-3), 55.1 (C-2), 54.2 (C-2), 49.4 (C-9), 48.7 (C-9), 42.1 (C-8), 41.1 (C-8), 38.1 (C-11), 38.0 (C-11), 35.83 (C-12), 35.82 (C-12), 29.5 (C-4), 29.4 (C-4), 28.7 (C(*Me*)$_3$), 25.2 (C-7), 24.9 (C-7), 22.3, 22.1, 22.0, 21.9 (C-5, C-6), 14.4 (C-16) (30 out of 32 signals present); HRMS found MH^+, 341.2437. $C_{18}H_{33}N_2O_4$ requires 341.2435. The stereochemistry was assigned through positive NOESY interaction between 8-H and 11-H_2.

tert-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)piperidine-1-carboxylate 241

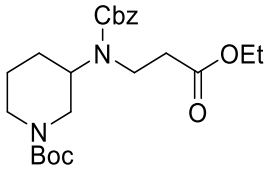


241

Compound **241** was synthesised using general method C using benzyl chloroformate (55.0 µL, 0.385 mmol), amino ester **231** (100 mg, 0.35 mmol) and $NaHCO_3$ (175 mg, 2.1 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **241** as a 60:40 mixture of rotamers (120 mg, 82%) as a pale yellow oil, R_f 0.55 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2936, 2860, 1752, 1687 (C=O), 1409, 1364, 1238, 1177, 1149, 1113, 1028, 992, 771 and 698; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.20 (0.8H, s, Cbz CH_2), 5.12 (1.2H, s, Cbz CH_2), 4.23–3.84 (7H, m, 2-H_A, 6-H_A, 3-H, 8-H_2, 11-H_2), 2.72 (0.6H, app. t, *J* 11.8, 6-H_B), 2.65 (0.4H, app. t, *J* 11.8, 6-H_B), 2.60–2.45 (1H, m, 2-H_B), 2.02–1.89 (1H, m, 4-H_A), 1.77–1.69 (1H, m, 5-H_A), 1.59–1.47 (2H, m, 4-H_B, 5-H_B), 1.45

(5.4H, m, $C(Me)_3$), 1.40 (3.6H, m, $C(Me)_3$), 1.28 (1.8H, t, *J* 7.1, 12-H_3), 1.17 (1.2H, t, *J* 7.1, 12-H_3); δ_C (125 MHz, $CDCl_3$) 170.1 (C=O C-9), 156.3 (C=O Cbz), 155.5 (C=O Cbz), 154.9 (C=O Boc), 154.8 (C=O Boc), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 127.9 (Ph), 79.9 (*C*$(Me)_3$), 67.9 (CH_2 Cbz), 67.5 (CH_2 Cbz), 61.4 (C-11), 53.3 (C-3), 47.3 (C-6), 45.7 (C-8), 43.4 (C-2), 29.1 (C-4), 28.5 (C(*Me*)$_3$), 24.8 (C-5), 14.3 (C-12), 14.2 (C-12) (24 out of 36 signals present); HRMS found MNa^+, 443.2157. $C_{22}H_{32}N_2O_6Na$ requires 443.2153. Spectroscopic data are consistent with those reported in the literature.[182]

tert-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)piperidine-1-carboxylate 242[60]

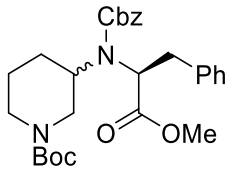


242

Compound **242** was synthesised using general method C using benzyl chloroformate (22.0 µL, 0.169 mmol), amino ester **232** (46.2 mg, 0.154 mmol) and $NaHCO_3$ (77.0 mg, 0.924 mmol) in DCM (2 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **242** as a 55:45 mixture of rotamers (66.9 mg, 100%) as a colourless oil, R_f 0.42 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2937, 2867, 1732, 1688 (C=O), 1416, 1264, 1239, 1149, 1112, 770 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.27 (5H, m, Ph), 5.12 (2H, s, Cbz CH_2), 4.17–3.93 (4H, m, 2-H_A, 6-H_A, 12-H_2), 3.72 (1H, app. t, *J* 10.8, 3-H), 3.59–3.40 (2H, m, 8-H_2), 2.92–2.81 (0.55H, m, 2-H_B), 2.80–2.69 (0.45H, m, 2-H_B), 2.67–2.43 (3H, m, 6-H_B, 9-H_2), 1.85–1.65 (3H, m, 4-H_2, 5-H_A), 1.57–1.33 (10H, m, 5-H_B, $C(Me)_3$), 1.24 (3H, t, *J* 7.1, 13-H_3); δ_C (125 MHz, $CDCl_3$) 171.6 (C=O C-10), 171.2 (C=O C-10), 155.8 (C=O Boc), 155.6 (C=O Boc), 154.8 (C=O Cbz), 136.6 (*ipso*-Ph), 128.6 (Ph), 128.1 (Ph), 127.9 (Ph), 79.9 (*C*$(Me)_3$), 67.3 (CH_2 Cbz), 60.7 (C-12), 60.5 (C-12), 54.5 (C-3), 54.1 (C-3), 47.0 (C-2),

44.0 (C-6), 43.2 (C-6), 40.9 (C-8), 35.4 (C-9), 34.7 (C-9), 29.2 (C-4), 28.5 (C(*Me*)$_3$), 25.0 (C-5), 14.29 (C-13), 14.27 (C-13) (25 out of 38 signals present); HRMS found MNa^+, 457.2319. $C_{23}H_{34}N_2O_6Na$ requires 457.2309.

tert-Butyl 3-(((benzyloxy)carbonyl)((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)piperidine-1-carboxylate _(S)_-243

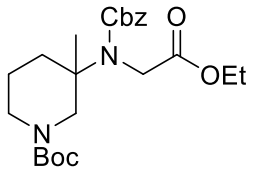


(S)-**243**

Compound *(S)*-**243** was synthesised using general method C using benzyl chloroformate (52 µL, 0.364 mmol), amino ester *(S)*-**233** (120 mg, 0.331 mmol) and $NaHCO_3$ (167 mg, 1.99 mmol) in DCM (5 mL) for 96 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield impure *carbamate (S)*-**243** as an unknown mixture of diastereomers and rotamers (53.3 mg, ~32%) as a colourless oil, R_f 0.67 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2950, 2859, 1743 (C=O), 1688 (C=O), 1420, 1268, 1238, 1174, 1149, 754 and 700; δ_H (500 MHz, $CDCl_3$) 7.41–7.32 (6H, m, Ph), 7.25–7.17 (2H, m, Ph), 7.13–7.06 (2H, m, Ph), 5.34–5.03 (2H, m, Cbz CH_2), 4.31–3.83 (3H, m, 2-H_A, 6-H_A, 8-H), 3.80–3.48 (4H, m, OMe, 3-H), 3.45–3.37 (1H, m, CH_2Ph), 3.34–3.04 (1H, m, CH_2Ph), 2.82–2.54 (1H, m, 2-H_B), 2.47–2.24 (1H, m, 6-H_B), 1.66–1.52 (1H, m, 5-H_A), 1.59–1.34 (9H, m, C(Me)$_3$), 1.35–1.22 (1H, m, 5-H_B), 1.21–0.78 (2H, m, 4-H_2); δ_C (125 MHz, $CDCl_3$) 171.6 (C=O CO_2Me), 171.4 (C=O CO_2Me), 155.6, 155.3, 154.8, 154.6 (C=O Cbz/Boc), 138.4 (*ipso*-Ph), 138.1 (*ipso*-Ph), 136.6 (*ipso*-Ph), 136.2 (*ipso*-Ph), 129.8 (Ph), 129.6 (Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 128.0 (Ph), 127.7 (Ph), 127.1 (Ph), 79.7 (*C*(Me)$_3$), 79.6 (*C*(Me)$_3$), 67.6 (Cbz CH_2), 67.4 (Cbz CH_2), 59.4 (C-8), 54.1 (C-3), 53.7 (C-3), 52.5 (OMe), 52.4 (OMe), 47.3 (C-2), 43.5 (C-6), 37.2 (CH_2Ph), 35.9 (CH_2Ph), 28.9 (C-4), 28.53 (C(*Me*)$_3$), 28.50 (C(*Me*)$_3$), 25.0

(C-5) (35 out of 44 signals present); HRMS found MH^+, 497.2656. $C_{28}H_{37}N_2O_6$ requires 497.2646.

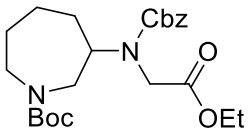
tert-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)-3-methylpiperidine-1-carboxylate 244



244

Compound **244** was synthesised using general method C using benzyl chloroformate (34 µL, 0.239 mmol), amino ester **238** (65.0 mg, 0.217 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **244** as an undetermined mixture of rotamers (73.7 mg, 78%) as a colourless oil, R_f 0.54 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2977, 2934, 2868, 1750 (C=O), 1699 (C=O), 1425, 1227, 1189, 1156, 1114, 775 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.26 (5H, m, Ph), 5.12 (2H, br s, Cbz CH_2), 4.25–3.99 (4H, br m, 11-H_2, 8-H_2), 3.97–3.75 (1H, br m, 2-H_A), 3.66–3.44 (1H, br m, 6-H_A), 3.42–3.01 (2H, br m, 2-H_B, 6-H_B), 2.95–2.37 (1H, br m, 4-H_A), 1.73–1.50 (3H, br m, 4-H_B, 5-H_2), 1.44 (9H, s, $C(Me)_3$), 1.42 (3H, br s, 13-Me), 1.23–1.13 (3H, br m, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.2 (C=O C-9), 154.7 (C=O Boc/Cbz), 136.6 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 127.1 (Ph), 80.1 ($C(Me)_3$), 67.2 (Cbz CH_2), 61.1 (C-11), 57.7 (C-3), 52.8 (C-2), 46.7 (C-8), 43.4 (C-6), 34.6 (C-4), 28.5 ($C(Me)_3$), 22.8 (C-5), 21.8 (Me-13), 14.2 (C-12); HRMS found MH^+, 435.2490. $C_{23}H_{35}N_2O_6$ requires 435.2490.

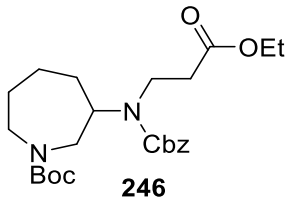
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)azepane-1-carboxylate 245**



245

Compound **245** was synthesised using general method C using benzyl chloroformate (34 µL, 0.239 mmol), amino ester **234** (65.0 mg, 0.217 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **245** as a 65:35 mixture of rotamers (65.5 mg, 70%) as a colourless oil, R_f 0.64 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2930, 1691 (C=O), 1394, 1365, 1156, 981 and 768; δ_H (500 MHz, $CDCl_3$) 7.42–7.27 (5H, m, Ph), 5.23–5.14 (0.7H, m, Cbz CH_2), 5.14–5.04 (1.3H, m, Cbz CH_2), 4.19 (0.7H, q, *J* 7.1, 12-H_2), 4.15–4.02 (1.95H, m, 3-H, 12-H_2), 4.01–3.86 (2.35H, m, 3-H, 9-H_2), 3.81–3.68 (0.65H, m, 2-H_A), 3.66–3.43 (1.35H, m, 2-H_A, 7-H_A), 3.38–3.02 (2H, m, 2-H_B, 7-H_B), 2.01–1.72 (3H, m, 4-H_A, 5-H_A, 6-H_A), 1.70–1.51 (3H, m, 4-H_B, 5-H_B, 6-H_B), 1.50–1.42 (7.5H, m, $C(Me)_3$), 1.38 (1.5H, s, $C(Me)_3$), 1.27 (1.05H, t, *J* 6.8, 13-H_3), 1.17 (1.95H, t, *J* 6.8, 13-H_3); δ_C (125 MHz, $CDCl_3$) 170.2 (C=O C-10), 170.3 (C=O C-10), 156.1 (C=O Boc), 155.5 (C=O Cbz), 136.6 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.91 (Ph), 127.87 (Ph), 79.9 ($C(Me)_3$), 79.6 ($C(Me)_3$), 67.4 (Cbz CH_2), 61.3 (C-12), 61.2 (C-12), 58.5 (C-3), 58.0 (C-3), 49.5 (C-2), 49.0 (C-2), 47.6 (C-7), 47.2 (C-7), 46.9 (C-9), 46.5 (C-9), 31.8 (C-4), 31.0 (C-4), 28.6 ($C(Me)_3$), 28.5 ($C(Me)_3$), 28.1 (C-6), 27.5 (C-6), 23.8 (C-5), 23.6 (C-5), 14.3 (C-13), 14.2 (C-13) (34 out of 38 signals present); HRMS found MH^+, 435.2494. $C_{23}H_{35}N_2O_6$ requires 435.2490.

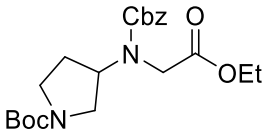
***tert*-Butyl 3-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)azepane-1-carboxylate 246**



246

Compound **246** was synthesised using general method C using benzyl chloroformate (27.5 µL, 0.193 mmol), amino ester **235** (55.0 mg, 0.175 mmol) and $NaHCO_3$ (87.9 mg, 1.05 mmol) in DCM (2 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **246** as an undetermined mixture of rotamers (72.7 mg, 93%) as a colourless oil, R_f 0.52 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2933, 2869, 1731 (C=O), 1692 (C=O), 1657 (C=O), 1416, 1213, 1162, 1115, 770 and 699; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m , Ph), 5.19–5.06 (2H, br m, Cbz CH_2), 4.19–4.03 (2H, br m, 13-H_2), 3.81–2.95 (7H, m, 2-H_2, 3-H, 7-H_2, 9-H_2), 2.72–2.49 (2H, m, 10-H_2), 2.01–1.68 (4H, br m, 4-H_2, 5-H_A, 6-H_A) 1.63–1.58 (1H, m, 6-H_B), 1.52–1.37 (9H, br m, $C(Me)_3$), 1.33–1.18 (4H, br m, 5-H_B, 14-H_3); δ_C (125 MHz, $CDCl_3$) 171.7 (C=O C-11), 171.6 (C=O C-11), 155.7, 155.4 (C=O Boc, Cbz), 136.8 (*ipso*-Ph), 128.71 (Ph), 128.67 (Ph), 128.6 (Ph), 128.1 (Ph), 127.8 (Ph), 127.1 (Ph), 80.0 ($C(Me)_3$), 79.6 ($C(Me)_3$), 67.4 (Cbz CH_2), 67.1 (Cbz CH_2), 60.7 (C-13), 60.6 (C-13), 59.6 (C-3), 49.5 (C-2), 48.9 (C-2), 46.7 (C-7), 46.1 (C-7), 43.2 (C-9), 42.7 (C-9), 35.0 (C-10), 34.4 (C-10), 32.1 (C-4), 31.6 (C-4), 28.6 ($C(Me)_3$), 27.5 (C-6), 27.2 (C-6), 24.1 (C-5), 23.5 (C-5), 14.3 (C-14) (28 out of 40 signals present); HRMS found MH^+, 449.2652. $C_{24}H_{37}N_2O_6$ requires 449.2646.

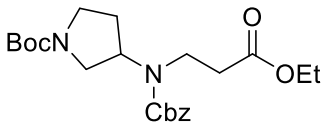
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)pyrrolidine-1-carboxylate 247**



247

Compound **247** was synthesised using general method C using benzyl chloroformate (43 μL, 0.304 mmol), amino ester **236** (75.0 mg, 0.276 mmol) and $NaHCO_3$ (139 mg, 1.66 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **247** as a 60:40 mixture of rotamers (105 mg, 94%) as a colourless oil, R_f 0.37 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2977, 2877, 1750 (C=O), 1694 (C=O), 1404, 1365, 1198, 1169, 1135, 771 and 643; δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.17 (0.8H, br s, Cbz CH_2), 5.13 (1.2H, br s, Cbz CH_2), 4.86–4.75 (0.6H, br m, 3-H), 4.70–4.59 (0.4H, br m, 3-H), 4.26–4.15 (0.8H, br m, 10-H_2), 4.15–4.06 (1.2H, br m, 10-H_2), 4.04–3.81 (2H, m, 7-H_2), 3.61 (1H, dd, *J* 11.3, 7.9, 2-H_A), 3.53–3.36 (1H, br m, 5-H_A), 3.35–3.21 (1H, br m, 5-H_B), 3.20–3.09 (1H, dd, br m, 2-H_B), 2.16–2.04 (1H, br m, 4-H_B), 1.95–1.83 (1H, br m, 4-H_B), 1.44 (9H, s, $C(Me)_3$), 1.30–1.22 (1.2H, br m, 11-H_3), 1.22–1.13 (1.8H, br m, 11-H_3); δ_C (125 MHz, $CDCl_3$) 170.0 (C=O C-8), 154.8 (C=O Cbz), 154.5 (C=O Boc), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.0 (Ph), 79.8 ($C(Me)_3$), 68.0 (Cbz CH_2), 67.8 (Cbz CH_2), 61.5 (C-10), 55.3 (C-3), 54.6 (C-3), 55.3 (C-2), 54.6 (C-2), 45.5 (C-7), 45.2 (C-7), 44.5 (C-5), 43.9 (C-5), 28.6 ($C(Me)_3$), 28.5 (C-4), 14.2 (C-11) (25 out of 34 signals present); HRMS found MH^+, 407.2172. $C_{21}H_{31}N_2O_6$ requires 407.2177.

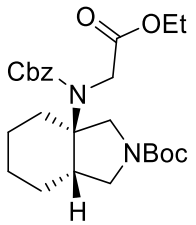
***tert*-Butyl 3-((3-ethoxy-3-oxopropyl)amino)pyrrolidine-1-carboxylate 248**



248

Compound **248** was synthesised using general method C using benzyl chloroformate (47 μL, 0.327 mmol), amino ester **237** (85.0 mg, 0.297 mmol) and $NaHCO_3$ (149 mg, 1.78 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **248** as a mixture of rotamers (112 mg, 89%) as a colourless oil, R_f 0.37 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2978, 2894, 1733 (C=O), 1694 (C=O), 1404, 1168, 1132 and 771; δ_H (500 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 5.15 (2H, s, Cbz CH_2), 4.66–4.49 (1H, br m, 3-H), 4.11 (2H, q, *J* 7.0, 11-H_2), 3.64–3.41 (4H, m, 2-H_A, 5-H_A, 7-H_2), 3.31–3.09 (2H, m, 2-H_B, 5-H_B), 2.66–2.47 (2H, br m, 8-H_2), 2.05–1.97 (2H, br m, 4-H_2), 1.45 (9H, s, $C(Me)_3$), 1.24 (3H, t, *J* 6.9, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.5 (C=O C-9), 155.9 (C=O Cbz), 154.8 (C=O Boc), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.1 (Ph), 79.7 ($C(Me)_3$), 67.6 (Cbz CH_2), 60.8 (C-11), 55.9 (C-3), 55.1 (C-3), 47.5 (C-2), 44.4 (C-5), 43.9 (C-5), 40.3 (C-7), 34.9 (C-8), 29.1 (C-4), 28.6 ($C(Me)_3$), 14.3 (C-12) (20 out of 36 signals present); HRMS found MH^+, 421.2331. $C_{22}H_{33}N_2O_6$ requires 421.2333.

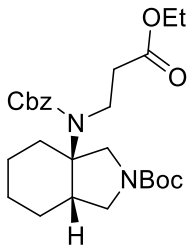
***tert*-Butyl 3a-(((benzyloxy)carbonyl)(2-ethoxy-2-oxoethyl)amino)octahydro-2H-isoindole-2-carboxylate *cis*-249**



cis-**249**

Compound *cis*-**249** was synthesised using general method C using benzyl chloroformate (66 µL, 0.465 mmol), amino ester *cis*-**239** (138 mg, 0.423 mmol) and $NaHCO_3$ (212 mg, 2.54 mmol) in DCM (4 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 8:2 hexane−EtOAc to yield *carbamate cis*-**249** as a 60:40 mixture of rotamers (133 mg, 68%) as a pale yellow oil, R_f 0.50 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2976, 2931, 2863, 1749, 1691 (C=O), 1393, 1365, 1174, 1128, 1100, 774 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.22–4.98 (2H, m, Cbz CH_2), 4.45–4.19 (1H, m, 2-H_A), 4.07–4.15 (2H, m 14-H_2), 4.00–3.72 (2H, m, 2-H_B, 11-H_A), 3.57 (1H, d, *J* 15.8, 11-H_B), 3.49–3.40 (1H, m, 9-H_A), 3.25 (0.6H, dd, *J* 10.8, 7.3, 9-H_B), 3.14 (0.4H, dd, *J* 10.7, 5.0, 9-H_B), 2.70–2.54 (0.4H, m, 8-H), 2.52–2.41 (0.6H, m, 8-H), 1.75–1.61 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.53–1.47 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.45 (4.5H, s, $C(Me)_3$), 1.44 (4.5H s, $C(Me)_3$), 1.40–1.33 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.33–1.24 (2H, m, 4-H_2 or 5-H_2, 6-H_2 or 7H_2), 1.24–1.12 (3H, m, 15-H_3); δ_C (125 MHz, $CDCl_3$) 170.9 (C=O C-12), 170.7 (C=O C-12), 154.8 (C=O Boc or Cbz), 128.6 (Ph), 128.1 (Ph), 128.0 (Ph), 79.64 (*C*$(Me)_3$), 79.57 (*C*$(Me)_3$), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 61.4 (C-14), 61.3 (C-14), 60.6 (C-3), 50.2 (C-9), 48.8 (C-9), 47.0 (C-11), 38.9 (C-8), 28.4 (C-4), 28.6 (C(*Me*)$_3$), 26.2 (C-7), 22.3, 21.6 (C-5, C-6), 14.4 (C-15), 14.3 (C-15) (24 out of 42 signals present); HRMS found MNa^+, 483.2478. $C_{25}H_{36}N_2O_6Na$ requires 483.2466.

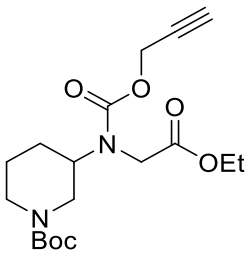
tert-Butyl 3a-(((benzyloxy)carbonyl)(3-ethoxy-3-oxopropyl)amino)octahydro-2H-isoindole-2-carboxylate _cis_-250



cis-**250**

Compound *cis*-**250** was synthesised using general method C using benzyl chloroformate (16 µL, 0.109 mmol), amino ester *cis*-**240** (33.6 mg, 99.0 µmol) and $NaHCO_3$ (50.0 mg, 0.594 mmol) in DCM (1 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 8:2 hexane−EtOAc to yield *carbamate cis*-**250** as a 60:40 mixture of rotamers (43.0 mg, 92%) as a pale yellow oil, R_f 0.56 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2975, 2930, 1733, 1691 (C=O), 1397, 1365, 1165, 1126, 1097, 774 and 698; δ_H (500 MHz, $CDCl_3$) 7.38–7.28 (5H, m, Ph), 5.18–5.07 (2H, Cbz CH_2), 4.10 (1.2H, q, *J* 7.1, 15-H_2), 4.08 (0.8H, q, *J* 7.1, 15-H_2), 3.84–3.75 (1H, m, 11-H_A), 3.73 (0.4H, d, *J* 12.5, 2-H_A), 3.72 (0.6H, d, *J* 12.5, 2-H_A), 3.59–3.46 (2H, m, 2-H_B, 11-H_B), 3.43 (0.6H, dd, *J* 10.8, 7.2, 9-H_A), 3.39 (0.4H, dd, *J* 10.7, 6.7, 9-H_A), 3.21 (0.6H, dd, *J* 10.8, 5.3, 9-H_B), 3.11 (0.4H, dd, *J* 10.7, 4.1, 9-H_B), 3.00–2.92 (0.4H, m, 8-H), 2.89–2.80 (0.6H, m, 8-H), 2.64–2.46 (2H, m, 12-H_2), 2.35–2.25 (1H, m, 4-H_A), 1.79–1.69 (1H, m, 7-H_A), 1.64–1.49 (3H, m, 4-H_B, 5-H/6-H), 1.48–1.43 (12H, m, 5-H/6-H, 7-H_B $C(Me)_3$), 1.23 (1.8H, t, *J* 7.1, 16-H_3), 1.22 (1.2H, t, *J* 7.1, 16-H_3); δ_C (125 MHz, $CDCl_3$) 171.4 (C=O C-13), 155.61 (C=O Cbz), 155.56 (C=O Cbz), 154.9 (C=O Boc), 154.8 (C=O Boc), 128.66 (Ph), 128.65 (Ph), 128.14 (Ph), 128.10 (Ph), 127.91 (Ph), 127.86 (Ph), 79.7 (*C*$(Me)_3$), 79.6 (*C*$(Me)_3$), 67.14 (Cbz CH_2), 67.08 (Cbz CH_2), 65.9 (C-3), 65.7 (C-3), 60.70 (C-15), 60.66 (C-15), 54.0 (C-2), 52.4 (C-2), 50.4 (C-9), 49.5 (C-9), 40.8 (C-11), 40.7 (C-11), 39.8 (C-8), 38.9 (C-8), 35.7 (C-12), 35.5 (C-12), 29.19 (C-4), 29.16 (C-4), 28.6 (C(*Me*)$_3$), 28.1 (C-7), 27.4 (C-7), 22.9, 22.72, 22.65, 22.3 (C-5, C-6), 14.29 (C-16), 14.25 (C-16) (40 out of 44 signals present); HRMS found MNa^+, 497.2631. $C_{26}H_{38}N_2O_6Na$ requires 497.2622.

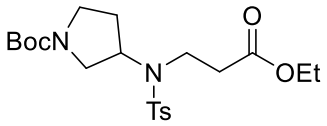
***tert*-Butyl 3-((2-ethoxy-2-oxoethyl)((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate 251**



251

Compound **251** was synthesised using general method C using propargyl chloroformate (40 µL, 0.322 mmol), amino ester **231** (83.9 mg, 0.293 mmol) and $NaHCO_3$ (145 mg, 1.76 mmol) in DCM (3 mL) for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **251** as a 55:45 mixture of rotamers (96.9 mg, 91%) as a colourless oil, R_f 0.30 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3250 (C≡C-H), 2978, 2941, 2864, 2132 (C≡C), 1750 (C=O), 1684 (C=O), 1409, 1366, 1299, 1264, 1238, 1176, 1147, 1108, 1026, 991 and 769; δ_H (500 MHz, $CDCl_3$) 4.81–4.65 (2H, m, POC 3-H_2), 4.21 (0.9H, q, *J* 7.1, 11-H_2), 4.19 (1.1H, q, *J* 7.1, 11-H_2), 4.16–3.79 (5H, m, 2-H_A, 3-H, 6-H_A, 8-H_2), 2.72 (0.55H, app. t, *J* 11.9, 6-H_B), 2.66 (0.45H, app. t, *J* 11.9, 6-H_B), 2.61–2.49 (1H, m, 2-H_B), 2.47 (0.45H, t, *J* 2.2, POC 5-H), 2.43 (0.55H, t, *J* 2.1, POC 5-H), 2.01–1.90 (1H, m, 4-H_A), 1.76–1.67 (1H, m, 5-H_A), 1.59–1.50 (2H, m, 4-H_B, 5-H_B), 1.46 (4.05H, s, C(Me)$_3$), 1.45 (4.95H, m, C(Me)$_3$), 1.27 (3H, t, *J* 7.3, 12-H_3); δ_C (125 MHz, $CDCl_3$) 169.9 (C=O C-9), 155.5, 154.9, 154.8, 154.7 (C=O POC/Boc), 80.0 (*C*(Me)$_3$), 78.2 (POC C-4), 75.0 (POC C-5), 74.7 (POC C-5), 61.51 (C-11), 61.47 (C-11), 53.6 (C-3), 53.4 (POC C-3), 53.3 (POC C-3), 45.8 (br, C-6/C-8), 43.4 (br, C-2), 29.0 (C-4), 28.5 (C(*Me*)$_3$), 28.4 (C-4), 24.8 (C-5), 14.31 (C-12), 14.28 (C-12) (22 out of 32 signals present); HRMS found MH^+, 369.2019. $C_{18}H_{29}N_2O_6$ requires 369.2020.

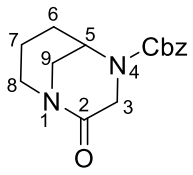
***tert*-Butyl 3-((*N*-(3-ethoxy-3-oxopropyl)-4-methylphenyl)sulfonamido)pyrrolidine-1-carboxylate 252**



252

Tosyl chloride (195 mg, 0.341 mmol), DIPEA (169 µL, 0.341 mmol) and DMAP (4.1 mg, 5 mol%) were added in sequence to a mixture of amino ester **237** (195 mg, 0.681 mmol) in DCM (7 mL). The mixture was stirred for 16 h at room temperature, and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **252** as a 1:1 mixture of rotamers (287 mg, 96%) as a yellow oil, R_f 0.31 (6:4 hexane-EtOAc); ν_{max}/cm^{-1} 2978, 2933, 2884, 1731 (C=O), 1694 (C=O), 1402, 1344, 1157, 1108, 663 and 548; δ_H (500 MHz, $CDCl_3$) 7.75–7.66 (2H, m, Ar), 7.35–7.27 (2H, m, Ar), 4.52–4.42 (0.5H, br m, 3-H), 4.42–4.32 (0.5H, br m, 3-H), 4.14 (2H, q, *J* 7.1, 11-H_2), 3.52–3.26 (4H, m, 2-H_A, 5-H_A, 7-H_2), 3.21–3.11 (1H, m, 5-H_B), 2.96–2.85 (1H, m, 2-H_B), 2.85–2.67 (2H, br m, 8-H_2), 2.44 (3H, s, Me), 2.05–1.95 (0.5H, br m, 4-H_2), 1.91–1.80 (1H, br m, 4-H_2), 1.80–1.71 (0.5H, br m, 4-H_2), 1.42 (9H, s, $C(Me)_3$), 1.26 (3H, t, *J* 7.1, 12-H_3); δ_C (125 MHz, $CDCl_3$) 171.4 (C=O C-9), 144.0 (*ipso*-Ar), 135.7 (*ipso*-Ar), 135.6 (*ipso*-Ar), 130.1 (Ar), 127.8 (Ar), 79.9 ($C(Me)_3$), 60.9 (C-11), 56.7 (C-3), 56.1 (C-3), 47.6 (C-2), 46.4 (C-2), 43.9 (C-5), 43.5 (C-5), 39.84 (C-7), 39.75 (C-7), 36.72 (C-8), 36.65 (C-8), 29.4 (C-4), 27.9 (C-4), 28.5 ($C(Me)_3$), 21.7 (Me), 14.3 (C-12) (23 out of 34 signals present); HRMS found MNa^+, 463.1877. $C_{21}H_{32}N_2O_6SNa$ requires 463.1873.

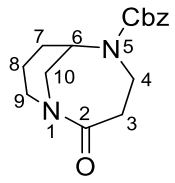
Benzyl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 253



253

Compound **253** was synthesised using general method D using NaOH (11.5 mg, 0.288 mmol), amino ester **241** (110 mg, 0.262 mmol), 1:1 MeOH:water (4.4 mL), HCl (2.9 mL, 6 N), EtOAc (0.4 mL), toluene (3.5 mL) and *n*-Bu_2SnO (65.7 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate* **253** as a 55:45 mixture of rotamers (41.7 mg, 58%) as a colourless oil, R_f 0.35 (EtOAc); ν_{max}/cm^{-1} 2927, 2859, 1686 (C=O), 1407, 1156, 1090, 1008, 765 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (5H, m, Ph), 5.22–5.06 (2H, s, Cbz CH_2), 4.50 (0.45H, d, *J* 15.5, 3-H_A), 4.41 (0.55H, d, *J* 15.3, 3-H_A), 4.15–4.04 (2H, m, 8-H_A, 5-H), 3.55 (1H, app. d, *J* 14.3, 9-H_A), 3.82 (0.55H, d, *J* 15.3, 3-H_B), 3.77 (0.45H, d, *J* 15.3, 3-H_B), 3.21 (1H, app. t, *J* 15.0, 9-H_B), 2.94 (1H, app. qd, *J* 13.1, 3.2, 8-H_B), 2.27–2.19 (0.55H, m, 6-H_B), 2.13–2.04 (0.45H, m, 6-H_A), 1.89–1.76 (1H, m, 7-H_A), 1.72–1.66 (1H, m, 6-H_B), 1.45–1.35 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$) 180.2 (C=O C-2), 155.4 (C=O Cbz), 154.9 (C=O Cbz), 136.4 (*ipso*-Ph), 136.3 (*ipso*-Ph), 128.70 (Ph), 128.69 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 67.63 (CH_2 Cbz), 67.56 (CH_2 Cbz), 52.1 (C-8), 51.9 (C-8), 51.2 (C-9), 51.1 (C-9), 50.2 (C-5), 49.7 (C-5), 48.8 (C-3), 48.7 (C-3), 28.8 (C-6), 27.7 (C-6), 21.1 (C-7), 21.0 (C-7) (21 out of 26 signals present); HRMS found MNa^+, 297.1209. $C_{15}H_{18}N_2O_3Na$ requires 297.1210.

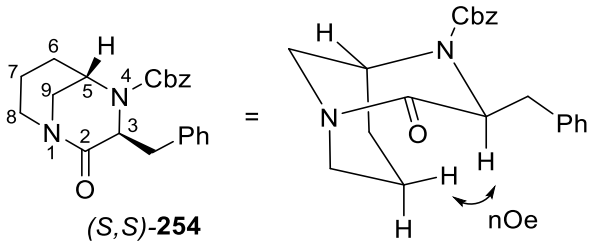
Benzyl 2-oxo-1,5-diazabicyclo[4.3.1]decane-5-carboxylate 225[60]



225

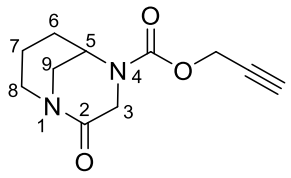
Compound **225** was synthesised using general method D using NaOH (50.9 mg, 0.127 mmol), amino ester **242** (50.0 mg, 0.115 mmol), 1:1 MeOH:water (2 mL), HCl (1.3 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (29.0 mg). The crude product was purified by flash column chromatography, eluting with 3:1 EtOAc-hexane to yield bicyclic carbamate **225** as a 1:1 mixture of rotamers (25.4 mg, 77%) as a colourless oil, R_f 0.30 (EtOAc); ν_{max}/cm^{-1} 2931, 1688 (C=O), 1657 (C=O), 1409, 1223, 1093, 1067, 1008, 735 and 698; δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 5.15 (1H, d, *J* 12.3, Cbz CH_2), 5.11 (1H, d, *J* 12.3, Cbz CH_2), 4.48 (1H, app. dd, *J* 11.6, 5.8, 6-H), 4.35 (1H, ddd, *J* 14.0, 7.7, 6.0, 9-H_A), 4.28 (1H, app. d, *J* 11.6, 4-H_A), 3.72 (1H, app. d, *J* 15.6, 10-H_A), 3.36 (1H, app. t, *J* 11.6, 4-H_B), 3.25 (1H, app. dd, *J* 15.1, 5.0, 10-H_B), 3.05 (1H, app. dt, *J* 14.2, 3.6, 3-H_A), 2.95 (1H, app. dt, *J* 12.8, 5.7, 9-H_B), 2.49 (1H, ddd, *J* 14.3, 5.4, 2.2, 3-H_B), 1.88–1.79 (1H, m, 7-H_A), 1.78–1.65 (2H, m, 8-H_A, 7-H_B), 1.56–1.49 (1H, m, 8-H_B); δ_C (125 MHz, $CDCl_3$) 176.8 (C=O C-2), 156.2 (C=O Cbz), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 67.8 (CH_2 Cbz), 50.0 (C-6), 49.4 (C-10), 45.6 (C-9), 39.8 (C-4), 36.9 (C-3), 24.0 (C-7), 20.6 (C-8); HRMS found MNa^+, 311.1374. $C_{16}H_{20}N_2O_3Na$ requires 311.1366. Spectroscopic data are consistent with those reported in the literature.[60]

Benzyl (3S,5S)-3-benzyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate *(S,S)*-254



Compound *(S,S)*-**254** was synthesised using general method D using NaOH (4.4 mg, 0.111 mmol), amino ester *(S,S)*-**243** (50.0 mg, 0.101 mmol), 1:1 MeOH:water (2 mL), HCl (1.1 mL, 6 N), EtOAc (0.2 mL), toluene (1.3 mL) and *n*-Bu_2SnO (25.3 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate (S,S)*-**254** as a single diastereomer and as a 60:40 mixture of rotamers (4.4 mg, 12%) as a colourless oil, R_f 0.62 (EtOAc); ν_{max}/cm^{-1} 2956, 2869, 1684 (C=O), 1404, 1266, 1160, 1108 and 699; δ_H (500 MHz, $CDCl_3$) 7.40–7.31 (5H, m, Ph), 7.31–7.26 (1H, m, Ph), 7.25–7.16 (3H, m, Ph), 7.06–7.02 (1H, m, Ph), 5.19 (0.4H, d, *J* 12.4, Cbz CH_2), 5.16 (0.4H, d, *J* 12.4, Cbz CH_2), 5.08 (0.6H, d, *J* 12.0, Cbz CH_2), 4.99 (0.6H, d, *J* 12.0, Cbz CH_2), 4.90 (0.4H, dd, *J* 9.8, 5.3, 5-H), 4.77 (0.6H, dd, *J* 9.2, 5.9, 5-H), 4.20 (0.6H, app. br s, 2-H), 4.10 (0.4H, app. br s, 2-H), 4.08–4.01 (1H, m, 8-H_A), 3.71 (0.6H, app. d, *J* 14.5, 9-H_A), 3.55 (0.4H, app. d, *J* 14.5, 9-H_A), 3.28 (0.4H, dd, *J* 13.4, 5.3, CH_2Ph), 3.22 (0.6H, dd, *J* 14.5, 1.5, 9-H_B), 3.14–3.19 (1H, m, 9-H_B, CH_2Ph), 3.09–3.02 (1H, m, CH_2Ph), 3.02–2.89 (1H, m, 8-H_B), 2.20 (0.6H, app. d, *J* 13.3, 7-H_A), 2.03 (0.4H, app. d, *J* 13.3, 6-H_A), 1.86–1.65 (2H, m, 6-H_B, 7-H_A), 1.47–1.35 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$) 181.4 (C=O C-2), 179.9 (C=O C-2), 136.8 (*ipso*-Ph), 136.7 (*ipso*-Ph), 129.4 (Ph), 129.2 (Ph), 128.8 (Ph), 128.48 (Ph), 128.45 (Ph), 128.3 (Ph), 128.1 (Ph), 127.1 (Ph), 67.7 (CH_2 Cbz), 67.5 (CH_2 Cbz), 62.8 (C-3), 53.6 (C-8), 53.5 (C-8), 49.8 (C-9), 49.7 (C-5), 49.1 (C-5), 40.4 (CH_2Ph), 39.4 (CH_2Ph), 29.0 (C-6), 27.8 (C-6), 21.52 (C-7), 21.45 (C-7) (26 out of 36 signals present); HRMS found MH^+, 365.1871. $C_{22}H_{25}N_2O_3$ requires 365.1860. Stereochemistry of *(S,S)*-**254** assigned by a positive nOe observed between 3-H and 7-H_A.

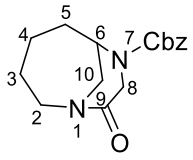
Prop-2-yn-1-yl 2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 255



255

Compound **255** was synthesised using general method D using NaOH (7.0 mg, 0.175 mmol), amino ester **251** (58.5 mg, 0.159 mmol), 1:1 MeOH:water (2.4 mL), HCl (1.5 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (39.5 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate* **255** as a 55:45 mixture of rotamers (18.7 mg, 53%) as a colourless oil, R_f 0.49 (EtOAc); ν_{max}/cm^{-1} 3247, 2953, 2867, 2126 (C≡C), 1691 (C=O), 1409, 1382, 1159, 1093, 1009 and 764; δ_H (500 MHz, $CDCl_3$) 4.78–4.72 (1.45H, m, POC 3-H_2), 4.68 (0.55, dd, *J* 15.6, 2.4, POC 3-H_2), 4.48 (0.45H, d, *J* 15.5, 3-H_A), 4.39 (0.55H, d, *J* 15.3, 3-H_A), 4.14–4.04 (2H, m, 8-H_A, 5-H), 3.84 (0.55H, d, *J* 15.3, 3-H_B), 3.77 (0.45H, d, *J* 15.3, 3-H_B), 3.56 (1H, app. d, *J* 14.3, 9-H_A), 3.23 (1H, dd, *J* 14.3, 4.4, 9-H_B), 3.00–2.89 (1H, m, 8-H_B), 2.48 (0.55H, t, *J* 2.4, POC 5-H), 2.46 (0.45H, t, *J* 2.4, POC 5-H), 2.22 (0.55H, app. d, *J* 14.0, 6-H_A), 2.13 (0.45H, app. d, *J* 14.0, 6-H_B), 1.88–1.76 (1H, m, 7-H_A), 1.75–1.66 (1H, m, 6-H_B), 1.41 (1H, app. d, *J* 14.1, 7-H_B); δ_C (125 MHz, $CDCl_3$) 179.9 (C=O C-2), 154.6 (C=O POC), 154.0 (C=O POC), 78.2 (POC C-4), 78.2 (POC C-4), 75.0 (POC C-5), 74.9 (POC C-5), 53.31 (POC C-3), 53.27 (POC C-3), 52.0 (C-8), 51.9 (C-8), 51.2 (C-9), 51.1 (C-9), 50.4 (C-5), 49.7 (C-5), 48.74 (C-3), 48.72 (C-3), 28.7 (C-6), 27.5 (C-6), 21.1 (C-7), 21.0 (C-7) (21 out of 22 signals present); HRMS found MNa^+, 245.0897. $C_{11}H_{14}N_2O_3Na$ requires 245.0897.

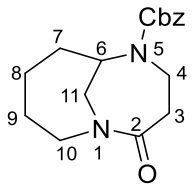
Benzyl 9-oxo-1,7-diazabicyclo[4.3.1]decane-7-carboxylate 256



256

Compound **256** was synthesised using general method D using NaOH (6.06 mg, 0.152 mmol), amino ester **245** (60 mg, 0.138 mmol), 1:1 MeOH:water (2.4 mL), HCl (1.5 mL, 6 N), EtOAc (0.2 mL), toluene (1.8 mL) and *n*-Bu_2SnO (34.6 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **256** as a 60:40 mixture of rotamers (28.9 mg, 73%) as a colourless oil, R_f 0.30 (EtOAc); ν_{max}/cm^{-1} 2928, 2860, 1667 (C=O), 1403, 1331, 1191, 1126, 1072, 765 and 699; δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (5H, m, Ph), 5.21–5.07 (2H, m, Cbz CH_2), 4.46 (0.4H, d, *J* 15.6, 8-H_A), 4.41 (0.6H, d, *J* 15.4, 8-H_A), 4.35–4.24 (1H, m, 2-H_A), 4.20 (0.6H, m, 6-H), 4.13 (0.4H, m, 6-H), 3.82 (0.6H, d, *J* 15.4, 8-H_B), 3.77 (0.4H, d, *J* 15.6, 8-H_B), 2.93–2.84 (1H, m, 2-H_B), 3.64 (1H, dd, *J* 14.6, 2.2, 10-H_A), 3.26 (0.6H, dd, *J* 14.6, 1.0, 10-H_B), 3.21 (0.4H, app. d, *J* 14.6, 10-H_B), 2.25 (0.6H, app. dd, *J* 15.1, 2.8, 5-H_A), 2.14 (0.4H, app. dd, *J* 14.8, 3.3, 5-H_A), 2.05–1.93 (1H, m, 3-H_A), 1.65–1.52 (2H, m, 3-H_B, 4-H_A), 1.50–1.41 (1H, m, 5-H_B), 1.29–1.14 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 170.9 (C=O C-9), 155.2 (C=O Cbz), 155.0 (C=O Cbz), 136.5 (*ipso*-Ph), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 67.6 (CH_2 Cbz), 67.5 (CH_2 Cbz), 51.8 (C-6), 51.3 (C-6), 47.9 (C-8), 47.8 (C-8), 47.7 (C-10), 47.5 (C-10), 44.01 (C-2), 43.97 (C-2), 35.8 (C-5), 34.8 (C-5), 27.3 (C-3), 27.1 (C-3), 20.5 (C-4) (24 out of 28 signals present); HRMS found MH^+, 289.1544. $C_{16}H_{21}N_2O_3$ requires 289.1547.

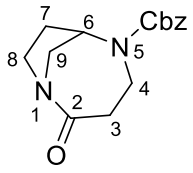
Benzyl 2-oxo-1,5-diazabicyclo[4.4.1]undecane-5-carboxylate 257



257

Compound **257** was synthesised using general method D using NaOH (6.85 mg, 0.172 mmol), amino ester **246** (70 mg, 0.156 mmol), 1:1 MeOH:water (2.8 mL), HCl (1.7 mL, 6 N), EtOAc (0.2 mL), toluene (2 mL) and *n*-Bu_2SnO (39.1 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **257** as a 55:45 mixture of rotamers (35.8 mg, 75%) as a white crystalline solid, R_f 0.20 (EtOAc); m.p. 122–124 °C; ν_{max}/cm^{-1} 2931, 2858, 1689 (C=O), 1647 (C=O), 1418, 1312, 1236, 1210, 1158 and 658; δ_H (500 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ph), 5.13 (2H, s, Cbz CH_2), 4.76–4.65 (0.55H, m, 6-H), 4.62–4.51 (0.45H, m, 6-H), 4.44 (1H, app. d, *J* 12.7, 10-H_A), 4.38 (0.45H, app. d, *J* 11.7, 4-H_A), 4.24 (0.55H, app. d, *J* 11.7, 4-H_A), 3.85 (1H, app. d, *J* 16.1, 11-H_A), 3.41 (1H, app. t, *J* 16.7, 11-H_B), 3.31-3.14 (1H, m, 4-H_B), 2.87–2.74 (1H, m, 3-H_B), 2.54–2.51 (2H, m, 5-H_A, 3-H_B), 2.02–1.89 (1H, m, 7-H_A), 1,89–1.79 (1H, m, 8-H_A), 1.79–1.67 (2H, m, 9-H_2), 1.56–1.30 (2H, m, 7-H_B, 8-H_B); δ_C (125 MHz, $CDCl_3$) 172.80 (C=O C-2), 172.75 (C=O C-4), 155.5 (C=O Cbz), 136.6 (*ipso*-Ph), 136.5 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 67.7 (CH_2 Cbz), 53.6 (C-11), 53.5 (C-11), 53.0 (C-6), 52.7 (C-6), 48.6 (C-10), 38.2 (C-3), 38.0 (C-3), 36.9 (C-4), 29.8 (C-9), 29.7 (C-9), 28.2 (C-7), 27.5 (C-7), 23.2 (C-8) (22 out of 30 signals present); HRMS found MH^+, 303.1702. $C_{17}H_{23}N_2O_3$ requires 303.1703. X-ray crystallographic data was collected (see section 7.4). CCDC deposition number 2192693.

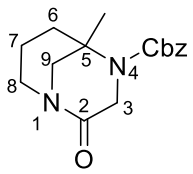
Benzyl 2-oxo-1,5-diazabicyclo[4.2.1]nonane-5-carboxylate 259



259

Compound **259** was synthesised using general method D using NaOH (11.5 mg, 0.288 mmol), amino ester **248** (110 mg, 0.262 mmol), 1:1 MeOH:water (4.4 mL), HCl (2.9 mL, 6 N), EtOAc (0.4 mL), toluene (3.5 mL) and *n*-Bu_2SnO (65.7 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate* **259** as a 1:1 mixture of rotamers (22.4 mg, 31%) as a colourless oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 2928, 1680 (C=O), 1406, 1262, 1217, 1098, 1008, 771 and 699; δ_H (500 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 5.18–5.01 (2H, s, Cbz CH_2), 4.73–4.50 (1H, m, 6-H), 4.22 (0.5H, dt, *J* 9.0, 2.8 8-H_A), 4.20 (0.5H, dt, *J* 9.0, 2.8 8-H_A), 3.99–3.86 (2H, m, 4-H_A, 9-H_A), 3.74–3.60 (1H, m, 4-H_B), 3.09 (1H, ddd, *J* 14.6, 8.1, 6.9, 3-H_A), 2.89–2.73 (2H, m, 5-H_B, 9-H_B), 2.61–2.45 (1H, m, 3-H_B), 2.20–2.10 (1H, m, 7-H_2), 2.09–1.55 (1H, m, 7-H_2); δ_C (125 MHz, $CDCl_3$) 182.1 (C=O C-2), 182.0 (C=O C-2), 156.4 (C=O Cbz), 156.2 (C=O Cbz), 136.3 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.2 (Ph), 67.8 (CH_2 Cbz), 54.3 (C-6), 54.0 (C-6), 53.5 (C-9), 49.5 (C-8), 40.1 (C-4), 36.6 (C-3), 33.0 (C-7), 32.1 (C-7) (17 out of 26 signals present); HRMS found MH^+, 275.1389. $C_{15}H_{19}N_2O_3$ requires 275.1390.

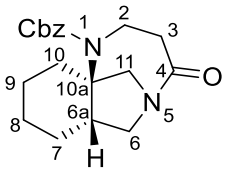
Benzyl 5-methyl-2-oxo-1,4-diazabicyclo[3.3.1]nonane-4-carboxylate 260



260

Compound **260** was synthesised using general method D using NaOH (7.1 mg, 0.177 mmol), amino ester **244** (70.0 mg, 0.161 mmol), 1:1 MeOH:water (2.8 mL), HCl (1.8 mL, 6 N), EtOAc (0.2 mL), toluene (2.1 mL) and *n*-Bu_2SnO (40.4 mg). The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *bicyclic carbamate* **260** as a 65:35 mixture of rotamers (35.9 mg, 77%) as a colourless oil, R_f 0.47 (EtOAc); ν_{max}/cm^{-1} 2935, 1684 (C=O), 1401, 1378, 1349, 1313, 1200, 1117, 766 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.20–5.17 (0.7H, m, Cbz CH_2), 5.15 (0.65H, d, *J* 12.4, Cbz, CH_2), 5.05 (0.65H, d, *J* 12.4, Cbz, CH_2), 4.67 (0.35H, d, *J* 15.2, 3-H_A), 4.52 (0.65H, d, *J* 15.2, 3-H_A), 4.09–4.01 (1H, m, 8-H_A), 3.80 (0.65H, d, *J* 15.2, 3-H_B), 3.75 (0.35H, d, *J* 15.2, 3-H_B), 3.49–3.42 (1H, m, 9-H_A), 2.95–2.75 (2.65H, m, 8-H_B, 9-H_B, 6-H_A), 2.51–2.44 (0.35H, m, 6-H_A), 1.73–1.64 (1H, m, 7-H_A), 1.43 (1.95H, s, Me), 1.40–1.31 (3.05H, m, 6-H_B, 7-H_B, Me); δ_C (125 MHz, $CDCl_3$) 179.7 (C=O C-2), 156.1 (C=O Cbz), 153.8 (C=O Cbz), 136.4 (*ipso*-Ph), 136.2 (*ipso*-Ph), 128.72 (Ph), 128.67 (Ph), 128.37 (Ph), 128.35 (Ph), 128.2 (Ph), 128.0 (Ph), 67.9 (CH_2 Cbz), 67.1 (CH_2 Cbz), 58.7 (C-8), 58.3 (C-8), 56.2 (C-5), 55.6 (C-5), 50.8 (C-9), 50.6 (C-9), 48.9 (C-3), 48.7 (C-3), 34.2 (C-6), 32.5 (C-6), 24.2 (C-7), 22.9 (C-7), 21.8 (Me), 21.7 (Me) (27 out of 28 signals present); HRMS found MH^+, 289.1548. $C_{16}H_{21}N_2O_3$ requires 289.1547.

Benzyl (6aS*,10aR*)-4-oxooctahydro-5,10a-methanobenzo[b][1,5]diazocine-1(2H)-carboxylate *cis*-262

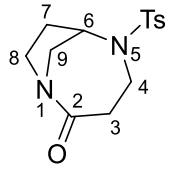


cis-**262**

Compound *cis*-**262** was synthesised using general method D using NaOH (3.7 mg, 92.7 µmol), amino ester *cis*-**250** (40.0 mg, 84.3 µmol), 1:1 MeOH:water (2 mL), HCl (1 mL, 6 N), EtOAc (0.2 mL), toluene (1.5 mL) and *n*-Bu_2SnO (21.1 mg). The crude product

was purified by flash column chromatography, eluting with 1:1 EtOAc-hexane to yield *bicyclic carbamate cis*-**262** as a 75:25 mixture of rotamers (6.8 mg, 25%) as a pale yellow oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 2925, 2858, 1680 (C=O), 1400, 1359, 1248, 1101, 1047, 1023, 797 and 697; δ_H (500 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ph), 5.14 (1.5H, d, *J* 11.6, Cbz CH_2), 4.98 (0.5H, d, *J* 12.2, Cbz CH_2), 4.64–4.40 (0.25H, m, 2-H_A), 4.39–4.23 (1.75H, m, 2-H_A, 11-H_A), 3.68 (1H, app. d, *J* 13.9, 6-H_A), 3.44–3.28 (1.75H, m, 2-H_A, 6a-H), 3.23 (1H, app. d, *J* 13.8, 6-H_B), 3.13–3.02 (0.25H, m, 6a-H), 2.94 (1H, ddd, *J* 14.8, 10.2, 2.8, 3-H_A), 2.77–2.66 (1H, m, 3-H_B), 2.61 (1H, d, *J* 12.2, 11-H_B), 2.25–2.11 (1H, m, 10-H_A), 2.05–1.90 (2H, m, 7-H_A, 10-H_B), 1.81–1.70 (1H, m, 8-H/9-H_A), 1.65–1.57 (1H, m, 8-H/9-H_A), 1.49–1.40 (1H, m, 8-H/9-H_A), 1.21–1.09 (2H, m, 7-H_B, 9-H_B); δ_C (125 MHz, $CDCl_3$) 179.9 (C=O C-4), 155.6 (C=O Cbz), 155.0 (C=O Cbz), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.8 (Ph), 67.0 (Cbz CH_2), 66.7 (C-10a), 56.1 (C-11), 52.5 (C-6), 39.7 (C-6a), 38.5 (C-2), 35.1 (C-3), 33.4 (C-7), 25.7 (C-10), 23.6 (C-8, C-9) (19 out of 32 signals present); HRMS found MNa^+, 351.1681. $C_{18}H_{24}N_2O_3Na$ requires 351.1679.

5-Tosyl-1,5-diazabicyclo[4.2.1]nonan-2-one 263

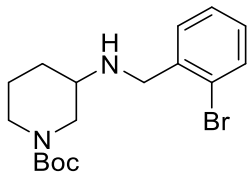


263

Compound **263** was synthesised using general method D using NaOH (27.9 mg, 0.700 mmol), amino ester **252** (280 mg, 0.636 mmol), 1:1 MeOH:water (10 mL), HCl (7 mL, 6 N), EtOAc (1 mL), toluene (8 mL) and *n*-Bu_2SnO (159 mg). The crude product was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic sulfonamide* **263** (39.4 mg, 21%) as a colourless oil, R_f 0.38 (EtOAc); ν_{max}/cm^{-1} 3061, 2925, 1682 (C=O), 1639 (C=O), 1598, 1442, 1338, 1158, 1091, 662 and 549; δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.3, Ar), 7.31 (2H, d, *J* 8.0, Ar), 4.69–4.60 (1H, m, 6-H), 4.05

(1H, ddt, *J* 11.7, 9.0, 2.5, 8-H_A), 2.92 (1H, app. dt, *J* 13.8, 4.6, 4-H_B), 3.76 (1H, d, *J* 14.2, 9-H_A), 3.15 (1H, ddd, *J* 13.9, 11.1, 3.9, 3-H_A), 2.88 (1H, ddd, *J* 13.9, 11.1, 2.9, 4-H_B), 2.81–2.71 (2H, m, 8-H_B, 9-H_B), 2.46–2.42 (1H, m, 3-H_B), 2.42 (3H, s, Me), 1.91 (1H, app. dtd, *J* 14.6, 8.3, 2.3, 7-H_2), 1.44 (1H, app. dtt, *J* 14.5, 8.9, 1.7, 7-H_2); δ_C (125 MHz, $CDCl_3$) 183.1 (C=O C-2), 144.1 (*ipso*-Ar), 135.7 (*ipso*-Ar), 130.1 (Ar), 127.3 (Ar), 54.8 (C-9), 54.5 (C-6), 51.1 (C-8), 41.7 (C-4), 37.7 (C-3), 29.5 (C-7) 21.7 (Me); HRMS found MNa^+, 317.0939. $C_{14}H_{18}N_2O_3SNa$ requires 317.0930.

tert-Butyl 3-((2-bromobenzyl)amino)piperidine-1-carboxylate 274

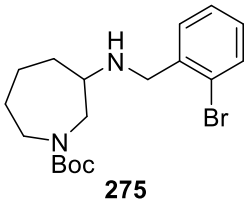


274

Compound **274** was synthesised using general method E using enecarbamate **65** (45.8 mg, 0.25 mmol). Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **274** as a 1:1 mixture of rotamers (255 mg, 69%) as a colourless oil, R_f 0.39 (EtOAc); ν_{max}/cm^{-1} 2974, 2930, 2856, 1686 (C=O), 1420, 1364, 1260, 1238, 1174, 1150, 1024 and 750; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, d, *J* 5.5, 3-Ar), 7.41 (1H, dd, *J* 7.6, 1.6, 6-Ar), 7.28 (1H, td, *J* 7.5, 0.9, 5-Ar), 7.12 (1H, td, *J* 7.8, 1.5, 4-Ar), 4.25–3.93 (1H, m, 2-H_A), 3.93 (1H, d, *J* 13.8, benzyl CH_2), 3.86 (1H, d, *J* 13.8, benzyl CH_2), 3.86–3.74 (1H, br m, 6-H_A), 3.00–2.65 (2H, m, 2-H_B, 6-H_B), 2.64–2.52 (1H, m, 3-H), 1.97–1.86 (1H, br m, 4-H_A), 1.74–1.64 (1H, br m, 5-H_A), 1.63–1.48 (2H, m, NH, 5-H_A), 1.46 (9H, s, $C(Me)_3$), 1.40–1.29 (1H, br m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Boc), 139.5 (*ipso*-Ar-2), 133.0 (Ar-3), 130.4 (Ar-6), 128.8 (Ar-5), 127.6 (Ar-4), 124.1 (*ipso*-Ar-1), 79.6 ($C(Me)_3$), 53.2 (C-3), 51.2 (benzyl CH_2), 49.5 (C-2), 48.9 (C-2), 44.9 (C-6), 44.1 (C-6), 31.7 (C-4), 28.6 ($C(Me)_3$), 23.7 (C-5)

(17 out of 30 signals present); HRMS found MNa^+, 391.0994. $C_{17}H_{25}{}^{79}BrN_2O_2Na$ requires 391.0992.

tert-Butyl 3-((2-bromobenzyl)amino)azepane-1-_carboxylate_ 275

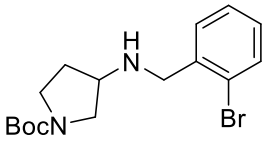


275

Compound **275** was synthesised using general method E using enecarbamate **54** (49.3 mg, 0.25 mmol). Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **275** as a 55:45 mixture of rotamers (94.6 mg, 25%) as a yellow oil, R_f 0.39 (EtOAc); ν_{max}/cm^{-1} 2973, 2926, 2858, 1684 (C=O), 1466, 1412, 1364, 1160, 1044 and 750; δ_H (500 MHz, $CDCl_3$) 7.54 (0.55H, d, *J* 8.0, 3-Ar), 7.52 (0.45H, d, *J* 8.0, 3-Ar), 7.47 (0.45H, d, *J* 7.5, 6-Ar), 7.41 (0.55H, d, *J* 7.5, 6-Ar), 7.31–7.26 (1H, m, 5-Ar), 7.15–7.07 (1H, m, 4-Ar), 3.86 (0.45H, dd, *J* 14.1, 3.6, 2-H_A), 3.78 (0.55H, dd, *J* 14.1, 3.6, 2-H_A), 3.91 (0.9H, s, benzyl CH_2), 3.89 (1.1H, s, benzyl CH_2), 3.68 (0.55H, ddd, *J* 13.2, 7.6, 5.1, 7-H_A), 3.48 (0.45H, ddd, *J* 13.1, 7.6, 5.1, 7-H_A), 3.23 (0.45H, app. td, *J* 13.9, 5.9, 7-H_B), 3.16 (0.55H, app. td, *J* 13.6, 5.5, 7-H_B), 3.00 (0.45H, dd, *J* 13.9, 8.3, 2-H_B), 2.88 (0.55H, dd, *J* 14.1, 8.9, 2-H_B), 2.87–2.81 (0.45H, m, 3-H), 2.74–2.81 (0.55H, m, 3-H), 1.93–1.71 (3H, m, 4-H_A, 5-H_A, 6-H_A), 1.61–1.54 (2H, br m, NH, 6-H_B), 1.47 (4.05H, s, $C(Me)_3$), 1.45 (4.95H, s, $C(Me)_3$), 1.43–1.33 (2H, m, 4-H_B, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.0 (C=O Boc), 155.7 (C=O Boc), 139.6 (*ipso*-Ar-2), 133.0 (Ar-3), 132.8 (Ar-3), 130.8 (Ar-6), 130.2 (Ar-6), 128.8 (Ar-5), 128.7 (Ar-5), 127.7 (Ar-4), 127.6 (Ar-4), 124.13 (*ipso*-Ar-1), 124.05 (*ipso*-Ar-1), 78.0 (*C*$(Me)_3$), 79.3 (*C*$(Me)_3$), 57.9 (C-3), 57.5 (C-3), 51.7 (benzyl CH_2), 51.6 (benzyl CH_2), 51.1 (C-2), 50.9 (C-2), 48.1 (C-7), 47.1 (C-7), 35.1 (C-4), 34.1 (C-4), 28.7

(C(*Me*)$_3$), 28.6 (C(*Me*)$_3$), 28.0 (C-6), 27.7 (C-6), 23.0 (C-5), 22.7 (C-5) (31 out of 32 signals present); HRMS found MH$^+$, 383.1339. $C_{18}H_{28}{}^{79}BrN_2O_2$ requires 383.1329.

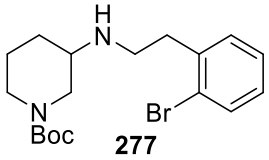
tert-Butyl 3-((2-bromobenzyl)amino)pyrrolidine-1-carboxylate 276



276

Compound **276** was synthesised using general method E using enecarbamate **81** (42.3 mg, 0.25 mmol). Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield *amine* **276** as a 1:1 mixture of rotamers (242 mg, 68%) as a pale yellow oil, R_f 0.34 (EtOAc); ν_{max}/cm^{-1} 2974, 2931, 2876, 1699 (C=O), 1404, 1365, 1168, 1119, 1025 and 752; δ_H (500 MHz, $CDCl_3$) 7.54 (1H, d, *J* 7.9, 3-Ar), 7.38 (1H, app. t, *J* 7.4, 6-Ar), 7.28 (1H, t, *J* 6.8, 5-Ar), 7.13 (1H, t, *J* 7.3, 4-Ar), 3.88 (1H, s, benzyl CH_2), 3.85 (1H, s, benzyl CH_2), 3.60–3.41 (1H, m, 2-H_A, 5-H_A), 3.41–3.28 (2H, br m, 3-H, 5-H_B), 3.20 (0.5H, dd, *J* 10.9, 4.7, 2-H_B), 3.12 (0.5H, dd, *J* 10.7, 5.1, 2-H_B), 2.08–1.98 (1H, br m, 4-H_A), 1.82–1.70 (1H, br m, 4-H_B), 1.58 (1H, br s, NH), 1.45 (9H, s, C(Me)$_3$); δ_C (125 MHz, $CDCl_3$) 154.8 (C=O Boc), 139.2 (*ipso*-Ar-2), 139.1 (*ipso*-Ar-2), 133.0 (Ar-3), 130.6 (Ar-6), 130.5 (Ar-6), 129.0 (Ar-5), 127.7 (Ar-4), 124.1 (*ipso*-Ar-1), 79.3 (*C*(Me)$_3$), 57.3 (C-3), 56.2 (C-3), 52.3 (benzyl CH_2), 52.1 (C-2), 51.6 (C-2), 44.5 (C-5), 44.2 (C-5), 31.5 (C-4), 31.3 (C-4), 28.7 (C(*Me*)$_3$) (20 out of 28 signals present); HRMS found MH$^+$, 355.1021. $C_{16}H_{24}{}^{79}BrN_2O_2$ requires 355.1016.

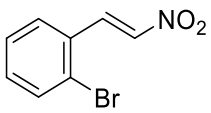
tert-Butyl 3-((2-bromophenethyl)amino)piperidine-1-carboxylate 277



277

Compound **277** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF$_6$] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%), 2-(2-Bromophenyl)ethan-1-amine **279** (99.5 mg, 0.5 mmol) and enecarbamate **65** (45.8 mg, 0.25 mmol). Toluene (5 mL) was then added under N_2 and the resultant mixture was stirred for 16 h under irradiation with a blue LED and fan cooling. Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. Then, the solvent was evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography eluting with EtOAc to yield *amine* **277** as an undetermined mixture of rotamers (207 mg, 54%) as a yellow oil, R_f 0.19 (EtOAc); ν_{max}/cm^{-1} 2974, 2932, 2857, 1687 (C=O), 1421, 1365, 1239, 1174, 1151 and 752; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, d, *J* 7.9, 3-Ar), 7.25–7.22 (2H, m, 5-Ar, 6-Ar), 7.14–7.10 (1H, m, 4-Ar), 4.23–3.82 (1H, br m, 2-H$_A$), 3.79 (1H, app. d, *J* 13.1, 6-H$_A$), 2.96–2.88 (4H, m, benzylamine CH_2), 2.88–2.77 (1H, m, 6-H$_B$), 2.77–2.49 (1H, br m, 2-H$_B$, 3-H), 1.96–1.87 (1H, br m, 4-H$_A$), 1.66 (1H, app. ddt, 12.4, 8.1, 3.9, 5-H$_A$), 1.48–1.42 (11H, m, NH, 5-H$_A$, C(Me)$_3$), 1.31–1.22 (1H, br m, 4-H$_B$); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Boc), 139.4 (*ipso*-Ar-2), 133.0 (Ar-3), 130.9 (Ar-6), 128.1 (Ar-5), 127.6 (Ar-4), 124.7 (*ipso*-Ar-1), 79.6 (*C*(Me)$_3$), 53.8 (C-3), 49.7 (C-2), 49.0 (C-2), 46.8 (benzyl NCH_2), 44.6 (C-6), 43.9 (C-6), 37.1 (benzyl CH_2Ar), 31.7 (C-4), 28.6 (C(*Me*)$_3$), 24.0 (C-5), 23.5 (C-5) (19 out of 32 signals present); HRMS found MH$^+$, 383.1335. $C_{18}H_{28}{}^{79}BrN_2O_2$ requires 383.1329.

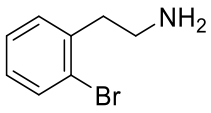
(*E*)-1-Bromo-2-(2-nitrovinyl)benzene 278[183]



278

2-Bromobenzaldehyde (5.84 mL, 50.0 mmol) was added to a mixture of NH_4OAc (6.76 g) in AcOH (140 mL). Nitromethane (9.25 mL) was slowly added with stirring over 5 min. The mixture was heated at reflux for 4h and then ice-cold water (100 mL) added. The organics were extracted with DCM (100 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane–Et_2O to yield *alkene* **278** (10.4 g, 92%) as a yellow amorphous solid, R_f 0.54 (1:1 hexane-Et_2O); ν_{max}/cm^{-1} 3110, 3055, 2974, 2850, 1663, 1512, 1466, 1337, 1284, 1046, 1027, 960, 758 and 744; δ_H (400 MHz, $CDCl_3$) 8.40 (1H, d, *J* 13.7, C*H*Ar), 7.69 (1H, dd, *J* 7.8, 1.4, 6-Ar), 7.57 (1H, dd, *J* 7.6, 1.8, 3-Ar), 7.42–7.31 (2H, m, 4,5-Ar), 7.54 (1H, d, *J* 13.6, C*H*NO_2); δ_C (100 MHz, $CDCl_3$) 139.0 ($CHNO_2$), 137.7 (CHAr), 134.2 (Ar-6), 133.1 (Ar-4/5), 130.5 (*ipso*-2-Ar), 128.6 (Ar-4/5), 128.2 (Ar-3), 126.5 (*ispo*-1-Ar); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[183]

2-(2-Bromophenyl)ethan-1-amine 279[184]

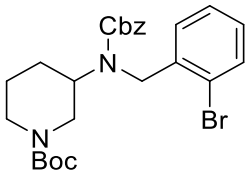


279

$LiAlH_4$ (33.3 mL of a 2.4 M solution in THF, 80.0 mmol) was added dropwise to a solution of alkene **278** (4.54 g, 20.0 mmol) in THF (120 mL) at 0 °C and the mixture was stirred at 0 °C for 5h. Then, water (15 mL), 20% NaOH (15 mL) and water (32 mL)

were added in sequence. The resulting precipitate was filtered and washed with Et_2O (100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with 90:10 EtOAc−MeOH to yield slightly impure *amine* **279** (1.40 g, ~35%) as a brown oil, R_f 0.13 (9:1 EtOAc-MeOH); ν_{max}/cm^{-1} 3057 (NH), 2930, 2855, 1566, 1470, 1439, 1023, 749 and 658; δ_H (500 MHz, $CDCl_3$) 7.54 (1H, d, *J* 8.6, 6-Ar), 7.25–7.22 (1H, m, 3,4-Ar), 7.10–7.05 (2H, m, 5-Ar), 3.00–2.96 (2H, m, CH_2NH$_2$), 2.92–2.88 (2H, m, CH_2Ar), 1.78 (2H, br s, NH_2); δ_C (125 MHz, $CDCl_3$) 139.2 (*ipso*-2-Ar), 133.1 (Ar-6), 131.2 (Ar-3/4), 128.1 (Ar-5), 127.6 (Ar-3/4), 124.8 (*ispo*-1-Ar), 42.2 (CH_2NH_2), 40.3 (*C*H_2Ar); Expected mass not observed in HRMS. Spectroscopic data are consistent with those reported in the literature.[184]

tert-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)piperidine-1-carboxylate 280

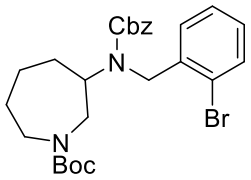


280

Compound **280** was synthesised using general method C using benzyl chloroformate (103 µL, 0.721 mmol), amine **274** (241 mg, 0.655 mmol) and $NaHCO_3$ (329 mg, 3.93 mmol) in DCM (6 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **280** as an undetermined mixture of rotamers (243 mg, 74%) as a colourless oil, R_f 0.65 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3055, 2978, 2861, 1686 (C=O), 1413, 1264, 1240, 1149, 731 and 699; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, d, *J* 7.9, 3-Ar), 7.46–7.14 (7H, br m, 5-Ar, 6-Ar, Ph), 7.1 (1H, t, *J* 7.5, 4-Ar), 4.29–5.04 (2H, br m, Cbz CH_2), 4.68–4.40 (2H, br m, benzyl CH_2), 4.22–3.79 (3H, br m, 2-H_A, 3-H, 6-H_A), 2.93–2.62 (1H, br m, 2-H_B), 2.59–2.41 (1H, m, 6-H_B), 1.89–1.75 (1H, br m, 4-H_A), 1.73–1.59 (2H, br m, 4-H_B, 5-H_A), 1.56–

1.31 (10H, br m, C(Me)$_3$, 5-H$_B$); δ_C (125 MHz, $CDCl_3$) 154.8 (C=O Boc), 137.7 (*ipso*-Ar-2), 136.6 (*ipso*-Ph), 132.8 (Ar-3), 128.64, 128.57, 128.1, 128.0, 127.6 (Ar-4,5,6, Ph), 122.3 (*ipso*-Ar-1), 79.8 (*C*(Me)$_3$), 67.9 (Cbz CH_2), 67.4 (Cbz CH_2), 54.2 (C-3), 48.4 (benzyl CH_2), 47.0 (C-2), 44.1 (C-6), 43.4 (C-6), 29.1 (C-4), 28.5 (C(*Me*)$_3$), 25.0 (C-5) (21 out of 42 signals present); HRMS found MH^+, 503.1555. $C_{25}H_{32}{}^{79}BrN_2O_4$ requires 503.1540.

tert-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)azepane-1-carboxylate 281

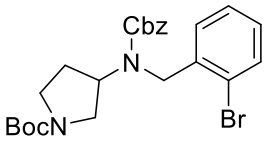


281

Compound **281** was synthesised using general method C using benzyl chloroformate (38 μL, 0.266 mmol), amine **275** (92.3 mg, 0.242 mmol) and $NaHCO_3$ (122 mg, 1.45 mmol) in DCM (2 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **281** as 60:40 mixture of rotamers (101 mg, 81%) as a colourless oil, R_f 0.67 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2973, 2930, 2864, 1691 (C=O), 1414, 1365, 1249, 1162 and 749; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, app. t, *J* 8.6, 3-Ar), 7.47–7.05 (8H, br m, Ar), 5.22 (0.8H, br s, Cbz CH_2), 5.11 (1.2H, br s, Cbz CH_2), 4.72–4.41 (2H, br m, benzyl CH_2), 4.00–3.81 (1H, m, 3-H), 3.82–3.73 (0.4H, br m, 2-H$_A$), 3.72–3.64 (0.6H, br m, 2-H$_A$), 3.58 (0.6H, ddd, *J* 14.4, 8.8, 5.8, 7-H$_A$), 3.54–3.20 (1.4H, br m, 7-H$_B$, 2-H$_B$), 3.19–2.99 (1H, br m, 7-H$_A$, 2-H$_B$), 1.92–1.62 (4H, m, 4-H$_2$, 5-H$_A$, 6-H$_A$), 1.60–1.33 (10H, s, C(Me)$_3$, 6-H$_B$), 1.33–1.16 (1H, m, 5-H$_B$); δ_C (125 MHz, $CDCl_3$) 156.6, 156.0, 155.8, 155.5 (C=O Boc/Cbz), 137.8 (*ipso*-Ar-2), 137.6 (*ipso*-Ar-2), 136.7 (*ipso*-Ph), 136.5 (*ipso*-Ph), 132.8 (Ar-3), 132.7 (Ar-3), 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.0 (Ar-4,5,6, Ph), 122.6 (*ipso*-Ar-1), 122.4 (*ipso*-Ar-1), 79.8 (*C*(Me)$_3$), 79.5 (*C*(Me)$_3$), 67.8 (Cbz CH_2), 67.1 (Cbz

CH_2), 59.0 (C-3), 58.7 (C-3), 49.8 (benzyl CH_2), 49.7 (benzyl CH_2), 49.4 (C-2), 49.2 (C-2), 47.0 (C-7), 46.1 (C-7), 31.9 (C-4), 31.3 (C-4), 28.6 (C(*Me*)$_3$), 28.5 (C(*Me*)$_3$), 27.7 (C-6), 27.3 (C-6), 24.3 (C-5), 23.6 (C-5) (41 out of 44 signals present); HRMS found MH^+, 517.1705. $C_{26}H_{34}{}^{79}BrN_2O_4$ requires 517.1696.

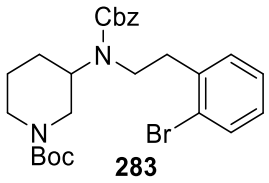
tert-Butyl 3-(((benzyloxy)carbonyl)(2-bromobenzyl)amino)pyrrolidine-1-carboxylate 282



282

Compound **282** was synthesised using general method C using benzyl chloroformate (104 µL, 0.730 mmol), amine **276** (235 mg, 0.664 mmol) and $NaHCO_3$ (334 mg, 3.98 mmol) in DCM (6 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *carbamate* **282** as 1:1 mixture of rotamers (313 mg, 97%) as a colourless oil, R_f 0.53 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2882, 1695 (C=O), 1442, 1169, 1135 and 749; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, app. t, *J* 7.3, 3-Ar), 7.44–7.01 (8H, br m, 4,5,6-Ar, Ph), 5.30–5.02 (2H, br m, Cbz CH_2), 4.87–4.64 (1H, br m, 3-H), 4.62–4.39 (2H, s, benzyl CH_2), 3.64–3.53 (1H, m, 2-H_A), 3.51–3.44 (0.5H, br m, 5-H_A), 3.44–3.35 (0.5H, br m, 5-H_A), 3.28–3.17 (1H, br m, 5-H_B), 3.14 (1H, dd, *J* 9.6, 5.1, 2-H_B), 2.06–1.78 (2H, br m, 4-H_2), 1.42 (9H, s, C(Me)$_3$); δ_C (125 MHz, $CDCl_3$) 156.5 (C=O Cbz), 154.5 (C=O Boc), 137.4 (*ipso*-Ar-2), 136.4 (*ipso*-Ph), 132.9 (Ar-3), 128.7, 128.6, 128.2, 128.1, 127.7, 127.1 (Ar-4,5,6, Ph), 122.2 (*ipso*-Ar-1), 79.7 (*C*(Me)$_3$), 67.6 (Cbz CH_2), 55.6 (C-3), 54.9 (C-3), 47.7 (benzyl CH_2), 47.1 (C-2), 44.3 (C-5), 43.9 (C-5), 29.0 (C-4), 28.6 (C(*Me*)$_3$) (22 out of 40 signals present); HRMS found MH^+, 489.1390. $C_{24}H_{30}{}^{79}BrN_2O_4$ requires 489.1383.

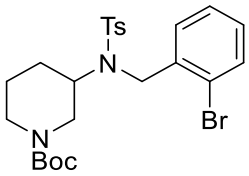
***tert*-Butyl 3-(((benzyloxy)carbonyl)(2-bromophenethyl)amino)piperidine-1-carboxylate 283**



283

Compound **283** was synthesised using general method C using benzyl chloroformate (82 μL, 0.576 mmol), amine **277** (200 mg, 0.524 mmol) and $NaHCO_3$ (200 mg, 0.524 mmol) in DCM (5 mL) for 72 h. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **283** as 60:40 mixture of rotamers (263 mg, 87%) as a colourless oil, R_f 0.64 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 2936, 2862, 1692 (C=O), 1471, 1416, 1365, 1265, 1242, 1170, 1150, 752 and 698; δ_H (500 MHz, $CDCl_3$) 7.58–7.46 (1H, br m, 3-Ar), 7.44–7.30 (5H, m, Ar, Ph), 7.25–6.94 (3H, m, Ar, Ph), 5.27–5.04 (2H, br m, CH_2 Cbz), 4.27–3.87 (2H, br m, 2-H_A, 6-H_A), 3.79 (1H, app. ddd, *J* 15.3, 10.9, 4.2, 3-H), 3.49–3.29 (2H, br m, benzylamine NCH_2), 3.08–2.90 (2H, br m, benzylamine CH_2Ar), 2.89–2.80 (0.6H, m, 2-H_B), 2.79–2.66 (0.4H, m, 2-H_B), 2.64–2.40 (1H, br m, 6-H_B), 1.85–1.64 (3H, br m, 4-H_2, 5-H_A), 1.57–1.32 (10H, br m, 4-H_B, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 155.9, 154.9 (C=O Boc/Cbz), 138.5 (*ipso*-Ar-2), 136.7 (*ipso*-Ph), 132.9 (Ar-3), 131.2 (Ar-6), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 124.6 (*ipso*-Ar-1), 79.9 (*C*$(Me)_3$), 67.4 (CH_2 Cbz), 54.4 (C-3), 47.1 (C-2), 44.9 (benzyl NCH_2), 43.3 (C-6), 37.2 (benzyl CH_2Ar), 29.2 (C-4), 28.6 (C(*Me*)$_3$), 25.1 (C-5) (21 out of 22 signals present); HRMS found MH^+, 517.1714. $C_{26}H_{34}{}^{79}BrN_2O_4$ requires 517.1696.

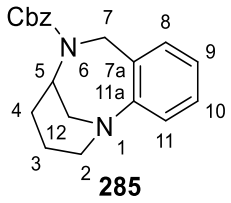
***tert*-Butyl 3-((*N*-(2-bromobenzyl)-4-methylphenyl)sulfonamido)piperidine-1-carboxylate 284**



284

Tosyl chloride (179 mg, 0.937 mmol), DIPEA (155 µL, 0.937 mmol) and DMAP (3.8 mg, 5 mol%) were added in sequence to a mixture of amino ester **274** (230 mg, 0.625 mmol) in DCM (6 mL). The mixture was stirred for 16 h at room temperature, and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield *carbamate* **284** as an undetermined mixture of rotamers (210 mg, 64%) as a colourless oil, R_f 0.24 (8:2 hexane-EtOAc); ν_{max}/cm^{-1} 2974, 2930, 2862, 1689 (C=O), 1419, 1341, 1265, 1241, 1091, 856, 753 and 656; δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.3 Ts Ar), 7.68 (1H, d, *J* 7.7, 6-Ar), 7.48 (1H, d, *J* 7.9, 3-Ar), 7.35–7.29 (3H, m, 5-Ar, Ts Ar), 7.12 (1H, t, *J* 7.4, 4-Ar), 4.56–4.39 (2H, br m, benzyl CH_2), 4.05–3.86 (2H, br m, 2-H_A, 6-H_A), 3.84–3.64 (1H, m, 3-H), 2.58–2.29 (5H, m, 2-H_B, 6-H_B, Me), 1.67–1.53 (2H, br m, 4-H_A, 5-H_A), 1.44–1.32 (11H, m, 4-H_B, 5-H_B, $C(Me)_3$); δ_C (125 MHz, $CDCl_3$) 154.5 (C=O Boc), 143.6 (Ts *ipso*-Ar), 137.9 (*ipso*-Ar-2), 137.4 (Ts *ipso*-Ar), 132.5 (Ar-3), 130.0 (Ts Ar), 129.9 (Ar-6), 129.0 (Ar-5), 127.8 (Ar-4), 127.1 (Ts Ar), 122.0 (*ipso*-Ar-1), 79.9 (*C*$(Me)_3$), 53.5 (C-3), 48.2 (C-2), 47.8 (benzyl CH_2), 47.0 (C-2), 43.9 (C-6), 43.1 (C-6), 29.3 (C-4), 28.4 (C(*Me*)$_3$), 25.0 (C-5), 21.6 (Me) (22 out of 40 signals present); HRMS found MH^+, 523.1274. $C_{24}H_{32}{}^{79}BrN_2O_4S$ requires 523.1261.

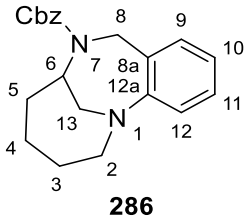
Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate 285



285

Compound **285** was synthesised using general method F using carbamate **280** (120 mg, 0.239 mmol), HCl (2.6 mL, 6 N), EtOAc (0.4 mL), $Pd_2(dba)_3$ (8.8 mg), BINAP (11.9 mg), NaO*t*Bu (46.0 mg, 0.454 mmol) and toluene (4 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 2:1 hexane−EtOAc to yield *carbamate* **285** as a 60:40 mixture of rotamers (28.1 mg, 37%) as a yellow oil, R_f 0.65 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3061, 3060, 2924, 2860, 1689 (C=O), 1490, 1400, 1346, 1177, 1074, 747 and 697; δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 7.16 (1H, app. td, *J* 7.5, 1.0, 10-H), 7.07–7.00 (1H, br m, 8-H), 6.97 (1H, d, *J* 8.0, 11-H), 6.84 (1H, app. td, *J* 7.5, 1.0, 9-H), 5.27–4.98 (3H, br m, 7-H_A, Cbz CH_2), 4.81 (1H, d, *J* 16.6, 7-H_B), 4.04 (1H, dd, *J* 15.7, 2.2, 12-H_A), 3.84 (1H, app. s, 5-H), 3.65 (1H, dd, *J* 13.6, 1.6, 2-H_A), 3.29–3.15 (2H, m, 2-H_B, 12-H_B), 3.00–2.47 (1H, br m, 4-H_A), 1.80 (0.4H, dt, *J* 6.6, 3.6, 3-H_A), 1.64 (1H, app. tt, *J* 13.9, 3.3, 4-H_B), 1.73 (0.6H, dt, *J* 6.6, 3.6, 3-H_A), 1.23–1.12 (1H, br m, 3-H_B); δ_C (125 MHz, $CDCl_3$) 149.3 (C-11a), 136.8 (*ipso*-Ph), 130.4 (Ar-8), 129.1 (C-7a), 128.7 (Ar-10), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 124.5 (C-11), 121.4 (C-9), 67.4 (Cbz CH_2), 53.5 (C-5), 52.6 (C-5), 57.2 (C-2), 50.8 (C-12), 49.8 (C-7), 28.6 (C-4), 30.3 (C-4), 18.0 (C-3) (19 out of 36 signals present); HRMS found MH^+, 323.1756. $C_{20}H_{23}N_2O_2$ requires 323.1754.

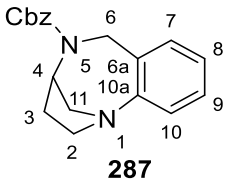
Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate 286



286

HCl (0.7 mL of a 6 M solution) was added to a solution of *N*-Boc amine **281** (33.2 mg, 0.0659 mmol) in EtOAc (0.2 mL) and stirred for 3 h. The solvent was then removed under reduced pressure to give the NH amine. $Pd(OAc)_2$ (1.3 mg, 10 mol%), BINAP (8.1 mg, 2 mol%), Cs_2CO_3 (23.8 mg, 0.0725 mmol) and toluene (3 mL) were then added and the resulting mixture stirred at 110 °C for 96 h. The mixture was then allowed to cool to rt, filtered through celite, and washed with DCM (20 mL). The solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 2:1 hexane−EtOAc to yield *carbamate* **286** (7.4 mg, 33%) as a colourless oil, R_f 0.57 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3064, 3031, 2925, 2855, 1690 (C=O), 1599, 1493, 1414, 1303, 1244, 1157, 748 and 698; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 7.14–7.09 (1H, m, 11-H), 7.03 (1H, d, *J* 6.7, 9-H), 6.78 (1H, d, *J* 8.3, 12-H), 6.63, (1H, td, *J* 7.4, 1.0, 10-H), 5.16 (1H, d, *J* 12.4, Cbz CH_2), 5.13 (1H, d, *J* 12.4, Cbz CH_2), 5.08 (1H, d, *J* 15.5, 8-H_A), 4.77–4.62 (1H, br m, 8-H_B), 4.43–4.17 (2H, br m, 6-H, 13-H_A), 4.07 (1H, app. d, *J* 14.2, 2-H_A), 3.33 (1H, dd, *J* 16.4, 5.0, 13-H_B), 2.92 (1H, app. t, *J* 12.1, 2-H_A), 2.44–2.34 (1H, m, 5-H_A), 1.83–1.70 (2H, br m, 3-H_A, 4-H_A), 1.68–1.59 (1H, br m, 3-H_B), 1.53–1.36 (2H, br m, 4-H_B, 5-H_B); δ_C (125 MHz, $CDCl_3$) 155.1 (C=O Cbz), 149.0 (C-12a), 137.0 (*ipso*-Ph), 132.4 (C-9), 129.0 (C-11), 128.5 (Ph), 127.94 (Ph), 127.88 (Ph), 123.5 (8a), 118.1 (C-10), 115.6 (C-12), 67.1 (Cbz CH_2), 57.6 (C-3), 54.8 (C-2), 53.9 (C-13), 48.7 (C-8), 32.2 (C-5), 28.2 (C-3), 25.5 (C-4); HRMS found MH^+, 337.1914. $C_{21}H_{25}N_2O_2$ requires 337.1911.

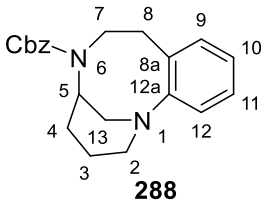
Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate 287



287

Compound **287** was synthesised using general method F using carbamate **282** (299 mg, 0.612 mmol), HCl (6.8 mL, 6 N), EtOAc (1 mL), $Pd_2(dba)_3$ (22.5 mg), BINAP (30.5 mg), NaO*t*Bu (118 mg, 1.16 mmol) and toluene (5 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **287** as a 55:45 mixture of rotamers (120 mg, 64%) as a brown oil, R_f 0.28 (EtOAc); ν_{max}/cm^{-1} 2948, 2877, 1687 (C=O), 1485, 1449, 1408, 1346, 1332, 1222, 1123, 1093, 763, 735 and 697; δ_H (500 MHz, $CDCl_3$) 7.39–7.28 (5H, m, Ph), 7.23–7.14 (1H, br m, Ar), 7.13–7.09 (1H, br m, Ar), 7.05–6.97 (2H, br m, 7-Ar, Ar), 5.19–5.05 (2H, br m, Cbz CH_2), 4.58 (0.45H, app. t, *J* 4.0, 4-H), 4.51 (0.55H, app. t, *J* 4.9, 4-H), 4.93 (0.55H, d, *J* 16.4, 6-H_A), 4.77 (0.45H, d, *J* 16.6, 6-H_A), 4.74–4.68 (1H, m, 6-H_B), 3.42 (0.45H, ddd, *J* 12.2, 9.7, 6.7, 2-H_A), 3.35 (0.55H, ddd, *J* 12.1, 9.9, 6.8, 2-H_A), 3.27–3.18 (1H, br m, 3-H_B), 3.84 (0.55H, app. d, *J* 14.0, 11-H_A), 3.76 (0.45H, app. d, *J* 13.9, 11-H_A), 2.93 (0.45H, dd, *J* 13.9, 3.9, 11-H_B), 2.87 (0.55H, dd, *J* 14.0, 4.2, 11-H_B), 2.23–2.13 (1.45H, br m, 3-H_2), 2.13–2.05 (0.55H, br m, 3-H_2); δ_C (125 MHz, $CDCl_3$) 155.9 (C=O Cbz), 155.4 (C=O Cbz), 152.6 (C-10a), 152.0 (C-10a), 132.2 (C-6a), 131.5 (C-6a), 136.8 (*ipso*-Ph), 130.4, 130.0, 128.7, 128.63, 128.61, 128.1, 128.0, 127.6 (Ar-8/9/10, Ph), 124.3 (C-7), 124.2 (C-7), 67.5 (Cbz CH_2), 67.3 (Cbz CH_2), 58.3 (C-4), 57.8 (C-4), 56.8 (C-2), 56.7 (C-2), 55.5 (C-11), 54.9 (C-11), 47.1 (C-6), 46.9 (C-6), 34.9 (C-3), 33.5 (C-3) (29 out of 34 signals present); HRMS found MNa^+, 331.1416. $C_{19}H_{20}N_2O_2Na$ requires 331.1417.

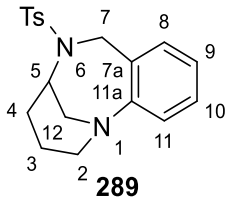
Benzyl 2,3,4,5,7,8-hexahydro-6H-1,5-methanobenzo[b][1,6]diazecine-6-carboxylate 288



288

Compound **288** was synthesised using general method F using carbamate **283** (110 mg, 0.213 mmol), HCl (2.3 mL, 6 N), EtOAc (0.4 mL), $Pd_2(dba)_3$ (7.8 mg), BINAP (10.6 mg), NaO*t*Bu (41.0 mg, 0.405 mmol) and toluene (4 mL). Heated at reflux for 96 h. The crude product was purified by flash column chromatography, eluting with 9:1 hexane−EtOAc to yield *carbamate* **288** as a 55:45 mixture of rotamers (1.3 mg, 2%) as an orange oil, R_f 0.48 (7:3 hexane-EtOAc); ν_{max}/cm^{-1} 2924, 2852, 1690 (C=O), 1497, 1455, 1420, 1226, 1174, 753 and 698; δ_H (500 MHz, $CDCl_3$) 7.34–7.24 (5H, br m, Ph), 7.05 (1H, td, *J* 7.7, 0.8, 11-H), 6.97 (0.55H, d, *J* 7.5, 9-H), 6.93 (0.45H, d, *J* 7.3, 9-H), 6.74 (1H, d, *J* 8.0, 12-H), 6.67 (0.55H, t, *J* 7.4, C-10), 6.66 (0.45H, t, *J* 7.4, C-10), 5.15–5.07 (2H, br m, Cbz CH_2), 4.68 (0.55H, dd, *J* 14.8, 10.3, 7-H_A), 4.42 (0.45H, dd, *J* 15.2, 10.2, 7-H_A), 4.37–4.32 (0.45H, br m, 5-H), 4.20–4.16 (0.55H, br m, 5-H), 3.58–3.48 (2H, br m, 2-H_A, 13-H_A), 3.48–3.38 (1H, m, 7-H_B), 3.38–3.21 (2H, m, 2-H_B, 13-H_B), 3.21–3.10 (1H, m, 8-H_A), 2.82 (1H, app. dd, *J* 17.9, 6.1, 8-H_B), 1.92–1.68 (3H, br m, 4-H_2, 5-H_A), 1.40–1.46 (1H, br m, 5-H_B); δ_C (125 MHz, $CDCl_3$) 156.6 (C=O Cbz), 156.0 (C=O Cbz), 148.8 (C-12a), 148.7 (C-12a), 137.2 (*ipso*-Ph), 137.1 (*ipso*-Ph), 132.2 (C-9), 132.1 (C-9), 129.7 (C-8a), 129.3 (C-8a), 128.7 (Ph), 128.1 (Ph), 128.0 (Ph), 127.5 (C-11), 127.4 (C-11), 119.5 (C-12), 119.4 (C-12), 119.3 (C-10), 119.2 (C-10), 67.4 (Cbz CH_2), 67.3 (Cbz CH_2), 50.22, 50.18, 49.8 (C-2/13), 49.3 (C-5), 49.0 (C-5), 42.5 (C-7), 41.7 (C-7), 38.0 (C-8), 37.6 (C-8), 30.2 (C-4), 29.9 (C-4), 21.9 (C-5) (33 out of 38 signals present); HRMS found MNa^+, 359.1727. $C_{21}H_{24}N_2O_2Na$ requires 359.1730.

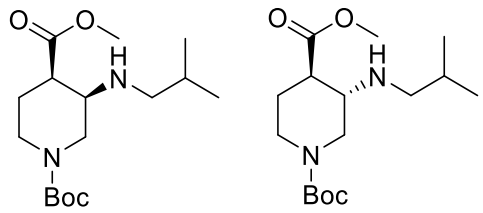
6-Tosyl-2,3,4,5,6,7-hexahydro-1,5-methanobenzo[b][1,5]diazonine 289



289

Compound **289** was synthesised using general method F using carbamate **284** (200 mg, 0.383 mmol), HCl (4.2 mL, 6 N), EtOAc (0.5 mL), $Pd_2(dba)_3$ (14.1 mg), BINAP (19.1 mg), NaO*t*Bu (73.8 mg, 0.723 mmol) and toluene (5 mL). Heated at reflux for 16 h. The crude product was purified by flash column chromatography, eluting with 1:1 hexane−EtOAc to yield *carbamate* **289** (59.2 mg, 45%) as a brown oil, R_f 0.40 (1:1 hexane-EtOAc); ν_{max}/cm^{-1} 3054, 2921, 2860, 1491, 1336, 1189, 1101, 729 and 679; δ_H (500 MHz, $CDCl_3$) δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.3, Ts Ar), 7.31 (2H, d, *J* 8.0, Ts Ar), 7.15 (1H, app. t, *J* 7.2, 10-H), 6.98 (1H, dd, *J* 7.7, 1.4, 8-H), 6.93 (1H, dd, *J* 8.2, 0.9, 11-H), 6.82 (1H, app. td, *J* 7.5, 1.1, 9-H), 4.67 (1H, d, *J* 15.7, 7-H_A), 4.46 (1H, d, *J* 15.6, 7-H_B), 3.78 (1H, dd, *J* 15.7, 2.2, 12-H_A), 3.64 (1H, dd, *J* 13.8, 1.9, 2-H_A), 3.56–3.51 (1H, br m, 5-H), 3.23–3.12 (2H, m, 2-H_B, 12-H_B), 2.79 (1H, app. ddq, *J* 14.1, 5.5, 3.0, 4-H_A), 2.43 (3H, s, Me), 1.93 (1H, app. qt, *J* 13.3, 3.8, 3-H_A), 1.71 (1H, app. tt, *J* 13.8, 3.3, 4-H_B), 1.24–1.17 (1H, br m, 3-H_B); δ_C (125 MHz, $CDCl_3$) 149.2 (C-11a), 143.6 (*ipso*-Ar Ts), 135.1 (*ipso*-Ar Ts), 130.6 (C-8), 129.8 (Ar Ts), 128.7 (C-10), 128.0 (C-7a), 127.7 (Ar Ts), 124.2 (Ar-11), 121.4 (C-9), 56.6 (C-2), 54.3 (C-5), 51.8 (C-7), 50.9 (C-12), 31.6 (C-4), 21.7 (Me), 17.9 (C-3); HRMS found MNa^+, 365.1296. $C_{19}H_{22}N_2O_2SNa$ requires 365.1294.

1-(*tert*-Butyl) 4-methyl (3*R,4*R**)-3-(*iso*-butylamino)piperidine-1,4-dicarboxylate *cis*-296 and 1-(*tert*-butyl) 4-methyl (3S*,4R*)-3-(*iso*-butylamino)piperidine-1,4-dicarboxylate *trans*-296**

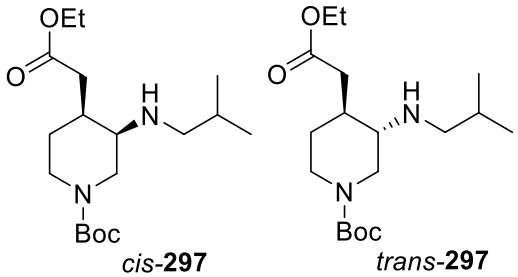


cis-**296** *trans*-**296**

Compound **296** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF$_6$] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%) and enecarbamate **56** (60.3 mg, 0.25 mmol). Isobutylamine (0.12 mL, 1.25 mmol) and toluene (5 mL) were then added under N_2 and the resultant mixture was stirred for 96 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product which contained a 55:45 mixture of *trans*-**296** and *cis*-**296** as a mixture of rotamers. The crude product was purified by flash column chromatography, eluting with 75:25 hexane−EtOAc to yield slightly impure *amine cis*-**296** as an undetermined mixture of rotamers (11.3 mg, 14%) as a colourless oil, and then 2:1 hexane−EtOAc to yield *amine trans*-**296** as an undetermined mixture of rotamers (25.9 mg, 33%) as a colourless oil. Data for *cis*-**296**: R_f 0.47 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2952, 2869, 1735 (C=O), 1690 (C=O), 1159, 1126, 1036 and 990; δ_H (500 MHz, $CDCl_3$) 4.06 (1H, dd, *J* 13.4, 2.8, 2-H$_A$), 4.07–3.81 (1H, br m, 6-H$_A$), 3.68 (3H, s, OMe), 3.06–2.99 (1H, br m, 3-H), 2.97–2.89 (1H, m, 2-H$_B$), 2.89–2.72 (1H, br m, 6-H$_B$), 2.61 (1H, dt, *J* 10.6, 3.8, 4-H), 2.53 (1H, dd, *J* 11.3, 6.9, isobutylamine 2-H$_A$), 2.25 (1H, dd, *J* 10.7, 6.6, isobutylamine 2-H$_B$), 1.87 (1H, dtd, *J* 15.6, 11.3, 4.4, 5-H$_A$), 1.73–1.65 (1H, br m, 5-H$_B$), 1.60 (1H, app. septet, *J* 5.8, isobutylamine 3-H), 1.45 (9H, s, Boc CMe$_3$), 0.86 (3H, d, *J* 6.8, isobutylamine Me), 0.85 (3H, d, *J* 6.8, isobutylamine Me); δ_C (125 MHz, $CDCl_3$) 175.6 (C=O ester), 173.9 (C=O ester), 155.4 (Boc C=O), 79.8 (*C*Me$_3$), 55.8 (isobutylamine C-2), 54.3 (C-3), 52.0 (OMe), 51.7 (OMe), 46.0 (C-2), 45.5 (C-4), 45.4 (C-2), 43.0 (C-6), 42.2 (C-6), 28.7 (isobutylamine C-3), 28.54 (Boc C*Me*$_3$), 28.51 (Boc C*Me*$_3$), 23.1 (C-5), 20.8

(isobutylamine Me), 20.2 (isobutylamine Me) (19 out of 28 signals present); HRMS found MH^+, 315.2283. $C_{16}H_{31}N_2O_4$ requires 315.2278. Data for *trans*-**296** R_f 0.21 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2952, 2869, 1735 (C=O), 1691 (C=O), 1421, 1391, 1156, 1117, 1025 and 766; δ_H (500 MHz, $CDCl_3$) 4.43–4.05 (1H, br m, 2-H_A), 3.99 (1H, app. br d, *J* 12.9, 6-H_A), 3.70 (3H, s, OMe), 2.80–2.74 (1H, m, 6-H_B), 2.74 (1H, app. td, *J* 9.9, 5.0, 3-H), 2.62–2.39 (2H, m, 2-H_B, isobutylamine 2-H_A), 2.39–2.29 (2H, m, isobutylamine 2-H_B, 4-H), 1.86 (1H, app. ddd, *J* 13.2, 6.7, 3.2, 5-H_A), 1.73–1.60 (2H, br m, 5-H_B, isobutylamine 3-H), 1.46 (9H, s, Boc CMe_3), 0.87 (6H, d, *J* 6.6, isobutylamine Me); δ_C (125 MHz, $CDCl_3$) 174.8 (C=O ester), 155.7 (Boc C=O), 79.9 (*C*Me_3), 54.7 (C-3), 55.2 (isobutylamine C-2), 51.9 (OMe), 48.6 (C-4), 47.9 (C-2), 43.4 (C-6), 42.7 (C-6), 28.6 (isobutylamine C-3), 28.5 (Boc C*Me*$_3$), 27.7 (C-5), 20.60 (isobutylamine Me), 20.56 (isobutylamine Me) (15 out of 28 signals present); HRMS found MH^+, 315.2283. $C_{16}H_{31}N_2O_4$ requires 315.2278. Stereochemistry of *trans*-**296** assigned by the observation of two diaxial couplings for signal 3-H and stereochemistry of *cis*-**296** assigned by elimination.

tert-Butyl (3*R,4*S**)-4-(2-ethoxy-2-oxoethyl)-3-(*iso*-*b*utylamino)piperidine-1-carboxylate *cis*-297 and *tert*-butyl (3*S**,4*S**)-4-(2-ethoxy-2-oxoethyl)-3-(*iso*-butylamino)piperidine-1-carboxylate *trans*-297**



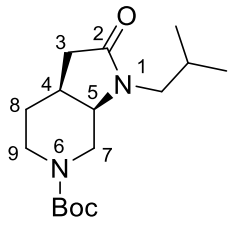
cis-**297** *trans*-**297**

Compound **297** was prepared by a variation on the method of Francis *et al*.[42] To a 7 mL vial were added [Ir(dF(Me)ppy)$_2$(dtbbpy)PF_6] (5.1 mg, 2 mol%), TRIP thiol (27 mg, 50 mol%) and enecarbamate **72** (67.3 mg, 0.25 mmol). Isobutylamine (0.12 mL, 1.25 mmol) and toluene (5 mL) were then added under N_2 and the resultant mixture was

stirred for 48 h under irradiation with a blue LED and fan cooling. Reaction was performed in quadruplicate and the contents of the four vials combined before work-up. Then, the solvent was evaporated under reduced pressure to give a crude product which contained a 1:1 mixture of *trans*-**297** and *cis*-**297** as a mixture of rotamers. The crude product was purified by flash column chromatography, eluting with 80:20 hexane−EtOAc to yield *amine cis*-**297** as an undetermined mixture of rotamers (83.8 mg, 24%) as a yellow oil, then with 2:1 hexane−EtOAc to yield *amine trans*-**297** as an undetermined mixture of rotamers (121 mg, 35%) as a yellow oil. Data for *cis*-**297**: R_f 0.59 (1:1 hexane−EtOAc); δ_H (500 MHz, $CDCl_3$) 4.12 (2H, app. qd, *J* 7.1, 1.7, OCH_2), 4.09–3.69 (2H, m, 2-H_A, 6-H_A), 2.96–2.67 (2H, br m, 2-H_B, 6-H_B), 2.65–2.52 (3H, m, isobutylamine CH_2, ester CH_2, 3-H), 2.25 (1H, dd, *J* 15.8, 7.0, ester CH_2), 2.22–2.13 (1H, br m, isobutylamine CH_2), 2.13–2.02 (1H, br m, 4-H), 1.60 (1H, br s, NH), 1.60 (1H, app. septet, *J* 6.6, isobutylamine 3-H), 1.50–1.35 (11H, m, 5-H_2, Boc CMe_3), 1.25 (3H, t, *J* 7.1, ester Me), 0.90 (3H, d, *J* 6.8, isobutylamine Me), 0.88 (3H, d, *J* 6.8, isobutylamine Me); δ_C (125 MHz, $CDCl_3$) 173.5 (C=O ester), 155.5 (Boc C=O), 79.6 (*C*Me_3), 60.3 (OCH_2), 56.1 (isobutylamine C-2), 55.0 (C-3), 46.5 (C-2), 43.1 (C-6), 36.9 (C-4, ester CH_2), 29.1 (isobutylamine C-3), 28.6 (Boc C*Me*$_3$), 26.9 (C-5), 20.9 (isobutylamine Me), 20.7 (isobutylamine Me), 14.4 (ester Me) (15 out of 16 signals present); Expected mass not observed in HRMS. Data for *trans*-**297**: R_f 0.51 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2973, 2931, 2870, 1731 (C=O), 1688 (C=O), 1417, 1365, 1237, 1153, 878 and 768; δ_H (500 MHz, $CDCl_3$) 4.50–4.16 (1H, br m, 2-H_A), 4.11 (2H, app. qd, *J* 7.1, 3.3, OCH_2), 4.04–3.89 (1H, m, 6-H_A), 2.83–2.68 (2H, m, 6-H_B, ester CH_2), 2.63–2.53 (1H, br m, isobutylamine CH_2), 2.40–2.24 (1H, br m, 2-H_B), 2.28 (1H, dd, *J* 11.4, 6.5, isobutylamine CH_2), 2.14 (1H, app. td, *J* 9.8, 4.1, 3-H), 2.08 (1H, dd, *J* 15.6, 7.4, ester CH_2), 1.79–1.70 (2H, br m, 4-H, 5-H_A), 1.60 (1H, app. septet, *J* 6.5, isobutylamine 3-H), 1.46 (9H, s, Boc CMe_3), 1.25 (3H, t, *J* 7.1, ester Me), 1.28–1.21 (1H, m, 5-H_B), 0.88 (3H, d, *J* 6.8, isobutylamine Me), 0.86 (3H, d, *J* 7.1, isobutylamine Me); δ_C (125 MHz, $CDCl_3$) 173.6 (C=O ester), 154.8 (Boc C=O), 79.7 (*C*Me_3), 60.4 (OCH_2), 59.2 (C-3), 55.2 (isobutylamine C-2), 48.9 (C-2), 44.1 (C-6), 38.5 (C-4), 38.3 (ester CH_2), 31.2 (C-5), 29.3 (isobutylamine C-3), 28.6 (Boc C*Me*$_3$), 20.7 (isobutylamine Me), 20.6 (isobutylamine Me), 14.4 (ester Me); HRMS found MNa^+, 365.24045.

$C_{18}H_{34}N_2O_4Na$ requires 365.2411. Stereochemistry of *trans*-**297** assigned by the observation of two diaxial couplings for signal 3-H and stereochemistry of *cis*-**297** assigned by elimination.

tert-Butyl (3a*S,7a*R**)-1-isobutyl-2-oxooctahydro-6H-pyrrolo[2,3-c]pyridine-6-carboxylate _cis_-299**

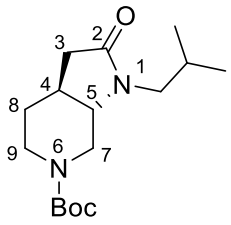


cis-**299**

Compound *cis*-**299** was prepared by a variation on the method of Hassan *et al*.[60] NaOH (3.9 mg, 95.5 µmol) was added to a solution of amino ester *cis*-**297** (30.0 mg, 87.7 µmol) in 1:1 MeOH:water (2 mL) and stirred at 70 °C for 2 h and the solvent then evaporated under reduced pressure. To a suspension of the crude carboxylate in toluene (1.5 mL) was added *n*-Bu_2SnO (21.8 mg) and refluxed under Dean-Stark for 16 h. The solvent was then evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate cis*-**299** as a 1:1 mixture of rotamers (18.0 mg, 69%) as a colourless oil, R_f 0.19 (EtOAc); ν_{max}/cm^{-1} 2960, 2930, 2871, 1681 (C=O), 1410, 1365, 1266, 1249, 1158, 1106, 873 and 768; δ_H (500 MHz, $CDCl_3$) 3.88–3.82 (0.5H, br m, 7-H_2/9-H_2), 3.80–3.71 (0.5H, br m, 7-H_2/9-H_2), 3.71–3.57 (1.5H, br m, 5-H, 7-H_2/9-H_2), 3.56–3.32 (2H, br m, isobutyl CH_2, 7-H_2/9-H_2), 3.31–3.11 (1H, br m, 7-H_2/9-H_2), 3.09–2.90 (0.5H, br m, 7-H_2/9-H_2), 2.83 (1H, dd, *J* 13.8, 5.8, isobutyl CH_2), 2.56–2.41 (2H, br m, 3-H_B, 4-H), 2.23–2.10 (1H, br m, 3-H_A), 1.87 (1H, septet, *J* 6.5, isobutyl CH), 1.77 (1H, dt, *J* 10.1, 5.8, 8-H_A), 1.59–1.48 (1H, m, 8-H_B), 1.45 (9H, s, Boc CMe_3), 0.92 (3H, d, *J* 6.5, Me), 0.83 (3H, d, *J* 6.5, Me); δ_C (125 MHz, $CDCl_3$) 174.9 (C=O C-2), 155.0 (C=O Boc), 154.6 (C=O Boc), 80.2 (Boc *C*Me_3), 56.0 (C-5), 47.5 (isobutyl CH_2), 42.6 (C-7/C-

9), 41.7 (C-7/C-9), 41.2 (C-7/C-9), 40.8 (C-7/C-9), 37.0 (C-3), 36.5 (C-3), 29.8 (C-4), 29.6 (C-4), 28.5 (Boc C*Me*$_3$), 26.7 (C-8), 26.6 (isobutyl CH), 20.5 (Me), 19.9 (Me) (19 out of 28 signals present); HRMS found MNa^+, 319.1996. $C_{16}H_{28}N_2O_3Na$ requires 319.1992.

tert-Butyl (3a*S,7a*S**)-1-isobutyl-2-oxooctahydro-6H-pyrrolo[2,3-c]pyridine-6-carboxylate _trans_-299**



trans-**299**

Method 1:

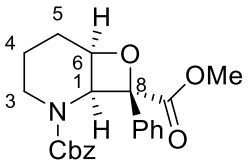
Compound *trans*-**299** was prepared by a variation on the method of Sunggak *et al*.[144] NaOH (3.9 mg, 95.5 µmol) was added to a solution of amino ester *trans*-**297** (30.0 mg, 87.7 µmol) in 1:1 MeOH:water (2.0 mL) and stirred at 70 °C for 2 h and the solvent then evaporated under reduced pressure. To a suspension of the crude carboxylate and triphenylphosphine (27.6 mg, 0.105 mmol) in MeCN (1 mL) were added NBS (18.7 mg, 0.105 mmol) and Et_3N (14.6 µL, 0.105 mmol) and the mixture was stirred at rt for 16 h. The solvent was then evaporated under reduced pressure and then DCM (10 mL) was added. The mixture was then washed with water (10 mL) and brine (10 mL), dried (MgSO4) and the solvent removed under reduced pressure to give the crude product. The crude product was purified by flash column chromatography, eluting with Et_2O to yield *bicyclic carbamate trans*-**299** (14.7 mg, 57%) as a colourless oil, R_f 0.17 (Et_2O); ν_{max}/cm^{-1} 2959, 2927, 2871, 1688 (C=O), 1400, 1237, 1154, 877 and 770; δ_H (500 MHz, $CDCl_3$) 4.64–4.40 (1H, br m, 7-H_A), 4.12–4.38 (1H, br m, 9-H_A), 3.27–3.04 (1H, br m, isobutyl CH_2), 3.02–2.85 (1H, br m, isobutyl CH_2), 2.95 (1H, app. td, *J* 10.9, 3.8, 5-H), 2.83–2.67 (1H, br m, 9-H_B), 2.66–2.50 (1H, br m, 7-H_B), 2.44 (1H, dd, *J* 15.6, 6.5, 3-H_B), 2.08 (1H, dd, *J* 15.5, 12.6, 3-H_B), 1.91–1.73 (3H, m, 4-H, 8-H_A, isobutyl

CH), 1.53–1.44 (10H, m, 8-H_B, Boc CMe_3), 0.91 (3H, d, *J* 5.8, Me), 0.86 (3H, d, *J* 6.3, Me); δ_C (125 MHz, $CDCl_3$) 175.9 (C=O C-2), 155.1 (C=O Boc), 80.4 (Boc *C*Me_3), 61.6 (C-5), 48.5 (isobutyl CH_2), 47.5 (C-7), 45.1 (C-9), 42.3 (C-4), 37.2 (C-3), 28.5 (Boc C*Me*$_3$), 28.3 (C-8), 27.9 (isobutyl CH), 20.4 (Me), 20.3 (Me); HRMS found MNa^+, 319.1995. $C_{16}H_{28}N_2O_3Na$ requires 319.1992.

Method 2:

Compound *trans*-**299** was prepared by a variation on the method of Hassan *et al*.[60] NaOH (3.9 mg, 95.5 µmol) was added to a solution of amino ester *trans*-**297** (30.0 mg, 87.7 µmol) in 1:1 MeOH:water (2 mL) and stirred at 70 °C for 2 h and the solvent then evaporated under reduced pressure. To a suspension of the crude carboxylate in toluene (1.5 mL) was added *n*-Bu_2SnO (21.8 mg) and refluxed under Dean-Stark for 16 h. The solvent was then evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography, eluting with EtOAc to yield *bicyclic carbamate trans*-**299** as an undetermined mixture of rotamers (12.6 mg, 49%) as a colourless oil, whose spectroscopic data matched that above.

2-Benzyl 8-methyl (1S,6R,8S)-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-2,8-dicarboxylate *cis,trans*-322



cis,*trans*-**322**

Method 1:

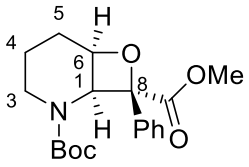
Compound *cis*,*trans*-**322** was prepared by a variation on the method of Rykaczewski *et al*.[156] To a 7 mL vial were added (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 (2.2 mg, 1 mol%), *N*-Cbz enecarbamate **66** (65.2 mg, 0.3 mmol), methyl benzoylformate (28.4 µL, 0.2 mmol) and MeCN (2 mL). The solution was then degassed with N_2 for 5 min and then

stirred for 1 h under irradiation with a blue LED and fan cooling. Then, the solvent was evaporated under reduced pressure to give a crude product to give a crude product containing *cis*,*trans*-**322** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *oxetane cis*,*trans*-**322** as a single diastereomer and 1:1 mixture of rotamers (as a single diastereomer and single rotamer at 363 K) (37.5 mg, 49%) as a colourless oil, R_f 0.43 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2951, 1735 (C=O), 1697 (C=O), 1408, 1324, 1241, 1111, 939, 732 and 697; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, d, *J* 7.1, Ph), 7.42–7.29 (9H, m, Ph), 5.51 (0.5H, d, *J* 8.2, 1-H), 5.47 (0.5H, d, *J* 8.2, 1-H), 5.42–5.37 (0.5H, m, 6-H), 5.35–5.24 (1.5H, m, 6-H, Cbz CH_2), 5.17 (0.5H, d, *J* 12.1, Cbz CH_2), 5.09 (0.5H, d, *J* 12.4, Cbz CH_2), 3.78 (1.5H, s, OMe), 3.62 (1.5H, s, OMe), 3.13 (0.5H, app. td, *J* 12.4, 5.2, 3-H_A), 3.08 (0.5H, app. td, *J* 12.4, 5.2, 3-H_A), 2.94–2.88 (0.5H, m, 3-H_B), 2.86–2.81 (0.5H, m, 3-H_B), 1.99–1.91 (1H, m, 5-H_A), 1.88–1.75 (1H, m, 4-H_A), 1.57–1.41 (2H, m, 4-H_B, 5-H_B); δ_H (500 MHz, d_6-DMSO, 363 K) 7.46–7.25 (10H, m, Ph), 5.42 (1H, d, *J* 8.1, 1-H), 5.33–5.28 (1H, br m, 6-H), 5.19–5.07 (2H, br m, Cbz CH_2), 3.78–3.58 (3H, br m, OMe), 3.10 (1H, app. td, *J* 11.8, 5.3, 3-H_A), 2.79–2.66 (1H, br m, 3-H_B), 1.84–1.78 (1H, m, 5-H_A), 1.75–1.64 (1H, m, 4-H_A), 1.64–1.55 (1H, m, 5-H_B), 1.46 (1H, app. ddd, *J* 13.8, 8.8, 4.4, 4-H_B); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O ester), 156.5 (C=O Cbz), 155.7 (C=O Cbz), 136.8 (*ipso*-Ph), 136.4 (*ipso*-Ph), 136.0 (*ipso*-Ph), 135.7 (*ipso*-Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.24 (Ph), 128.17 (Ph), 128.1 (Ph), 128.04 (Ph), 127.98 (Ph), 127.9 (Ph), 125.9 (Ph), 125.7 (Ph), 89.50 (C-8), 89.45 (C-8), 76.8 (C-6), 67.8 (Cbz CH_2), 67.4 (Cbz CH_2), 55.44 (C-1), 55.40 (C-1), 53.2 (Me), 52.9 (Me), 42.4 (C-3), 42.3 (C-3), 26.6 (C-5), 26.5 (C-5), 17.2 (C-4), 17.1 (C-4) (34 out of 36 signals present); δ_C (125 MHz, d_6-DMSO, 363 K) 171.2 (C=O ester), 135.8 (*ipso*-Ph), 127.8 (Ph), 127.4 (Ph), 127.20 (Ph), 127.15 (Ph), 124.9 (Ph), 88.4 (C-8), 75.5 (C-6), 66.3 (Cbz CH_2), 55.9 (C-1), 51.8 (Me), 41.3 (C-3), 25.5 (C-5), 16.5 (C-4) (15 out of 18 signals present); HRMS found MH^+, 382.1646. $C_{22}H_{24}NO_5$ requires 382.1649. Relative stereochemistry was assigned *via* analogy with *cis*,*trans*-**325** and *cis*,*trans*-**339**.

Method 2:

Compound *cis*,*trans*-**322** was synthesised using general method G using enecarbamate **66** (65.2 mg) and methyl benzoylformate (28.4 µL) to give a crude product containing *cis*,*trans*-**322** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *oxetane cis*,*trans*-**322** as a single diastereomer and 1:1 mixture of rotamers (29.7 mg, 56%) as a colourless oil.

2-(*tert*-Butyl) 8-methyl (1S,6R,8S)-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-2,8-dicarboxylate *cis*,*trans*-325

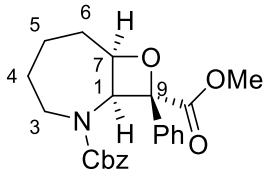


cis,*trans*-**325**

Compound *cis*,*trans*-**325** was synthesised using general method G using enecarbamate **65** (55.0 mg) and methyl benzoylformate (28.4 µL) to give a crude product containing *cis*,*trans*-**325** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield slightly impure *oxetane cis*,*trans*-**325** (30.5 mg). This was then dissolved in DCM (10 mL) and washed with 1M NaOH (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield *oxetane cis*,*trans*-**325** as a single diastereomer and a 1:1 mixture of rotamers (9.6 mg, 19%) as a white solid, R_f 0.47 (1:1 hexane−EtOAc); m.p. 110–114 °C, ν_{max}/cm^{-1} 2928, 1736 (C=O), 1692 (C=O), 1366, 1355, 1244, 1167, 734 and 7602; δ_H (500 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.2, Ph), 7.36–7.29 (3H, m, Ph), 5.44 (0.5H, d, *J* 8.2, 1-H), 5.41–5.36 (1H, m, 6-H, 1-H), 5.34–5.30 (0.5H, m, 6-H), 3.79 (1.5H, s, OMe), 3.76 (1.5H, s, OMe), 3.04 (0.5H, td, *J* 12.3, 5.2, 3-H_A), 2.95 (0.5H, td, *J* 12.4, 5.0, 3-H_A), 2.82 (0.5H, app. dd, *J* 12.6, 5.1, 3-H_B), 2.80–2.74 (0.5H, m, 3-H_B), 1.98–1.89 (1H, m, 5-H_A), 1.85–1.73 (1H, m, 4-H_A), 1.57 (4.5H, m, CMe_3), 1.55–1.47 (2H, m, 4-H_B, 5-H_B), 1.45 (4.5H, m, CMe_3); δ_C (125 MHz, $CDCl_3$) 172.9 (C=O ester), 172.7 (C=O ester),

155.8 (C=O Boc), 155.0 (C=O Boc), 136.3 (*ipso*-Ph), 136.0 (*ipso*-Ph), 128.2 (Ph), 128.1 (Ph), 127.9 (Ph), 127.2 (Ph), 126.1 (Ph), 125.8 (Ph), 89.8 (C-8), 80.8 (*C*Me_3), 80.2 (*C*Me_3), 55.7 (C-1), 55.0 (C-1), 53.2 (Me), 52.9 (Me), 42.5 (C-3), 41.9 (C-3), 28.6 (C*Me*$_3$), 28.4 (C*Me*$_3$), 26.8 (C-5), 26.7 (C-5), 17.41 (C-4), 17.40 (C-4) (25 out of 30 signals present, C-6 appears under $CDCl_3$); HRMS found MH^+, 348.1809. $C_{19}H_{26}NO_5$ requires 348.1805. X-ray crystallographic data was collected (see section 7.4).

2-Benzyl 9-methyl (1S,7R,9S)-9-phenyl-8-oxa-2-azabicyclo[5.2.0]nonane-2,9-dicarboxylate *cis*,*trans*-326

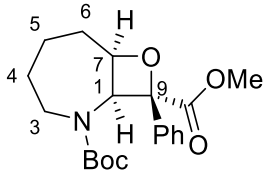


cis,*trans*-**326**

Compound *cis*,*trans*-**326** was synthesised using general method G using enecarbamate **69** (69.3 mg) and methyl benzoylformate (28.4 µL) to give a crude product containing *cis*,*trans*-**326** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 75:25 hexane−EtOAc to yield *oxetane cis*,*trans*-**326** as a single diastereomer and 55:45 mixture of rotamers (33.1 mg, 56%) as a colourless oil, R_f 0.44 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2929, 1738 (C=O), 1696 (C=O), 1432, 1247, 1216, 1171, 1032, 1003, 733 and 699; δ_H (500 MHz, $CDCl_3$) 7.37–7.20 (10H, m, Ph), 5.79 (0.55H, d, *J* 6.9, 1-H), 5.74 (0.45H, d, *J* 7.0, 1-H), 5.40 (0.55H, app. dt, *J* 6.6, 1.8, 7-H), 5.35 (0.45H, app. dt, *J* 6.6, 1.8, 7-H), 5.25 (0.45H, d, *J* 12.4, Cbz CH_2), 5.15 (0.55H, d, *J* 12.5, Cbz CH_2), 5.07 (1H, d, *J* 12.6, Cbz CH_2), 3.70 (1.65H, s, OMe), 3.66 (1.35H, s, OMe), 3.53 (0.45H, app. br d, *J* 14.7, 3-H_A), 3.40 (0.55H, app. br d, *J* 15.0, 3-H_A), 2.33–2.21 (1H, m, 3-H_B), 2.21–2.12 (1H, m, 6-H_A), 1.70–1.61 (1H, m, 5-H_A), 1.55–1.45 (3H, m, 4-H_A, 5-H_B, 6-H_B), 1.27–1.16 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 173.1 (C=O ester), 172.9 (C=O ester), 156.8 (C=O Cbz), 1556.1 (C=O Cbz), 136.74 (*ipso*-Ph), 136.66 (*ipso*-Ph), 136.4 (*ipso*-Ph), 136.2 (*ipso*-Ph), 128.7

(Ph), 128.63 (Ph), 128.59 (Ph), 128.5 (Ph), 128.3 (Ph), 128.14 (Ph), 128.07 (Ph), 128.0 (Ph), 127.9 (Ph), 127.7 (Ph), 124.9 (Ph), 124.7 (Ph), 88.4 (C-9), 88.1 (C-9), 82.6 (C-7), 67.8 (Cbz CH_2), 67.7 (Cbz CH_2), 62.7 (C-1), 62.5 (C-1), 53.3 (Me), 53.2 (Me), 45.4 (C-3), 45.3 (C-3), 31.5 (C-6), 31.3 (C-6), 30.6 (C-4), 30.2 (C-4), 22.5 (C-5), 22.4 (C-5) (37 out of 38 signals present); HRMS found MH^+, 396.1812. $C_{23}H_{26}NO_5$ requires 396.1805. Relative stereochemistry was assigned by analogy with *cis*,*trans*-**327**.

2-(*tert*-Butyl) 9-methyl (1S,7R,9S)-9-phenyl-8-oxa-2-azabicyclo[5.2.0]nonane-2,9-dicarboxylate *cis*,*trans*-327

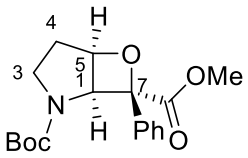


cis,*trans*-**327**

Compound *cis*,*trans*-**327** was synthesised using general method G using enecarbamate **54** (59.2 mg) and methyl benzoylformate (28.4 µL) to give a crude product containing *cis*,*trans*-**327** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 80:20 hexane−EtOAc to yield *oxetane cis*,*trans*-**327** as a single diastereomer and a 55:45 mixture of rotamers (34.7 mg, 64%) as a white solid, R_f 0.58 (1:1 hexane−EtOAc); m.p. 91–93 °C, ν_{max}/cm^{-1} 2975, 2930, 1733 (C=O), 1691 (C=O), 1247, 1221, 1156, 1034, 1004, 732 and 700; δ_H (500 MHz, $CDCl_3$) 7.35–7.20 (5H, m, Ph), 5.72 (0.55H, d, *J* 6.9, 1-H), 5.63 (0.45H, d, *J* 7.2, 1-H), 5.39 (0.55H, app. t, *J* 5.6, 7-H), 5.35 (0.45H, app. t, *J* 5.4, 7-H), 3.70 (3H, s, OMe), 3.50 (0.45H, app. br d, *J* 15.2, 3-H_A), 3.26 (0.55H, app. br d, *J* 15.0, 3-H_A), 2.28–2.07 (2H, m, 3-H_B, 6-H_A), 1.66–1.59 (1H, m, 5-H_A), 1.53–1.43 (6.05H, m, 4-H_A, 5-H_B, 6-H_B), 1.39 (4.95H, s, CMe_3), 1.26–1.17 (2H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 173.3 (C=O ester), 173.0 (C=O ester), 156.1 (C=O Boc), 155.3 (C=O Boc), 136.7 (*ipso*-Ph), 136.4 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.0 (Ph), 127.8 (Ph), 125.0 (Ph), 124.7 (Ph), 88.7 (C-9), 88.3 (C-9), 82.8 (C-6), 80.8 (*C*Me_3), 80.4(*C*Me_3), 62.7 (C-1), 62.0 (C-1), 53.2 (Me), 53.1 (Me),

45.3 (C-3), 44.4 (C-3), 31.5 (C-6), 31.3 (C-6), 30.5 (C-4), 30.2 (C-4), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$), 22.5 (C-5), 22.3 (C-5) (31 out of 32 signals present); HRMS found MH^+, 362.1965. $C_{20}H_{28}NO_5$ requires 362.1962. X-ray crystallographic data was collected (see section 7.4).

2-(*tert*-Butyl) 7-methyl (1S,5R,7S)-7-phenyl-6-oxa-2-azabicyclo[3.2.0]heptane-2,7-dicarboxylate *cis*,*trans*-328

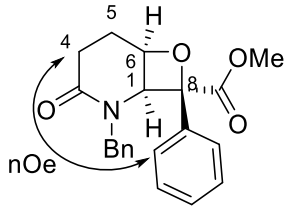


cis,trans-**328**

Compound *cis*,*trans*-**328** was synthesised using general method G using enecarbamate **81** (61.0 mg) and methyl benzoylformate (28.4 µL) to give a crude product containing *cis*,*trans*-**328** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield slightly impure *oxetane cis*,*trans*-**328** (13.6 mg). This was then dissolved in DCM (10 mL) and washed with 1M NaOH (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield *oxetane cis*,*trans*-**328** as a single diastereomer and a 1:1 mixture of rotamers (9.5 mg, 19%) as a colourless oil, R_f 0.34 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2974, 2929, 1734 (C=O), 1695 (C=O), 1403, 1256, 1163, 1110 and 700; δ_H (500 MHz, $CDCl_3$) 7.52–7.48 (2H, m, Ph), 7.35–7.28 (3H, m, Ph), 5.52 (1H, app. t, *J* 4.5, 5-H), 5.28 (0.45H, d, *J* 4.8, 1-H), 5.20 (0.55H, d, *J* 4.8, 1-H), 3.81–3.75 (3.55H, s, OMe, 3-H$_A$), 3.63 (0.45H, app. dd, *J* 10.8, 9.0, 3-H$_A$), 2.91 (0.55H, td, *J* 11.1, 6.6, 3-H$_B$), 2.89 (0.45H, td, *J* 11.0, 6.4, 3-H$_B$), 2.15–2.05 (1H, m, 4-H$_A$), 1.79–1.70 (1H, m, 4-H$_B$), 1.49 (4.95H, m, CMe$_3$), 1.33 (4.05H, m, CMe$_3$); δ_C (125 MHz, $CDCl_3$) 172.4 (C=O ester), 172.1 (C=O ester), 153.6 (C=O Boc), 153.0 (C=O Boc), 135.7 (*ipso*-Ph), 135.4 (*ipso*-Ph), 128.5 (Ph), 128.2 (Ph), 128.0 (Ph), 127.2 (Ph), 125.9 (Ph), 125.4 (Ph), 90.4 (C-7), 90.3 (C-7), 84.4 (C-5), 83.3 (C-5), 80.4 (*C*Me$_3$), 80.1 (*C*Me$_3$), 63.9 (C-1), 63.3 (C-1), 53.11

(Me), 53.06 (Me), 45.6 (C-3), 45.2 (C-3), 31.9 (C-4), 31.0 (C-4), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$); HRMS found MH$^+$, 334.1651. $C_{18}H_{24}NO_5$ requires 334.1649. Relative stereochemistry was assigned by analogy with *cis*,*trans*-**325** and *cis*,*trans*-**327**.

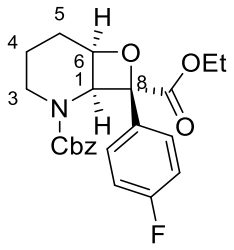
Methyl (1S,6R,8S)-2-benzyl-3-oxo-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-8-carboxylate *cis,trans*-330



cis,trans-**330**

Compound *cis*,*trans*-**330** was synthesised using general method G using enamide **324** (36.2 mg) and methyl benzoylformate (28.4 µL) to give a crude product which contained *cis*,*trans*-**330** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *oxetane cis,trans*-**330** as a single diastereomer (23.2 mg, 44%) as a colourless oil; R_f 0.21 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2951, 1727 (C=O), 1655 (C=O), 1466, 1265, 1237, 1021, 917, 731 and 700; δ_H (500 MHz, $CDCl_3$) 7.50 (2H, d, *J* 7.3, Ph), 7.41 (2H, t, *J* 7.5, Ph), 7.37–7.29 (4H, m, Ph), 7.23 (2H, d, *J* 7.0, Ph), 5.44 (1H, d, *J* 14.7, Bn CH_A), 5.25 (1H, app. d, *J* 8.2, 6-H), 4.88 (1H, d, *J* 7.6, 1-H), 3.79 (3H, s, OMe), 3.67 (1H, d, *J* 14.7, Bn CH_B), 2.54 (1H, ddd, *J* 16.3, 14.1, 5.4, 4-H_A), 2.23–2.17 (1H, m, 4-H_B), 2.20 (1H, ddt, *J* 14.8, 5.4, 2.0, 5-H_A), 1.70 (1H, app. tt, *J* 15.0, 4.4, 5-H_B); δ_C (125 MHz, $CDCl_3$) 173.0 (C=O ester), 171.2 (C=O C-3), 136.7 (*ipso*-Ph), 134.4 (*ipso*-Ph), 129.1 (Ph), 128.9 (Ph), 128.8 (Ph), 128.3 (Ph), 127.9 (Ph), 125.4 (Ph), 91.6 (C-8), 76.0 (C-6), 60.6 (C-1), 53.4 (Me), 49.6 (Bn CH_2), 28.8 (C-4), 25.5 (C-5); HRMS found MH$^+$, 352.1537. $C_{21}H_{22}NO_4$ requires 352.1543. Relative stereochemistry was assigned by the observation of a positive nOe interaction between 4-H_A and *o*-Ph (7.50 ppm).

2-Benzyl 8-ethyl (1S,6R,8S)-8-(4-fluorophenyl)-7-oxa-2-azabicyclo[4.2.0]octane-2,8-dicarboxylate *cis*,*trans*-331

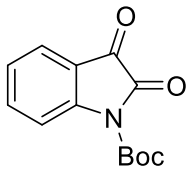


cis,*trans*-**331**

Compound *cis*,*trans*-**331** was synthesised using general method G using enecarbamate **66** (65.2 mg) and ethyl 2-(4-fluorophenyl)-2-oxoacetate (32.7 μL) to give a crude product that contained *cis*,*trans*-**331** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *oxetane cis*,*trans*-**331** as a single diastereomer and as a 55:45 mixture of rotamers (25.0 mg, 40%) as a colourless oil; R_f 0.38 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 2939, 1732 (C=O), 1690 (C=O), 1507, 1406, 1324, 1221, 1111, 846 and 698; δ_H (500 MHz, $CDCl_3$) 7.50 (1H, t, *J* 7.1, Ar), 7.41 (1H, t, *J* 7.2, Ar), 7.39–7.27 (5H, m, Ar), 6.94–6.88 (2H, m, Ar), 5.44–5.37 (1.55H, m, 1-H, 6-H), 5.34–5.30 (0.45H, br m, 6-H), 5.28 (0.45H, d, *J* 12.1, Cbz CH_2), 5.27 (0.55H, d, *J* 12.1, Cbz CH_2), 5.17 (0.55H, d, *J* 12.4, Cbz CH_2), 5.06 (0.45H, d, *J* 12.4, Cbz CH_2), 4.25 (0.45H, q, *J* 7.1, OCH_A), 4.25 (0.55H, q, *J* 7.1, OCH_A), 4.18–4.08 (1H, m, OCH_B), 3.16–3.04 (1H, m, 3-H_A), 3.00–2.95 (0.55H, br m, 3-H_B), 2.92–2.86 (0.45H, br m, 3-H_B), 1.95 (1H, app. br d, *J* 13.4, 5-H_A), 1.83–1.73 (1H, m, 4-H_A), 1.57–1.43 (2H, m, 4-H_B, 5-H_B), 1.26 (1.65H, t, *J* 7.1, Me), 1.12 (1.35H, t, *J* 7.1, Me); δ_C (125 MHz, $CDCl_3$) 171.91 (C=O ester), 171.88 (C=O ester), 162.5 (d, *J* 247, *ipso*-Ar), 162.5 (d, *J* 246, *ipso*-Ar), 156.5 (C=O Cbz), 155.7 (C=O Cbz), 136.7 (*ipso*-Ph), 136.3 (*ipso*-Ph), 131.9 (d, *J* 3.0, *ipso*-Ar), 131.6 (d, *J* 3.1, *ipso*-Ar), 128.9 (Ph), 128.7 (Ph), 128.63 (Ph), 128.55 (Ph), 128.3 (Ph), 128.1 (Ph), 127.9 (d, *J* 8.2, Ar), 127.7 (d, *J* 8.2, Ar), 115.2 (d, *J* 21.6, Ar), 114.9 (d, *J* 21.6, Ar), 89.2 (C-8), 89.1 (C-8), 76.9 (C-6), 76.8 (C-6), 67.8 (Cbz CH_2), 67.4 (Cbz CH_2), 62.1 (OCH_2), 62.0 (OCH_2), 55.43 (C-1), 55.36 (C-1), 42.5 (C-3), 42.4 (C-3), 26.6 (C-5), 26.5 (C-5), 17.29 (C-4), 17.27 (C-4), 14.2 (Me), 14.1 (Me); δ_F (376 MHz, $CDCl_3$) –114.1 (0.45F, s, ArF), –114.5 (0.55F, s, ArF); HRMS

found MH^+, 414.1707. $C_{23}H_{25}FNO_5$ requires 414.1711. Relative stereochemistry was assigned by analogy with *cis*,*trans*-**325** and *cis*,*trans*-**339**.

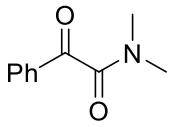
tert-Butyl 2,3-dioxoindoline-1-carboxylate 332[159]



332

Boc_2O (0.5 mL, 2.2 mmol) was added to a solution of isatin (295 mg, 2.0 mmol) and DMAP (12.2 mg, 0.1 mmol) in THF (10 mL) and stirred at rt for 16 h. Brine (20 mL) was then added and extracted with EtOAc (3 × 20 mL). The organic layers were then combined and washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield *N*-Boc isatin **332** (489 mg, 99%) as a yellow solid, m.p. 128–130 °C, lit. 130 °C;[159] ν_{max}/cm^{-1} 2984, 1780 (C=O), 1732 (C=O), 1609, 1589, 1462, 1337, 1249, 1152, 1137, 996, 834 and 762; δ_H (500 MHz, $CDCl_3$) 8.08 (1H, d, *J* 8.3, Ar), 7.74 (1H, d, *J* 7.5, Ar), 7.70 (1H, t, *J* 7.9, Ar), 7.28 (1H, d, *J* 7.6, Ar), 1.65 (9H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 180.4 (C=O ketone), 155.8 (C=O amide or Boc), 148.5 (*ispo*-Ar), 138.9 (Ar), 125.5 (Ar), 125.4 (Ar), 118.8 (*ipso*-Ar), 117.0 (Ar), 85.7 (*C*Me_3), 38.2 (C*Me*$_3$) (10 out of 11 signals present); HRMS found MNa^+, 270.0737. $C_{13}H_{13}NO_4Na$ requires 270.0737. Spectroscopic data are consistent with those reported in the literature.[159]

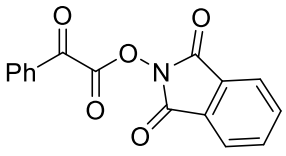
***N*,*N*-Dimethyl-2-oxo-2-phenylacetamide 333**[160]



333

Compound **333** was synthesised using general method H using phenylglyoxylic acid (375 mg, 2.5 mmol) and dimethylamine (1.9 mL of a 2 M solution in THF, 3.75 mmol). Then, water (20 mL) was added. The layers were then separated and the aqueous layer extracted with DCM (3 × 20 mL). The organic layers were then combined and washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield ketoamide **333** as a 1:1 mixture of rotamers (363 mg, 82%) as a colourless oil, ν_{max}/cm^{-1} 1677 (C=O), 1640 (C=O), 1595 (C=O), 1403, 1242, 1142, 992, and 721; δ_H (500 MHz, $CDCl_3$) 7.94 (2H, dd, *J* 8.1, 1.3, Ph), 7.64 (1H, t, *J* 7.4, Ph), 7.51 (2H, t, *J* 7.8, Ph), 3.12 (3H, s, Me), 2.96 (3H, s, Me); δ_C (125 MHz, $CDCl_3$) 181.9 (C=O ketone), 167.2 (C=O amide), 134.9 (Ph), 133.2 (*ipso*-Ph), 129.8 (Ph), 129.1 (Ph), 37.2 (Me), 34.1 (Me); HRMS found MH^+, 178.0858. $C_{10}H_{12}NO_2$ requires 178.0863. Spectroscopic data are consistent with those reported in the literature.[160]

1,3-Dioxoisoindolin-2-yl 2-oxo-2-phenylacetate 334

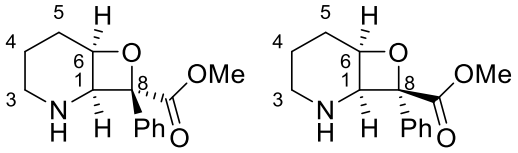


334

Compound **334** was synthesised using general method H using phenylglyoxylic acid (750 mg, 5.0 mmol) and *N*-hydroxyphthalimide (1.22 g, 7.5 mmol). The crude product was purified by flash column chromatography eluting with 75:25 hexane−EtOAc to yield activated ketoester **334** (970 mg, 66%) as a white solid, m.p. 150–151 °C, lit. 157–158 °C;[185] ν_{max}/cm^{-1} 1786 (C=O), 1739 (C=O), 1683 (C=O), 1273, 1183, 1110, 1078, 959, 874, 689 and 680; δ_H (500 MHz, $CDCl_3$) 8.11 (2H, d, *J* 7.3, Ph), 7.85 (2H, dd, *J* 5.5, 3.2, Ar), 7.78 (2H, dd, *J* 5.5, 3.2, Ar), 7.69 (1H, t, *J* 7.5, Ph), 7.53 (2H, t, *J* 7.8, Ph); δ_C (125 MHz, $CDCl_3$) 182.5 (C=O ketone), 161.2 (C=O amide), 159.4 (C=O ester), 136.1

(Ph), 135.2 (Ar), 131.7 (*ipso*-Ph), 130.2 (Ph), 129.3 (Ph), 128.5 (*ipso*-Ar), 124.2 (Ar); HRMS found MH^+, 296.0553. $C_{16}H_{10}NO_5$ requires 296.0553. Spectroscopic data are consistent with those reported in the literature.[185]

Methyl 8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-8-carboxylate *cis,trans*-335 and *cis*,*cis*-335

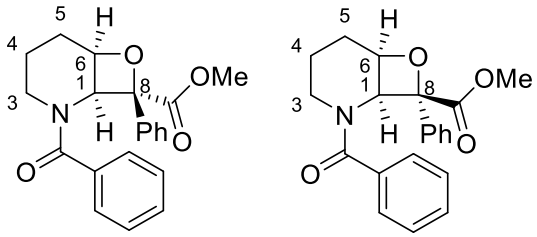


cis,*trans*-**335** *cis*,*cis*-**335**

A RBF was charged with *N*-Cbz oxetane *cis*,*trans*-**322** (50 mg, 0.131 mmol) and Pd/C (5 mg, 10 wt%) under N_2 and EtOAc (5 mL) added. The head space of the flask was exposed to a sequence of vacuum/H_2 flushes (× 3), then exposed to an atmosphere of H_2 (balloon) and stirred at rt for 16 h. The balloon was then removed and the reaction mixture was purged with a vacuum then with N_2 (with a gas outlet) for 5 minutes. The reaction mixture was filtered through Celite eluting with EtOAc, then concentrated *in vacuo* to give a crude product which contained a <95:5 mixture of diastereomeric oxetanes *cis*,*trans*-**335** and *cis*,*cis*-**335** The crude product was purified by flash column chromatography eluting with 9:1 EtOAc−MeOH to yield a 95:5 mixture of diastereomeric oxetanes *cis*,*trans*-**335** and *cis*,*cis*-**335** (15.3 mg, 47%) as a brown amorphous solid, R_f 0.51 (9:1 EtOAc−MeOH); ν_{max}/cm^{-1} 2949 (NH), 1730 (C=O), 1704 (C=O), 1448, 1434, 1245, 1163, 1032, 732 and 700; δ_H (500 MHz, $CDCl_3$) 7.64 (0.1H, d, *J* 7.2, Ph), 7.57 (1.9H, d, *J* 7.2, Ph), 7.40 (2H, t, *J* 7.5, Ph), 7.33 (1H, t, *J* 7.3, Ph), 5.03 (0.95H, td, *J* 5.9, 3.8, 6-H), 4.87–4.83 (0.05H, m, 6-H), 4.41 (0.95H, d, *J* 6.5, 1-H), 4.05 (0.05H, d, *J* 5.8, 1-H), 3.76 (3H, s, OMe), 3.02 (0.05H, app. dt, *J* 11.3, 5.4, 3-H_A), 2.69–2.62 (0.05H, m, 3-H_B), 2.47 (1.9H, app. t, *J* 5.9, 3-H_2), 1.99–1.91 (1H, app. ddd, *J* 15.1, 9.7, 5.6, 5-H_A), 1.83 (1H, ddt, *J* 14.8, 9.5, 5.4, 5-H_B), 1.69 (1H, br s, NH), 1.61–1.52 (1H, m, 4-H_A), 1.40–1.33 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 173.7 (C=O

ester, major), 171.2 (C=O ester, minor), 139.3 (*ipso*-Ph, minor), 136.4 (*ipso*-Ph, major), 128.4 (Ph, minor), 128.3 (Ph, major), 128.1 (Ph, major), 128.0 (Ph, minor), 125.8 (Ph, major), 125.7 (Ph, minor), 89.7 (C-8, major), 89.2 (C-8, minor), 76.0 (C-6, major), 73.7 (C-6, minor), 61.2 (C-1, minor), 57.4 (C-1, major), 52.9 (Me, major), 52.4 (Me, minor), 41.1 (C-3, minor), 40.5 (C-3, major), 27.0 (C-5, major), 26.7 (C-5, minor), 20.4 (C-4, minor), 20.0 (C-4, major); HRMS found MH^+, 248.1281. $C_{14}H_{18}NO_3$ requires 248.1281. Stereochemistry of *cis*,*trans*-**335** and *cis*,*cis*-**335** was assigned by analogy with *cis*,*trans*-**322**.

Methyl 2-benzoyl-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-8-carboxylate *cis*,*trans*-336 and *cis*,*cis*-336

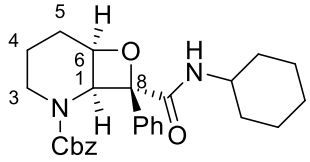


cis,*trans*-**336** *cis*,*cis*-**336**

Compound **336** was prepared by a variation on the method of Hu *et al*.[160] A 95:5 mixture of *NH* oxetanes *cis*,*trans*-**335** and *cis*,*cis*-**335** (10 mg, 0.0405 mmol) in DCM (0.5 mL) was slowly added to a solution of benzoyl chloride (4.7 µL, 0.0405 mmol) and Et_3N (11.3 µL, 0.0809 mmol) at 0 °C and the resultant mixture stirred at rt for 48 h. The mixture was then concentrated under reduced pressure to yield the crude product which contained an undetermined mixture of diastereomeric oxetanes *cis*,*trans*-**336** and *cis*,*cis*-**336**. The crude product was purified by flash column chromatography eluting with 1:1 hexane–EtOAc to yield an 85:15 mixture of diastereomeric *N*-Bz *oxetanes cis*,*trans*-**336** and *cis*,*cis*-**336** (9.8 mg, 69%) as a colourless oil, R_f 0.18 (1:1 hexane–EtOAc); ν_{max}/cm^{-1} 3060, 2951, 1737 (C=O), 1639 (C=O), 1402, 1245, 1020, 935, 736 and 702; δ_H (500 MHz, $CDCl_3$) 7.60 (1.7H, d, *J* 7.4, Ph), 7.52–7.46 (0.9H, m, Ph), 7.42 (2H, t, *J* 7.4, Ph), 7.39–7.28 (3.7H, m, Ph), 7.03

(1.7H, d, *J* 6.8, Ph), 5.91 (0.85H, d, *J* 7.7, 1-H), 5.46 (1H, dt, *J* 8.1, 4.7, 6-H, 1-H), 5.24 (0.15H, app. br d, *J* 8.1, 6-H), 3.84 (2.55H, s, OMe), 3.75–3.65 (0.15H, m, 3-H_A), 3.50 (0.45H, s, OMe), 2.99 (0.85H, ddd, *J* 13.8, 9.6, 4.4, 3-H_A), 2.92–2.86 (0.85H, m, 3-H_B), 2.69 (0.15H, app. dd, *J* 13.4, 4.4, 3-H_B), 2.06–1.97 (1H, m, 5-H_A), 1.87–1.77 (1H, m, 4-H_A), 1.72 (1H, app. ddd, *J* 14.8, 9.5, 4.5, 5-H_B), 1.46–1.38 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$) 172.6 (C=O amide, minor), 172.3 (C=O amide, major), 172.24 (C=O ester, minor), 172.18 (C=O ester, major), 136.4 (*ipso*-Ph, major), 136.03 (*ipso*-Ph, minor), 135.96 (*ipso*-Ph, major), 129.9 (Ph, minor), 129.6 (Ph, major), 128.7 (Ph, minor), 128.62 (Ph, minor), 128.55 (Ph, major), 128.3 (Ph, major), 128.1 (Ph, major), 127.1 (Ph, minor), 126.5 (Ph, major), 126.3 (Ph, major), 125.4 (Ph, minor), 89.5 (C-8, major), 77.9 (C-6, minor), 75.8 (C-6, major), 58.1 (C-1, minor), 54.0 (C-1, major), 53.2 (Me, major), 52.9 (Me, minor), 45.7 (C-3, major), 41.0 (C-3, minor), 27.1 (C-5, major), 26.2 (C-5, minor), 19.0 (C-4, major), 16.2 (C-4, minor) (31 out of 34 signals present); HRMS found MH^+, 352.1544. $C_{21}H_{22}NO_4$ requires 352.1543. Stereochemistry of *cis*,*trans*-**336** and *cis*,*cis*-**336** was assigned by analogy with *cis*,*trans*-**335** and *cis*,*cis*-**335**.

Benzyl (1S,6R,8S)-8-(cyclohexylcarbamoyl)-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate *cis*,*trans*-338

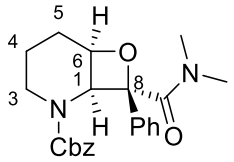


cis,*trans*-**338**

Compound *cis,trans*-**338** was prepared by a variation on the method of Hu *et al*.[160] To a solution of oxetane ester *cis*,*trans*-**322** (100 mg, 0.262 mmol) in a 1:1 mixture of THF:water (2 mL) was added lithium hydroxide monohydrate (22.0 mg, 0.525 mmol) and stirred at rt for 16 h. After this period the reaction mixture was concentrated i*n vacuo* and the residue was dissolved in water (10 mL). The solution was then washed with DCM (2 × 10 mL). To the aqueous layer, HCl (1 N) was added, until a pH of 1 was

reached, and then extracted with DCM (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield the impure carboxylic acid which was used without further purification (34.2 mg, ~36%). *Cis*,*trans*-**338** was then synthesised using general method H using the synthesised carboxylic acid (16 mg, 0.0436 mmol) and cyclohexylamine (7.5 µL, 0.0654 mmol) to give a crude product which contained *cis*,*trans*-**338** as a single diastereomer. The crude product was purified by flash column chromatography eluting with 1:1 hexane–EtOAc to yield *oxetane cis*,*trans*-**338** as a single diastereomer and as a 1:1 mixture of two rotamers by ^{1}H NMR spectroscopy and as a undetermined mixture of up to 4 rotamers by ^{13}C NMR spectroscopy (7.0 mg, 36%) as a colourless oil, R_f 0.60 (EtOAc); ν_{max}/cm^{-1} 3399, 3322, 9931 (NH), 2854 (NH), 1704 (C=O) 1679 (C=O), 1508, 1413, 1324, 1114, 734 and 700; δ_H (500 MHz, $CDCl_3$) 7.59 (1H, d, *J* 7.4, Ph), 7.43–7.31 (6H, br m, Ph), 7.22–7.16 (3H, br m, Ph), 6.84 (1H, app. d, *J* 8.1, NH), 5.35–5.27 (1.75H, m, 1-H, Cbz CH_2), 5.26–5.19 (1.75H, m, 6-H, Cbz CH_2), 5.08 (0.5H, d, *J* 12.3, Cbz CH_2), 3.80–3.68 (1H, m, cyclohexyl CH), 3.11 (1H, app. qd, *J* 11.9, 4.9, 3-H_A), 2.89–2.77 (1H, br m, 3-H_B), 2.02–1.81 (3H, m, cyclohexyl CH_2/4-H_2/5-H_2), 1.77–1.46 (7H, m, cyclohexyl CH_2/4-H_2/5-H_2), 1.43–1.28 (2H, m, cyclohexyl CH_2/4-H_2/5-H_2), 1.26–1.13 (2H, m, cyclohexyl CH_2/4-H_2/5-H_2); δ_C (125 MHz, $CDCl_3$) 171.3 (C=O amide), 156.9 (C=O Cbz), 155.9 (C=O Cbz), 137.3 (*ipso*-Ph), 136.7 (*ipso*-Ph), 136.4 (*ipso*-Ph), 128.9 (Ph), 128.63 (Ph), 128.61 (Ph), 128.34 (Ph), 128.30 (Ph), 128.2 (Ph), 127.98 (Ph), 127.96 (Ph), 127.7 (Ph), 127.6 (Ph), 125.5 (Ph), 90.2 (C-8), 90.1 (C-8), 76.7 (C-6), 75.7 (C-6), 67.6 (Cbz CH_2), 55.9 (C-1), 55.3 (C-1), 48.0 (cyclohexyl CH), 47.9 (cyclohexyl CH), 42.2 (C-3), 33.4 (cyclohexyl CH_2), 32.99 (cyclohexyl CH_2), 32.95 (cyclohexyl CH_2), 27.0, 26.5, 25.7, 25.6, 25.0, 24.9, 24.8 (cyclohexyl CH_2/5-H_2), 17.7 (C-4), 17.1 (C-4) (39 out of 84 signals present); HRMS found MH^+, 449.2443. $C_{27}H_{33}N_2O_4$ requires 449.2435. Stereochemistry was assigned by analogy with *cis*,*trans*-**339**.

Benzyl (1S,6R,8S)-8-(dimethylcarbamoyl)-8-phenyl-7-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate *cis*,*trans*-339

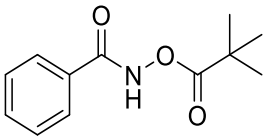


cis,*trans*-**339**

Compound *cis*,*trans*-**339** was prepared by a variation on the method of Hu *et al*.[160] To a solution of oxetane ester *cis*,*trans*-**322** (100 mg, 0.262 mmol) in a 1:1 mixture of THF:water (2 mL) was added lithium hydroxide monohydrate (22.0 mg, 0.525 mmol) and the mixture stirred at rt for 16 h. After this period the reaction mixture was concentrated i*n vacuo* and the residue was dissolved in water (10 mL). The solution was then washed with DCM (2 × 10 mL). To the aqueous layer, HCl (1 N) was added, until a pH of 1 was reached, and then extracted with DCM (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield the impure carboxylic acid which was used without further purification (34.2 mg, ~36%). *Cis*,*trans*-**339** was then synthesised using general method H using the synthesised carboxylic acid (16 mg, 0.0436 mmol) and dimethylamine (32.7 μL of a 2 M solution in THF, 0.0654 mmol) to give a crude product which contained *cis*,*trans*-**339** as a single diastereomer. The crude product was purified by flash column chromatography eluting with EtOAc to yield *oxetane cis*,*trans*-**339** as a single diastereomer and a 65:35 mixture of two rotamers by ^{1}H NMR spectroscopy and as a undetermined mixture of up to 4 rotamers by ^{13}C NMR spectroscopy (as a single diastereomer and single rotamer at 363 K) (12.7 mg, 74%) as a white solid, R_f 0.47 (EtOAc); m.p. 122–125 °C, ν_{max}/cm^{-1} 3031, 2929, 1702 (C=O), 1644 (C=O), 1405, 1323, 1261, 1114, 768 and 703; δ_H (500 MHz, $CDCl_3$) 7.56 (1.3H, d, *J* 7.4, Ph), 7.44 (0.7H, br d, *J* 5.6, Ph), 7.38 (1.35H, t, *J* 7.5, Ph), 7.35–7.27 (3H, m, Ph), 7.25–7.16 (3.65H, m, Ph), 5.89 (0.35H, d, *J* 7.9, 1-H), 5.80 (0.65H, d, *J* 7.6, 1-H), 5.29–5.21 (1H, br m, 6-H), 5.17 (1H, d, *J* 11.3, Cbz CH_2), 5.08 (0.65H, d, *J* 12.5, Cbz CH_2), 4.96 (0.35H, d, *J* 12.5, Cbz CH_2), 3.08 (1H, app. qd, *J* 12.1, 5.1, 3-H_A), 2.99–2.86 (4H, br m,

OMe, 3-H_B), 2.79 (1.05H, s, OMe), 2.74 (1.95H, s, OMe), 2.16–2.04 (0.7H, m, 4-H_A), 2.04–1.92 (1.3H, m, 4-H_A, 5-H_A), 1.63–1.45 (2H, m, 4-H_B, 5-H_B); δ_H (500 MHz, d_6-DMSO, 363 K) 7.40–7.23 (10H, m, Ph), 5.70 (1H, d, *J* 7.6, 1-H), 5.21 (0.65H, ddd, *J* 7.6, 3.9, 3.0, 6-H), 5.08 (1H, d, *J* 12.8, Cbz CH_2), 4.94 (1H, d, *J* 12.8, Cbz CH_2), 3.10 (1H, app. td, *J* 11.8, 5.3, 3-H_A), 2.83–2.72 (7H, m, OMe, 3-H_B), 2.02–1.93 (1H, m, 4-H_A), 2.02–1.93 (1H, app. dq, *J* 14.8, 3.6, 5-H_A), 1.65–1.57 (1H, m, 5-H_B), 1.53 (1H, app. dt, *J* 13.3, 4.5, 4-H_B); δ_C (125 MHz, $CDCl_3$) 171.3 (C=O amide), 171.1 (C=O amide), 156.1 (C=O Cbz), 155.9 (C=O Cbz), 137.2 (*ipso*-Ph), 136.9 (*ipso*-Ph), 136.7 (*ipso*-Ph), 136.3 (*ipso*-Ph), 129.8 (Ph), 129.2 (Ph), 128.6 (Ph), 128.49 (Ph), 128.45 (Ph), 128.09 (Ph), 128.05 (Ph), 128.0 (Ph), 127.8 (Ph), 127.5 (Ph), 125.5 (Ph), 125.4 (Ph), 92.3 (C-8), 91.9 (C-8), 75.9 (C-6), 75.5 (C-6), 67.1 (Cbz CH_2), 66.9 (Cbz CH_2), 57.0 (C-1), 56.6 (C-1), 42.2 (C-3), 42.0 (C-3), 37.2 (Me), 37.0 (Me), 36.8 (Me), 26.5 (C-5), 26.4 (C-5), 17.72 (C-4), 17.66 (C-4) (37 out of 72 signals present); HRMS found MH^+, 395.1972. $C_{23}H_{27}N_2O_4$ requires 395.1965. Stereochemistry was assigned by analysis of X-ray crystallographic data (see section 7.4).

_N_-(Pivaloyloxy)benzamide 359

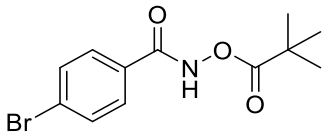


359

Compound **359** was prepared by a variation on the methods of Guimond *et al* and Webb *et al*.[162,161] A solution of benzoyl chloride (0.20 mL, 1.71 mmol) in THF (1.5 mL) was added to a solution of H_2NOPiv triflic acid salt (0.5 g, 1.71 mmol) and Et_3N (0.48 mL, 3.44 mmol) in THF (8.5 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (40 mL) and sat. $NaHCO_{3(aq)}$ (40 mL) added. The layers were then separated and the organic layer washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the

hydroxamate **359** (364 mg, 97%) as a pale pink solid, m.p. 135–137 °C, lit. 170–172 °C;[162] ν_{max}/cm^{-1} 3229 (NH), 2976, 1779 (C=O), 1651 (C=O), 1517, 1481, 1289, 1063, 1022 and 707; δ_H (400 MHz, $CDCl_3$) 9.30 (1H, br s, NH), 7.82 (2H, dt, *J* 8.5, 1.7, Ph), 7.57 (1H, tt, *J* 7.4, 2.0, Ph), 7.47 (2H, tt, *J* 7.8, 2.1, Ph), 1.37 (9H, m, 5-H_2); δ_C (100 MHz, $CDCl_3$) 177.2 (C=O), 132.9 (Ph), 131.1 (*ipso*-Ph), 129.0 (Ph), 127.6 (Ph), 38.6 (*C*Me_3), 27.2 (C*Me*$_3$) (7 out of 8 signals present); HRMS found MNa^+, 244.0938. $C_{12}H_{15}NNaO_3$ requires 244.0944. Spectroscopic data are consistent with those reported in the literature.[162]

4-Bromo-*N*-(pivaloyloxy)benzamide 360

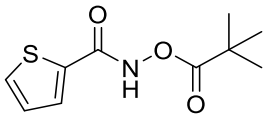


360

Compound **360** was prepared by a variation on the methods of Guimond *et al* and Webb *et al*.[162,161] A solution of 4-bromobenzoyl chloride (282 mg, 1.30 mmol) in THF (1 mL) was added to a solution of H_2NOPiv triflic acid salt (382 mg, 1.43 mmol) and Et_3N (0.36 mL, 2.60 mmol) in THF (8 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (40 mL) and sat. $NaHCO_{3(aq)}$ (40 mL) added. The layers were then separated and the organic layer washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane–EtOAc to yield the hydroxamate **360** (318 mg, 82%) as an amorphous white solid, R_f 0.28 (80:20 hexane–EtOAc); m.p. 138–139 °C, lit. 141.2–141.7 °C;[162] ν_{max}/cm^{-1} 3151 (NH), 2975, 1778 (C=O), 1648 (C=O), 1568, 1526, 1481, 1070, 1029, 1008, 843 and 745; δ_H (500 MHz, $CDCl_3$) 9.27 (1H, br s, NH), 7.68 (2H, d, *J* 8.5, Ar), 7.61 (2H, d, *J* 8.5, Ar), 1.36 (9H, s, $(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 177.2 (C=O hydroxamate), 166.1 (C=O Piv), 132.3 (Ar), 129.9 (*ipso*-Ar), 129.2 (Ar), 127.8 (*ipso*-Ar),

38.6 (*C*Me$_3$), 27.2 (C*Me*$_3$); HRMS found MNa$^+$, 322.0041. $C_{12}H_{14}{}^{79}BrNO_3Na$ requires 322.0049. Spectroscopic data are consistent with those reported in the literature.[162]

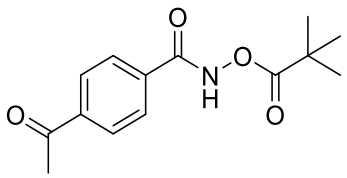
_N_-(Pivaloyloxy)thiophene-2-carboxamide 361



361

Compound **361** was prepared by a variation on the methods of Guimond *et al* and Webb *et al*.[162,161] A solution of 2-thiophenecarbonyl chloride (0.14 mL, 1.34 mmol) in THF (1 mL) was added to a solution of H_2NOPiv triflic acid salt (394 mg, 1.47 mmol) and Et_3N (0.37 mL, 2.68 mmol) in THF (8 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (40 mL) and sat. $NaHCO_{3(aq)}$ (40 mL) added. The layers were then separated and the organic layer washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane–EtOAc to yield the hydroxamate **361** (174 mg, 57%) as an amorphous white solid, R_f 0.22 (80:20 hexane–EtOAc); m.p. 150–151 °C, lit. 150–151 °C;[186] ν_{max}/cm^{-1} 3187 (NH), 2973, , 1787 (C=O), 1630 (C=O), 1529, 1066, 1023, 850 and 722; δ_H (500 MHz, $CDCl_3$) 9.18 (1H, s, NH), 7.67 (1H, dd, *J* 3.8, 0.9, Ar), 7.59 (1H, dd, *J* 5.0, 0.8, Ar), 7.13 (1H, dd, *J* 4.9, 3.9, Ar), 1.36 (9H, s, $(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 177.2 (C=O hydroxamate), 162.1 (C=O Piv), 133.8 (*ipso*-Ar), 131.9 (Ar), 130.6 (Ar), 128.0 (Ar), 38.6 (*C*Me$_3$), 27.2 (C*Me*$_3$); HRMS found MNa$^+$, 250.0498. $C_{10}H_{13}NO_3SNa$ requires 250.0508. Spectroscopic data are consistent with those reported in the literature.[162]

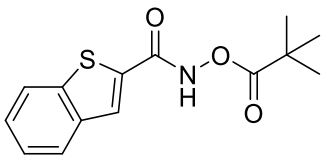
4-Acetyl-*N*-(pivaloyloxy)benzamide 363



363

Compound **363** was prepared by a variation on the method of Webb *et al*.[162] Oxalyl chloride (258 µL, 3.0 mmol) was added to a solution of 4-acetylbenzoic acid (410 mg, 2.5 mmol) in DCM (12.6 mL) with catalytic DMF and stirred at rt for 3 h. The solution was then concentrated under reduced pressure to give the crude acid chloride which was then dissolved in EtOAc (2.8 mL) and transferred to a flask containing a solution of H_2NOPiv triflic acid salt (736 mg, 2.76 mmol) and K_2CO_3 (690 mg, 5.0 mmol) in EtOAc (8.4 mL) and water (4.2 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (40 mL) and sat. $NaHCO_{3(aq)}$ (40 mL) added. The layers were then separated and the organic layer washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography, eluting with 2:1 hexane–EtOAc to yield the hydroxamate **363** (458 mg, 70%) as a white solid, R_f 0.20 (60:40 hexane–EtOAc); m.p. 125–127 °C, lit. 128–130 °C;[187] ν_{max}/cm^{-1} 3202 (NH), 2977, 1780 (C=O), 1684 (C=O), 1661 (C=O), 1517, 1264, 1071, 1030, 1014 and 854; δ_H (500 MHz, $CDCl_3$) 9.34 (1H, s, NH), 8.04 (2H, d, *J* 8.6, Ar), 7.90 (2H, d, *J* 8.6, Ar), 2.65 (3H, s, Me), 1.36 (9H, s, $(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 197.4 (C=O Ac), 177.1 (C=O hydroxamate), 140.3 (*ipso*-Ar), 134.9 (*ipso*-Ar), 128.8 (Ar), 128.0 (Ar), 38.7 (CMe_3), 27.2 (CMe_3), 27.0 (Me) (9 out of 10 signals present); HRMS found MH^+, 264.1220. $C_{14}H_{18}NO_4$ requires 264.1230. Spectroscopic data are consistent with those reported in the literature.[162]

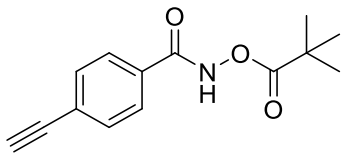
***N*-(Pivaloyloxy)benzo[b]thiophene-2-carboxamide 364**



364

Compound **364** was prepared by a variation on the method of Webb *et al*.[162] Oxalyl chloride (129 µL, 1.5 mmol) was added to a solution of benzothiophene-2-carboxylic acid (223 mg, 1.25 mmol) in DCM (6.3 mL) with catalytic DMF and stirred at rt for 3 h. The solution was then concentrated under reduced pressure to give the crude acid chloride which was then dissolved in EtOAc (1.4 mL) and transferred to a flask containing a solution of H_2NOPiv triflic acid salt (368 mg, 1.38 mmol) and K_2CO_3 (345 mg, 2.5 mmol) in EtOAc (4.2 mL) and water (2.1 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL) added. The layers were then separated and the organic layer washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography, eluting with 80:20 hexane–EtOAc to yield the hydroxamate **364** (285 mg, 82%) as a white solid, R_f 0.22 (80:20 hexane–EtOAc); m.p. 139–141 °C, lit. 134.0–134.6 °C;[162] ν_{max}/cm^{-1} 3141 (NH), 2970, 1779 (C=O), 1636 (C=O), 1527, 1304, 1122, 1064, 1021, 868 and 748; δ_H (500 MHz, $CDCl_3$) 9.34 (1H, s, NH), 7.92 (1H, s, Ar), 7.88 (2H, d, *J* 9.1, Ar), 7.47 (1H, app. td, *J* 7.2, 1.3, Ar), 7.43 (1H, app. td, *J* 7.2, 1.1, Ar), 1.38 (9H, s, $(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 177.1 (C=O hydroxamate), 162.2 (C=O Piv), 141.4 (*ipso*-Ar), 138.8 (*ipso*-Ar), 133.3 (*ipso*-Ar), 127.8 (Ar), 127.3 (Ar), 125.6 (Ar), 125.4 (Ar), 122.9 (Ar), 38.7 (CMe_3), 27.2 (CMe_3); HRMS found MH^+, 278.0836. $C_{14}H_{16}NO_3S$ requires 278.0845. Spectroscopic data are consistent with those reported in the literature.[162]

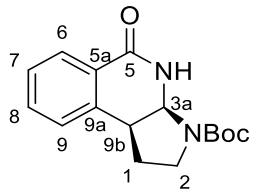
4-Ethynyl-*N*-(pivaloyloxy)benzamide 365



365

Compound **365** was prepared by a variation on the method of Webb *et al*.[162] Oxalyl chloride (64.5 µL, 0.75 mmol) was added to a solution of 4-ethynylbenzoic acid (91.3 mg, 0.625 mmol) in DCM (3.2 mL) with catalytic DMF and stirred at rt for 3 h. The solution was then concentrated under reduced pressure to give the crude acid chloride which was then dissolved in EtOAc (0.7 mL) and transferred to a flask containing a solution of H_2NOPiv triflic acid salt (193 mg, 0.69 mmol) and K_2CO_3 (173 mg, 1.25 mmol) in EtOAc (2.1 mL) and water (1.1 mL) at 0 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure and EtOAc (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL) added. The layers were then separated and the organic layer washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the *hydroxamate* **365** (98.6 mg, 64%) as a white solid, m.p. 156–158 °C; ν_{max}/cm^{-1} 3269, 3201 (NH), 2978, 1778 (C=O), 1645 (C=O), 1488, 1305, 1068, 1028 and 858; δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.3, Ar), 7.53 (2H, d, *J* 8.3, Ar), 3.23 (1H, s, C≡CH), 1.34 (9H, s, $(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 177.1 (C=O hydroxamate), 166.0 (C=O hydroxamate), 132.6 (Ar), 130.9 (*ipso*-Ar), 127.6 (Ar), 126.7 (*ipso*-Ar), 82.6 (*C*≡CH), 80.3 (C≡*C*H), 38.6 (*C*Me_3), 27.1 (C*Me*$_3$); HRMS found MNa^+, 268.0939. $C_{14}H_{15}NO_3Na$ requires 268.0944.

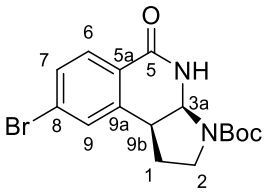
***tert*-Butyl 5-oxo-1,2,3a,4,5,9b-hexahydro-3H-pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-354**[162]



cis-**354**

Compound *cis*-**354** was synthesised using general method I using enecarbamate **81** (31.8 mg, 0.188 mmol) and hydroxamate **359** (27.7 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield carbamate *cis*-**354** as a 1:1 mixture of rotamers (22.5 mg, 62%) as a yellow solid, R_f 0.29 (1:1 hexane−EtOAc); m.p. 129–130 °C, lit. 161–165 °C;[162] ν_{max}/cm^{-1} 3216 (NH), 2975, 1682 (C=O), 1387, 1366, 1284, 1153, 1116, 757, 732 and 699; δ_H (500 MHz, $CDCl_3$) 8.13 (1H, dd, *J* 7.6, 2.9, 6-H), 7.49 (1H, ddd, *J* 7.4, 7.1, 3.4, 8-H), 7.39 (1H, t, *J* 7.6, 7-H), 7.26 (1H, d, *J* 7.4, 9-H), 6.54 (0.5H, s, NH), 6.22 (0.5H, s, NH), 5.60 (0.5H, d, *J* 6.7, 3a-H), 5.54 (0.5H, d, *J* 6.5, 3a-H), 3.58 (0.5H, app. t, *J* 9.2, 2-H_A), 3.53 (0.5H, app. t, *J* 8.6, 2-H_A), 3.48–3.36 (2H, m, 2-H_B, 9b-H), 2.34–2.25 (1H, m, 1-H_A), 2.19–2.07 (1H, m, 1-H_B), 1.52 (4.5H, s, CMe_3), 1.49 (4.5H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 163.5 (C-5 C=O), 163.2 (C-5 C=O), 154.7 (Boc C=O), 153.5 (Boc C=O), 138.1 (C-5a), 138.0 (C-5a), 132.9 (C-8), 132.7 (C-8), 128.7 (C-6), 127.9 (C-7), 127.8 (C-7), 127.5 (C-9), 126.5 (C-9a), 126.2 (C-9a), 81.5 (CMe_3), 80.9 (CMe_3), 67.5 (C-3a), 45.2 (C-2), 45.1 (C-2), 41.8 (C-9b), 40.7 (C-9b), 33.8 (C-1), 32.7 (C-1), 28.6 (CMe_3), 28.5 (CMe_3) (25 out of 28 signals present); HRMS found MH^+, 289.1536. $C_{16}H_{21}N_2O_3$ requires 289.1547. Spectroscopic data are consistent with those reported in the literature.[162]

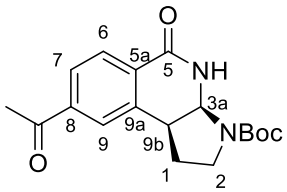
***tert*-Butyl 8-bromo-5-oxo-1,2,3a,4,5,9b-hexahydro-3H-pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-370**[162]



cis-**370**

Compound *cis*-**370** was synthesised using general method I using enecarbamate **81** (31.8 mg, 0.188 mmol) and hydroxamate **360** (37.4 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *carbamate cis*-**370** as a 55:45 mixture of rotamers (20.2 mg, 44%) as a yellow solid, R_f 0.36 (1:1 hexane−EtOAc); m.p. 170–172 °C; ν_{max}/cm^{-1} 3202 (NH), 2976, 1666 (C=O), 1593, 1387, 1366, 1285, 1154, 1122, 776 and 735; δ_H (500 MHz, $CDCl_3$) 7.99 (1H, dd, *J* 8.2, 3.0, 3.4, 6-H), 7.52 (1H, br d, *J* 8.3, 7-H), 7.43 (1H, d, *J* 1.2, 9-H), 6.60 (0.55H, s, NH), 6.38 (0.45H, s, NH), 5.59 (0.55H, d, *J* 6.7, 3a-H), 5.53 (0.45H, d, *J* 6.4, 3a-H), 3.59 (0.45H, app. t, *J* 9.4, 2-H_A), 3.54 (0.55H, t, *J* 8.9, 2-H_A), 3.50–3.44 (0.45H, br m, 2-H_B), 3.44–3.37 (1.55H, br m, 2-H_B, 9b-H), 2.35–2.27 (1H, br m, 1-H_A), 2.16–2.08 (1H, br m, 1-H_B), 1.52 (4.05H, s, CMe_3), 1.49 (4.95H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 162.9 (C-5 C=O), 162.4 (C-5 C=O), 154.7 (Boc C=O), 153.4 (Boc C=O), 140.0 (C-5a), 139.9 (C-5a), 131.3 (C-6), 131.2 (C-6), 130.54 (C-9), 130.50 (C-7), 130.46 (C-7), 127.6 (C-8), 127.4 (C-8), 125.5 (C-9a), 125.2 (C-9a), 81.7 (*C*Me_3), 81.1 (*C*Me_3), 67.4 (C-3a), 45.2 (C-2), 45.0 (C-2), 41.4 (C-9b), 40.3 (C-9b), 33.6 (C-1), 32.6 (C-1), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$) (25 out of 28 signals present); HRMS found MH^+, 367.0642. $C_{16}H_{20}{}^{79}BrN_2O_3$ requires 367.0652.

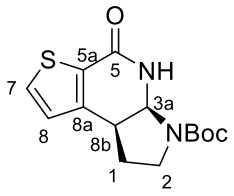
***tert*-Butyl 8-acetyl-5-oxo-1,2,3a,4,5,9b-hexahydro-3H-pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-371**



cis-**371**

Compound *cis*-**371** was synthesised using general method I using enecarbamate **81** (31.8 mg, 0.188 mmol) and hydroxamate **363** (32.9 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 75:25 EtOAc−hexane to yield *carbamate cis*-**371** as a 55:45 mixture of rotamers (22.8 mg, 55%) as a yellow semi-solid, R_f 0.15 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 3233 (NH), 2976, 1669 (C=O), 1390, 1366, 1259, 1157, 1123 and 700; δ_H (500 MHz, $CDCl_3$) 8.23 (1H, d, *J* 8.0, 6-H), 7.92 (1H, d, *J* 8.0, 7-H), 7.86 (1H, d, *J* 1.4, 9-H), 6.63 (0.55H, s, NH), 6.24 (0.45H, s, NH), 5.62 (0.55H, d, *J* 6.7, 3a-H), 5.56 (0.45H, d, *J* 6.4, 3a-H), 3.63–3.39 (3H, br m, 2-H_2, 9b-H), 2.64 (3H, s, Me), 2.39–2.30 (1H, br m, 1-H_A), 2.19–2.07 (1H, br m, 1-H_B), 1.52 (4.05H, s, CMe_3), 1.49 (4.95H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 197.6 (C=O Ac), 197.5 (C=O Ac), 162.4 (C-5 C=O), 162.1 (C-5 C=O), 154.7 (Boc C=O), 153.3 (Boc C=O), 140.3 (C-5a), 140.1 (C-5a), 138.5 (C-9a), 138.4 (C-9a), 130.2 (C-8), 130.0 (C-8), 129.2 (C-6), 127.8 (C-7), 127.7 (C-7), 127.3 (C-9), 81.7 (*C*Me_3), 80.1 (*C*Me_3), 67.4 (C-3a), 45.2 (C-2), 45.0 (C-2), 41.7 (C-9b), 40.6 (C-9b), 33.7 (C-1), 32.7 (C-1), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 27.0 (Me) (28 out of 32 signals present); HRMS found MNa^+, 353.1466. $C_{18}H_{22}N_2O_4Na$ requires 353.1472.

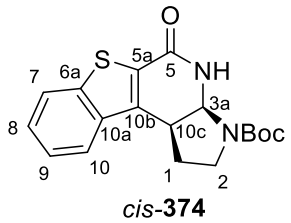
***tert*-Butyl 5-oxo-1,2,3a,4,5,8b-hexahydro-3H-pyrrolo[2,3-b]thieno[3,2-d]pyridine-3-carboxylate *cis*-373**



cis-**373**

Compound *cis*-**373** was synthesised using general method I using enecarbamate **81** (31.8 mg, 0.188 mmol) and hydroxamate **361** (28.4 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *carbamate cis*-**373** as a 55:45 mixture of rotamers (14.4 mg, 39%) as a yellow solid, R_f 0.21 (1:1 hexane−EtOAc); m.p. 179–181 °C; ν_{max}/cm^{-1} 3253 (NH), 2974, 2882, 1694 (C=O), 1635 (C=O), 1453, 1379, 1358, 1286, 1165, 1130, 772, 751 and 718; δ_H (500 MHz, $CDCl_3$) 7.56 (0.45H, d, *J* 5.2, 7-H), 7.55 (0.55H, d, *J* 4.9, 7-H), 6.98 (1H, d, *J* 4.6, 8-H), 6.50 (0.55H, s, NH), 5.98 (0.45H, s, NH), 5.56 (0.55H, d, *J* 7.1, 3a-H), 5.54 (0.45H, d, *J* 6.8, 3a-H), 3.61–3.55 (1H, br m, 8b-H), 3.54–3.48 (0.45H, br m, 2-H_A), 3.48–3.41 (1H, br m, 2-H_A, 2-H_B), 3.38–3.33 (0.55H, br m, 2-H_B), 2.34–2.26 (1H, m, 1-H_A), 2.18–2.09 (1H, m, 1-H_B), 1.53 (4.05H, s, CMe_3), 1.47 (4.95H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 160.4 (C-5 C=O), 160.3 (C-5 C=O), 154.8 (Boc C=O), 153.6 (Boc C=O), 144.0 (C-5a), 143.9 (C-5a), 132.5 (C-7), 132.3 (C-7), 130.4 (C-8a), 130.0 (C-8a), 126.4 (C-8), 126.3 (C-8), 81.5 (*C*Me_3), 80.9 (*C*Me_3), 69.5 (C-3a), 45.1 (C-2), 39.3 (C-8b), 38.1 (C-8b), 32.2 (C-1), 31.4 (C-1), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$) (22 out of 24 signals present); HRMS found MNa^+, 317.0920. $C_{14}H_{18}N_2O_3SNa$ requires 317.0930.

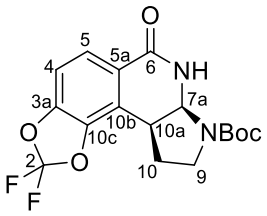
***tert-butyl* 5-oxo-1,2,3a,4,5,10c-hexahydro-3H-benzo[4,5]thieno[3,2-d]pyrrolo[2,3-b]pyridine-3-carboxylate *cis*-374**



cis-**374**

Compound *cis*-**374** was synthesised using general method I using enecarbamate **81** (31.8 mg, 0.188 mmol) and hydroxamate **364** (34.6 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 2:1 hexane−EtOAc to yield carbamate *cis*-**374** as a 55:45 mixture of rotamers (11.0 mg, 26%) as a white solid, R_f 0.40 (1:1 hexane−EtOAc); m.p. 177–179 °C; ν_{max}/cm^{-1} 3200 (NH), 2975, 2932, 2891, 1701 (C=O), 1651 (C=O), 1385, 1364, 1289, 1150, 1127, 913, 757 and 732; δ_H (500 MHz, $CDCl_3$) 7.93 (1H, d, *J* 7.6, 7-H), 7.77 (1H, d, *J* 7.4, 10-H), 7.52–7.42 (2H, br m, 8-H, 9-H), 6.59 (0.55H, s, NH), 6.14 (0.45H, s, NH), 5.79 (0.55H, d, *J* 7.3, 3a-H), 5.74 (0.45H, d, *J* 7.0, 3a-H), 3.79 (1H, dt, *J* 11.0, 7.2, 10c-H), 3.70–3.63 (0.45H, br m, 2-H_A), 3.63–3.52 (1H, br m, 2-H_A, 2-H_B), 3.52–3.44 (0.55H, br m, 2-H_B), 2.56–2.48 (1H, m, 1-H_A), 2.22–2.10 (1H, br m, 1-H_B), 1.54 (4.05H, s, CMe_3), 1.51 (4.95H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 160.8 (C-5 C=O), 160.5 (C-5 C=O), 154.7 (Boc C=O), 153.4 (Boc C=O), 142.4 (C-10a), 138.8 (C-10b), 138.5 (C-10b), 137.3 (C-6a), 137.2 (C-6a), 130.4 (C-5a), 130.0 (C-5a), 127.3 (C-9), 127.1 (C-9), 125.2 (C-8), 125.1 (C-8), 123.8 (C-10), 122.8 (C-7), 81.8 (*C*Me_3), 81.2 (*C*Me_3), 69.7 (C-3a), 45.4 (C-2), 38.2 (C-10c), 38.7 (C-10c), 31.9 (C-1), 30.8 (C-1), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$) (27 out of 32 signals present); HRMS found MNa^+, 367.1074. $C_{18}H_{20}N_2O_3SNa$ requires 367.1086.

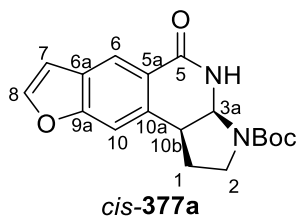
***tert*-Butyl 2,2-difluoro-6-oxo-6,7,7a,9,10,10a-hexahydro-8H-[1,3]dioxolo[4,5-f]pyrrolo[2,3-c]isoquinoline-8-carboxylate *cis*-376**



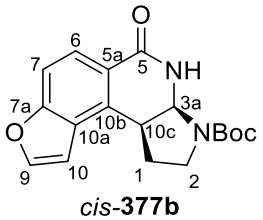
cis-**376**

Compound *cis*-**376** was synthesised using general method I using enecarbamate **81** (63.1 mg, 0.372 mmol) and hydroxamate **367** (74.8 mg, 0.248 mmol) in MeOH (1.3 mL). The crude product contained *cis*-**376** as a single regioisomer and was purified by flash column chromatography eluting with 1:1 petroleum ether−EtOAc to yield *carbamate cis*-**376** as a single regioisomer and as a 55:45 mixture of rotamers (16.5 mg, 18%) as a white solid, R_f 0.45 (1:1 petroleum ether−EtOAc); m.p. 156–158 °C; ν_{max}/cm^{-1} 3184 (NH), 3066, 2975, 1706 (C=O), 1682 (C=O), 1646, 1390, 1231, 1163, 1124, 1094 and 767; δ_H (500 MHz, $CDCl_3$) 7.98 (1H, d, *J* 8.4, 5-H), 7.08 (1H, d, *J* 8.4, 4-H), 6.56 (0.55H, s, NH), 6.15 (0.45H, s, NH), 5.61 (0.55H, d, *J* 6.8, 7a-H), 5.55 (0.45H, d, *J* 6.5, 7a-H), 3.67–3.55 (1.5H, m, 10a-H, 9-H_A), 3.55–3.39 (1.5H, m, 9-H_A, 9-H_B), 2.49–2.39 (1H, m, 10-H_A), 2.19–2.06 (1H, m, 10-H_B), 1.52 (4.05H, s, CMe_3), 1.50 (4.95H, s, CMe_3); δ_C (125 MHz, $CDCl_3$) 162.1 (C-6 C=O), 161.7 (C-6 C=O), 154.6 (Boc C=O), 153.2 (Boc C=O), 146.5 (C-3a), 146.4 (C-3a), 140.7 (C-10c), 132.0 (t, *J* 258, C-2), 125.5 (C-5), 122.6 (C-5a), 122.3 (C-5a), 120.7 (C-10b), 120.6 (C-10b), 108.8 (C-4), 108.7 (C-4), 81.5 (*C*Me_3), 81.3 (*C*Me_3), 67.4 (C-7a), 45.3 (C-9), 45.2 (C-9), 35.9 (C-10b), 34.9 (C-10b), 31.4 (C-10), 30.4 (C-10), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$) (26 out of 30 signals present); δ_F (376 MHz, $CDCl_3$) –48.8 (0.45F, d, *J* 93.4, CF), –48.9 (0.55F, d, *J* 93.3, CF), –49.4 (0.55F, d, *J* 93.3, CF), –49.6 (0.45F, d, *J* 93.1, CF); HRMS found MNa^+, 391.1073. $C_{17}H_{18}F_2N_2O_5Na$ requires 391.1076.

***tert*-Butyl 5-oxo-1,2,3a,4,5,10b-hexahydro-3H-furo[2,3-g]pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-377a and *tert*-Butyl 5-oxo-1,2,3a,4,5,10c-hexahydro-3H-furo[3,2-f]pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-377b**



cis-**377a**

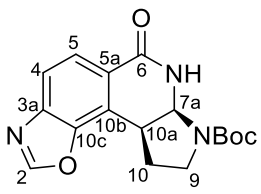


cis-**377b**

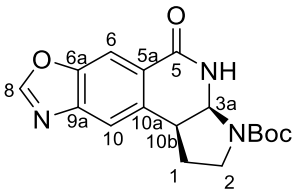
Compound **377** was synthesised using general method I using enecarbamate **81** (21.6 mg, 0.128 mmol) and hydroxamate **368** (22.2 mg, 0.085 mmol) in MeOH (0.5 mL). The crude product containing a 1:1 mixture of regioisomeric *carbamates* **377a** and **377b** and was purified by flash column chromatography eluting with 1:1 petroleum ether−EtOAc to yield a 60:40 mixture of regioisomeric *carbamates cis*-**377a** and *cis*-**377b** as a 1:1 mixture of rotamers (17.6 mg, 63%) as a pale yellow oil, R_f 0.21 (1:1 petroleum ether−EtOAc); ν_{max}/cm^{-1} 3209 (NH), 2977, 2933, 1657 (C=O), 1389, 1366, 1285, 1256, 1163, 1145, 1125 and 732; δ_H (500 MHz, $CDCl_3$) 8.45 (0.4H, s, 6-H **377a**), 8.14 (0.6H, dd, *J* 8.6, 3.7, 6-H, **377b**), 7.73 (0.6H, app. s, 8-H **377a**, 9-H **377b**), 7.66 (0.4H, d, *J* 3.7, 8-H **377a**, 9-H **377b**), 7.51 (0.6H, dd, *J* 8.7, 2.6, 7-H, **377b**), 7.38 (0.4H, s, 10-H, **377a**), 6.84 (1H, app. s, 7-H **377a,** 10-H **377b**), 6.54–6.46 (0.4H, s, NH **377a** and **377b**), 6.24–6.07 (0.6H, s, NH **377a** and **377b**), 5.71 (0.3H, d, *J* 6.8, 3a-H **377a**), 5.64 (0.5H, d, *J* 6.6, 3a-H **377a** and **377b**), 5.58 (0.2H, d, *J* 6.4, 3a-H **377b**), 3.79–3.37 (3H, m, 10b **377a**, 10c **377b**, 2-H_2 **377a** and **377b**), 2.48–2.40 (0.6H, m, 1-H_A **377a** or **377b**), 2.36–2.28 (0.4H, m, 1-H_A **377a** or **377b**), 2.23–2.09 (1H, m, 1-H_B **377a** and **377b**), 1.54–1.49 (9H, s, CMe_3 **377a** and **377b**); δ_C (125 MHz, $CDCl_3$) 163.8 (C-5 C=O), 163.5 (C-5 C=O), 157.35, 157.32, 157.25, 157.2 (C-9a **377a**, C-7a **377b**), 154.8 (Boc C=O), 154.7 (Boc C=O), 153.5 (Boc C=O), 153.4 (Boc C=O), 146.7, 146.6, 146.4, 146.3 (C-8 **377a**, C-9 **377b**), 134.7 (C-5a **377a**), 134.6 (C-5a **377a**), 132.1 (C-5a **377b**), 132.0 (C-5a **377b**), 125.7, 125.6 (C-6a **377a**, C-10a **377b**), 125.4 (C-6 **377b**), 125.3 (C-6 **377b**), 123.1 (C-6 **377a**), 121.9, 121.5, 121.2, 120.8 (C-10a **377a**, C-10b **377b**), 111.1 (C-10 **377a**), 111.0 (C-10 **377a**), 110.2 (C-7 **377b**), 110.1 (C-7 **377b**), 107.4, 104.81,

104.77 (C-7 **377a**, C-10 **377b**), 81.6 (*C*Me$_3$), 81.5 (*C*Me$_3$), 81.0 (*C*Me$_3$), 80.9 (*C*Me$_3$), 67.7 (C-3a), 67.5 (C-3a), 45.33 (C-2), 45.26 (C-2), 45.2 (C-2), 45.1 (C-2), 42.5, 41.4, 39.7, 38.6 (C-10b **377a**, C-10c **377b**), 34.2, 33.2, 32.7, 31.6 (C-1), 28.7 (C*Me*$_3$), 28.6 (C*Me*$_3$) (54 out of 64 signals present); HRMS found MH$^+$, 329.1487. $C_{18}H_{21}N_2O_4$ requires 329.1496.

tert-Butyl 6-oxo-6,7,7a,9,10,10a-hexahydro-8H-oxazolo[5,4-f]pyrrolo[2,3-c]isoquinoline-8-carboxylate _cis_-378a and _tert_-Butyl 5-oxo-1,2,3a,4,5,10b-hexahydro-3H-oxazolo[4,5-g]pyrrolo[2,3-c]isoquinoline-3-carboxylate _cis_-378b



cis-**378a**

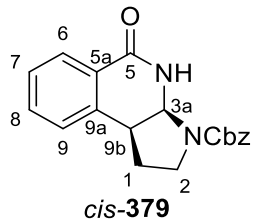


cis-**378b**

Compound **378** was synthesised using general method I using enecarbamate **81** (17.5 mg, 0.100 mmol) and hydroxamate **369** (18.0 mg, 0.0667 mmol) in MeOH (0.4 mL). The crude product contained a 75:25 mixture of *carbamates cis*-**378a** and *cis*-**378b** and crude product was purified by flash column chromatography eluting with 75:25 EtOAc–hexane to yield a 60:40 mixture of *carbamates cis*-**378a** and *cis*-**378b**, both as 55:45 mixtures of rotamers (1.3 mg, 6%) as a pale yellow oil, R_f 0.13 (1:1 hexane–EtOAc); ν_{max}/cm^{-1} 3246 (NH), 2925, 2854, 1660 (C=O), 1451, 1393, 1165, 1140 and 736; δ_H (500 MHz, $CDCl_3$) 8.29–8.18 (1.6H, m, 2-H, 5-H **378a**, 8-H **378b**), 7.79 (0.6H, dd, *J* 8.4, 2.6, 4-H, **378a**), 7.68 (0.4H, app. d, *J* 8.1, 6-H **378b**), 6.92 (0.4H, app. t, *J* 7.3, 10-H, **378b**), 6.59 (0.4H, s, NH **378a**), 6.54 (0.2H, s, NH **378a**), 6.21 (0.15H, s, NH **378b**), 6.15 (0.25H, s, NH **378a**), 5.70 (0.35H, d, *J* 7.0, 7a-H **378a**), 5.64 (0.3H, d, *J* 6.5, 7a-H **378a**), 5.57 (0.2H, d, *J* 6.5, 3a-H **378b**), 5.51 (0.15H, d, *J* 6.7, 3a-H **378b**), 3.96–3.87 (0.6H, m, 10a **378a**), 3.86–3.75 (0.4H, m, 10b **378b**), 3.70–3.54 (1.4H, m, 9-H_A **378a,** 2-H_2 **378b**), 3.53–3.45 (0.6H, m, 9-H_B **378a**), 2.59–2.48 (1H, m, 10-H_A **378a**, 1-H_A **378b**), 2.27–2.13 (0.6H, m, 10-H_B **378a**), 1.98–1.88 (0.4H, m, 1-H_B **378b**), 1.55–

1.49 (9H, m, CMe_3); δ_C (125 MHz, $CDCl_3$) 167.6 (C=O amide), 160.6 (C-2 **378a**), 154.6, 154.5 (Boc C=O, C-8 **378b**), 125.4 (C-5 **378a**), 120.8, 120.7 (C-6, C-10 **378b**), 119.6 (C-4 **378a**), 81.8 (*C*Me_3), 80.9 (*C*Me_3), 67.6 (C-7a **378a**, C-3a **378b**), 45.4, 45.3 (C-9 **378a**, C-2 **378b**), 35.8, 35.6 (C-10a **378a**, C-10b **378b**), 31.9, 30.9 (C-10 **378a**, C-1 **378b**), 28.7 (C*Me*$_3$), 28.6 (C*Me*$_3$) (19 out of 30 signals present due to weak sample); HRMS found MNa^+, 352.1261. $C_{17}H_{19}N_3NaO_4$ requires 352.1268.

Benzyl 5-oxo-1,2,3a,4,5,9b-hexahydro-3H-pyrrolo[2,3-c]isoquinoline-3-carboxylate *cis*-379

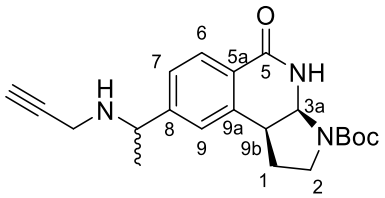


cis-**379**

Compound *cis*-**379** was synthesised using general method I using enecarbamate **68** (38.2 mg, 0.188 mmol) and hydroxamate **359** (27.7 mg, 0.125 mmol) in MeOH (0.6 mL). The crude product was purified by flash column chromatography eluting with 1:1 hexane−EtOAc to yield *carbamate cis*-**379** as a 55:45 mixture of rotamers (17.2 mg, 43%) as a yellow oil, R_f 0.18 (1:1 hexane−EtOAc); ν_{max}/cm^{-1} 3199 (NH), 2952, 2893, 1699 (C=O), 1661 (C=O), 1408, 1358, 1283, 1112, 757, 733 and 698; δ_H (500 MHz, $CDCl_3$) 8.15 (0.55H, d, *J* 7.7, 6-H), 8.12 (0.45H, d, *J* 7.8, 6-H), 7.82 (0.45H, d, *J* 7.1, 9-H), 7.50 (1H, td, *J* 7.5, 1.2, 8-H), 7.47–7.40 (1H, m, 7-H), 7.39–7.33 (5H, m, Ph), 7.28–7.25 (0.55H, m, 9-H), 6.48 (0.55H, s, NH), 6.11 (0.45H, s, NH), 5.66 (0.55H, d, *J* 6.7, 3a-H), 5.62 (0.45H, d, *J* 6.5, 3a-H), 5.28–5.14 (2H, m, CH_2 Cbz), 3.68–3.58 (1H, m, 2-H_A), 3.56–3.44 (2H, m, 2-H_B, 9b-H), 2.36–2.29 (1H, m, 1-H_A), 2.23–2.12 (1H, m, 1-H_B); δ_C (125 MHz, $CDCl_3$) 163.4 (C-5 C=O), 163.1 (C-5 C=O), 155.3 (Cbz C=O), 154.1 (Cbz C=O), 137.8 (C-5a), 137.7 (C-5a), 136.3 (*ipso*-Ph), 136.0 (*ipso*-Ph), 133.0 (C-8), 132.8 (C-8), 128.9 (Ar), 128.8 (Ar), 128.73 (Ar), 128.70 (Ar), 128.65 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.53 (Ar), 127.50 (Ar), 127.49 (Ar), 126.5 (C-9a),

126.2 (C-9a), 67.9 (C-3a), 67.8 (C-3a), 67.5 (CH_2 Cbz), 67.4 (CH_2 Cbz), 45.6 (C-2), 45.1 (C-2), 41.7 (C-9b), 40.6 (C-9b), 33.7 (C-1), 32.7 (C-1) (26 out of 34 signals present); HRMS found MNa^+, 345.1201. $C_{19}H_{18}N_2O_3Na$ requires 345.1210.

tert-Butyl 5-oxo-8-(1-(prop-2-yn-1-ylamino)ethyl)-1,2,3a,4,5,9b-hexahydro-3H-pyrrolo[2,3-c]isoquinoline-3-carboxylate _cis_-384



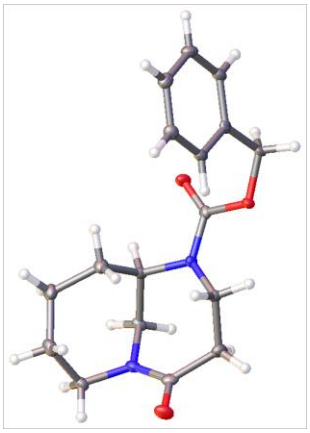
cis-**384**

Compound *cis*-**384** was prepared by a variation on the method of Burke *et al*.[163] Propargylamine (7.8 µL, 0.122 mmol) was added to a mixture of ketone *cis*-**371** (20.0 mg, 0.061 mmol) and NaOAc (10.0 mg, 0.122 mmol) in DCE (1 mL) and stirred at rt for 30 min. Then, $NaBH(OAc)_3$ (25.9 mg, 0.122 mmol) was added and the resultant mixture stirred for 72 h. The mixture was then concentrated under reduced pressure and DCM (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL) added. The layers were then separated and the organic layer washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 90:10 EtOAc−MeOH to yield *carbamate cis*-**384** as a 55:45 mixture of rotamers and an undetermined mixture of diastereomers (3.2 mg, 14%) as a colourless oil, R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 2951, 1736 (C=O), 1698 (C=O), 1410, 1392, 1328, 1254, 1160, 1115 and 701; δ_H (500 MHz, $CDCl_3$) 8.09 (1H, d, *J* 7.9, 6-H), 7.36 (1H, d, *J* 7.2, 7-H), 7.28 (1H, s, 9-H), 6.46 (0.55H, s, NH), 5.99 (0.45H, s, NH), 5.59 (0.55H, d, *J* 5.4, 3a-H), 5.56–5.51 (0.45H, br m, 3a-H), 4.08 (1H, q, *J* 6.5, ethyl-1H), 3.59 (0.45H, app. t, *J* 9.5, 2-H_A), 3.54 (0.55H, app. t, *J* 9.3, 2-H_A), 3.50–3.34 (3H, br m, 2-H_B, 9b-H, propynylamino-2H_A), 3.20–3.16 (0.55H, br m, propynylamino-2H_B), 3.16–3.12 (0.45H, br m, propynylamino-2H_B), 2.35–2.26 (1H, br m, 1-H_A), 2.23 (1H, t,

J 2.1, propynylamino-4H), 2.19–2.09 (1H, br m, 1-H_B), 1.52 (4.05H, s, CMe_3), 1.49 (4.95H, s, CMe_3), 1.37 (3H, t, *J* 6.6, ethyl-$2H_3$); δ_C (125 MHz, $CDCl_3$) 163.2 (C-5 C=O), 162.9 (C-5 C=O), 154.6 (Boc C=O), 153.4 (Boc C=O), 138.6 (C-9a), 138.3 (C-9a), 128.92 (C-6), 128.89 (C-6), 126.4 (C-7), 125.8 (C-7), 125.7 (C-9), 125.5 (C-9), 81.9 (propylamino-C3), 81.3 (*C*Me_3), 80.8 (*C*Me_3), 71.6 (propylamino-C4), 67.42 (C-3a), 67.38 (C-3a), 56.13 (ethyl-C1), 56.09 (ethyl-C1), 45.1 (C-2), 45.0 (C-2), 41.9 (C-9b), 40.7 (C-9b), 36.0 (propynylamino-C2), 33.7 (C-1), 32.6 (C-1), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$), 24.0 (ethyl-C2), 23.9 (ethyl-C2) (31 out of 38 signals present); HRMS found MH^+, 370.2125. $C_{21}H_{28}N_3O_3$ requires 370.2125.

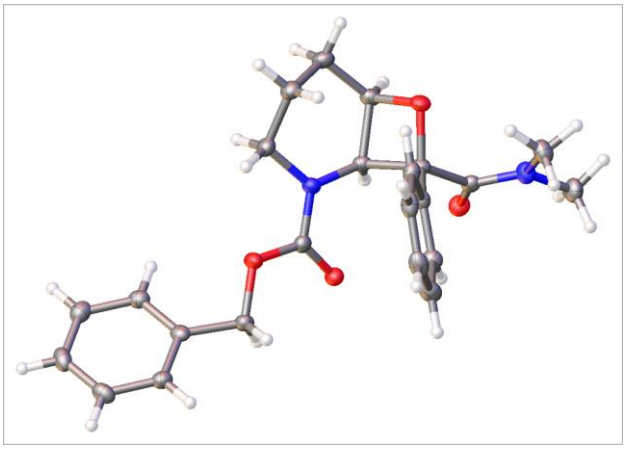
7.4 X-ray crystal structures

Table 7.1: Crystal data and structure refinement for **257** (Chapter 4). CCDC 2192693.



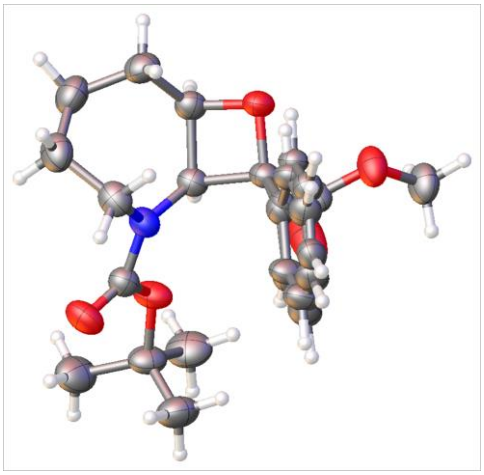
Identification code	AH_5_7_P
Empirical formula	$C_{17}H_{22}N_2O_3$
Formula weight	302.36
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.1041(10)
b/Å	11.5162(9)
c/Å	10.8177(8)
α/°	90
β/°	95.407(7)
γ/°	90
Volume/Å^3	1501.2(2)
Z	4
ρ_{calc}g/cm^3	1.338
μ/mm^{-1}	0.092
F(000)	648
Crystal size/mm^3	0.25 × 0.15 × 0.09
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.178 to 59.002
Index ranges	-16 ≤ h ≤ 12, -12 ≤ k ≤ 15, -14 ≤ l ≤ 14
Reflections collected	8357
Independent reflections	3554 [R_{int} = 0.0392, R_{sigma} = 0.0672]
Data/restraints/parameters	3554/0/199
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0628, wR_2 = 0.1184
Final R indexes [all data]	R_1 = 0.0913, wR_2 = 0.1305
Largest diff. peak/hole / e Å^{-3}	0.29/-0.27

Table 7.2: Crystal data and structure refinement for **339** (Chapter 5).



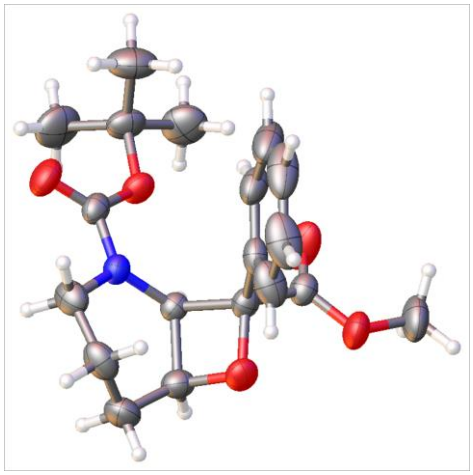
Identification code	AH_7_3__P_170223
Empirical formula	$C_{23}H_{26}N_2O_4$
Formula weight	394.46
Temperature/K	100.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.0346(3)
b/Å	9.2290(3)
c/Å	13.0819(4)
α/°	96.410(3)
β/°	100.682(3)
γ/°	111.053(3)
Volume/Å^3	981.25(6)
Z	2
ρ_{calc}g/cm^3	1.335
μ/mm^{-1}	0.743
F(000)	420.0
Crystal size/mm^3	0.17 × 0.11 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.01 to 145.722
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -16 ≤ l ≤ 16
Reflections collected	17811
Independent reflections	3704 [R_{int} = 0.0334, R_{sigma} = 0.0229]
Data/restraints/parameters	3704/0/264
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0379, wR_2 = 0.0935
Final R indexes [all data]	R_1 = 0.0422, wR_2 = 0.0969
Largest diff. peak/hole / e Å^{-3}	0.41/-0.21

Table 7.3: Crystal data and structure refinement for **327** (Chapter 5).



Identification code	AH_6_76_P2_170223
Empirical formula	$C_{20}H_{27}NO_5$
Formula weight	361.42
Temperature/K	250.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.5531(3)
b/Å	17.4550(6)
c/Å	13.4335(5)
α/°	90
β/°	107.071(4)
γ/°	90
Volume/Å^3	1917.18(12)
Z	4
ρ_{calc}g/cm^3	1.252
μ/mm^{-1}	0.732
F(000)	776.0
Crystal size/mm^3	0.16 × 0.13 × 0.07
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.548 to 145.79
Index ranges	-8 ≤ h ≤ 10, -15 ≤ k ≤ 21, -16 ≤ l ≤ 16
Reflections collected	7296
Independent reflections	3717 [R_{int} = 0.0266, R_{sigma} = 0.0327]
Data/restraints/parameters	3717/88/293
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0460, wR_2 = 0.1138
Final R indexes [all data]	R_1 = 0.0605, wR_2 = 0.1253
Largest diff. peak/hole / e Å^{-3}	0.51/-0.42

Table 7.4: Crystal data and structure refinement for **325** (Chapter 5).



Identification code	AH_6_79_P4_170223
Empirical formula	$C_{19}H_{25}NO_5$
Formula weight	347.40
Temperature/K	250.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.2798(2)
b/Å	22.8829(4)
c/Å	9.4074(2)
α/°	90
β/°	112.943(3)
γ/°	90
Volume/Å^3	1839.62(7)
Z	4
ρ_{calc}g/cm^3	1.254
μ/mm^{-1}	0.743
F(000)	744.0
Crystal size/mm^3	0.18 × 0.15 × 0.09
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.726 to 145.628
Index ranges	-11 ≤ h ≤ 11, -27 ≤ k ≤ 28, -11 ≤ l ≤ 11
Reflections collected	17449
Independent reflections	3604 [R_{int} = 0.0303, R_{sigma} = 0.0197]
Data/restraints/parameters	3604/0/230
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0416, wR_2 = 0.1059
Final R indexes [all data]	R_1 = 0.0498, wR_2 = 0.1130
Largest diff. peak/hole / e Å^{-3}	0.16/-0.20

7.5 Biological and chemical biological experimental

7.5.1 Evaluating antibacterial activity of isolated twisted lactams

All antibacterial screening was performed by Julian Chesti. Method employed as reported by Abbie Leggott.[188] Minimum inhibitory concentration (MIC) values for selected compounds were determined by broth microdilution against *S. aureus* strain $ATCC_{29213}$[189] according to CLSI guidelines for low solubility compounds except for using Iso-Sensitest Broth (ISB) in place of cation-adjusted Mueller-Hinton Broth (MHB-II).[190]

A 2-fold dilution series of the isolated compounds in DMSO was prepared, ranging from 6400–12.5 $\mu g mL^{-1}$. Each dilution was transferred into a 96-well format at a final volume of 1 µL and 99 µL of the standardised culture was added to each well to give final antibiotic concentrations of 64–0.125 $\mu g mL^{-1}$ (1% DMSO in ISB). Plates were incubated for 16 h at 37 °C (Inkubator 1000, Heidolph) and the minimum inhibitory concentration (MIC) was determined visually as the lowest concentration at which growth was inhibited. See appendix 9.3 for raw data and growth inhibition calculation details.

7.5.2 General procedures for gel-based imaging

All gel-based imaging experiments were carried out by Jack White (Chapter 4) or Julian Chesti (Chapter 5).

7.5.2.1 Buffer Preparation:

Phosphate-Buffered Saline (PBS): pH 7.4 (purchased as tablets from Sigma-Aldrich, 79382) containing phosphate (10 mM), potassium chloride (2.7 mM) and sodium chloride (137 mM).

SDS-PAGE Resolving Gel Buffer: pH 8.8, Tris (1.5 M)

SDS-PAGE Stacking Gel Buffer: pH 6.8, Tris (0.5 M)

SDS-PAGE Running Buffer: Tris (25 mM), Glycine (192 mM), SDS (0.1% w/v).

2 × Sample loading buffer (SLB): Tris (100 mM), SDS (4% w/v), Glycerol (20%), bromophenol blue (0.002% w/v) and a reducing agent* (0.4 M).

*When required DTT was added to the buffer mixture for use, or TCEP was added separately to reactions from a fresh 1 M stock made in water.

Coomassie Stain: Coomassie G250 (0.2% w/v), methanol (50%), acetic acid (10%).

Coomassie De-stain: methanol (50%), acetic acid (10%).

7.5.2.2 Protein Labelling with Alkyne Containing Probes:

On a 25 µL scale, cell lysate was diluted to 1 $mgmL^{-1}$ with PBS (pH 7.4) in an eppendorf. A 100-fold stock solution of the probe compound was prepared in DMSO and stored at –20 or –80 °C depending on probe stability. A fresh 10-fold stock was prepared for each reaction by dilution into PBS to give a final DMSO concentration of 10%. The probe stocks (2.5 µL, 10-fold stock) were prepared to give the final probe concentration as specified in each reaction, typically between 0.1 – 250 µM, with a final DMSO concentration of 1%. A DMSO-lysate control was also used containing 1% DMSO to explore the effect of probe addition on the proteins. The eppendorfs were then incubated with gentle agitation for 30 minutes at 25 °C.

7.5.2.3 Visualisation of Probe Labelling:

Labelling of alkyne or fluorophore containing probes used in the above experiments were visualised through SDS-PAGE following a standard procedure outlined below.

Click Reaction: As required (for alkyne-containing probes). A master mixture of click reagents was prepared as a fresh stock for each reaction. The reagents as stocks in DMSO or water were added together in the order given below and vortexed briefly. For experiments with a probe concentration for <100 μM, including the DMSO control, the click reagents (1.5 μL) was added to each reaction eppendorf and incubated at 25 °C for one hour with gentle agitation. For experiments with a probe concentration ≥ 100 μM, the master stock was added to give a final concentration of azide of 2 equivalents with respect to the probe (table 7.5).

Table 7.5: Concentrations and volumes of reagents employed in the click reaction.

Reagent	Final concentration	Reagent stock	Reaction volume (μL)
Fluorophore-azide	100 μM	10 mM in DMSO	0.6
$CuSO_4$	1 mM	50 mM in H_2O	1.2
TCEP	1 mM	50 mM in H_2O	1.2
TBTA	100 μM	10 mM in DMSO	0.6

After one hour incubation, the reaction was quenched with EDTA (0.5 μL, 0.5 M) to give a final concentration of 10 mM in solution.

Protein Precipitation: To remove excess probes and/or excess click reagents, the reactions were precipitated by addition of cold acetone (4 volumes), vortexed, and left to precipitate overnight at –20 °C. The suspension was then centrifuged, (20 min, 13000 × g) and the protein pellet washed with cold methanol (2 × volumes) with brief sonication. The pellet was then vortexed and centrifuged (10 min, 13000 × g) to remove additional reagents. The methanol was then removed, and the pellet left to air dry for 5 min.

Preparation of SDS-PAGE gels: Each gel-based experiment used a 1 mm gel with 10 lanes, containing a 12% acrylamide resolving gel, and a 5% acrylamide stacking gel.

SDS-PAGE gels were prepared following a standard recipe, by mixing the listed reagents in the order presented in table 7.6.

Table 7.6: SDS-PAGE ingredient recipe.

Reagent	Stacking Gel (5%)	Resolving Gel (12%)
Water	3 mL	4.2 mL
Acrylamide (40% w/v)	0.625 mL	3 mL
Stacking Gel Buffer	0.945 mL	–
Resolving Gel Buffer	–	2.6 mL
SDS (10% w/v)	50 mL	100 mL
APS (10% w/v)	50 mL	100 mL
TEMED	5 mL	10 mL

Running SDS-PAGE Gels and Imaging: Unless described otherwise, precipitated protein samples (25 μg) were resuspended in SDS solution (2% in PBS, 12.5 μL) and 2 × SLB (12.5 μL) with mixing. The samples were then boiled for 2 minutes at 95 °C and centrifuged briefly. Samples were loaded onto an SDS-PAGE gel (10 μL, 10 μg) along with an all-blue pre-stained protein standard (7.5 μL, Bio-Rad: 1610373). Gels were run with a Bio-Rad power supply unit at 180 V, 400 mA, for 40 – 60 minutes.

Gels were imaged using a BioRad ChemiDoc MP Imaging System. Imaging fluorescence using filters DyLight 550 602/50 green epifluorescence for rhodamine, and DyLight 488 532/28 filters for fluorescein. The pre-stained ladder was imaged with Coomassie filter 715/30 far red epifluorescence. Total protein visualisation was achieved by staining with Coomassie blue G250 solution overnight, before removing background with de-staining solution for gel imaging using the Coomassie filter.

7.6 pK_aH determinations and geometric predictions of twisted anilines

7.6.1 Nonaqueous pK_aH determinations

Nonaqueous (DMSO) pK_aH determinations were performed using the method published by Iggo *et. al*.[135] All experimental work was carried out at the University of Liverpool using associated instrumentation, equipment and reagents. Data processing was carried out using Topsin 4.1.4 with guidance provided by Krzysztof Baj and Jonathan A. Iggo. Processing tools were provided by the Iggo research group. Further experimental details as described by Iggo *et. al*.[135] are presented below:

Experiments were performed in Norell Sample Vault NMR tubes on a Bruker AV-I 400 spectrometer operating at 400.053 MHz for ^{1}H. CSI experiments were carried out using the gradient phase encoding sequence of Schenck *et al*.[135] This is based on the sequences of Trigo-Mourino *et al*[191] and Wallace *et al*.[136]

The phase encoding gradient pulse **g** was 267.52220 μs and varied from –27 to 27 Gcm^{-1} in 128 slices. Typically, 16 dummy scans preceded signal acquisition, with 8 scans acquired for each gradient increment, with an acquisition time of 1.278 s. A spoil gradient of 27 Gcm^{-1} was included after the acquisition period to destroy any remaining transverse magnetisation. Time domain data files were transformed without zero-filling using sine bell apodization. A 128 slice CSI experiment had a total acquisition time of 32 minutes with a theoretical spatial resolution of 0.15 mm.

All indicator 0.6 molL^{-1} stock solutions were prepared with dry d_6-DMSO as 2 ml stock solutions in a N_2 purged glovebox. Volatile reagents deleterious to the glovebox were added in air. A 33 mmolL^{-1} stock solution of hexamethyldisilane in dry d_6-DMSO was prepared to act as a pH independent internal chemical shift reference.

Benzyl 3,4-dihydro-2H-1,4-methanobenzo[b][1,5]diazocine-5(6H)-carboxylate **287**: The analyte was dissolved in 1144 μL of dry d_6-DMSO. The following volumes of stock solutions were then added: 15 μL of pyridine solution; 15 μL of 2,6-lutidine solution; 10 μL of 1-methylimidazole solution; 10 μL of *N,N*-dimethylbenzylamine solution and 6 μL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were **287** = 5.40 mmolL^{-1}; pyridine = 7.5 mmolL^{-1}; 2,6-lutidine =

7.5 mmolL^{-1}; 1-methylimidazole = 5 mmolL^{-1}; N,N-dimethylbenzylamine = 5 mmolL^{-1}; HMDS = 165 µmolL^{-1}.

Benzyl 2,3,4,5-tetrahydro-1,5-methanobenzo[b][1,5]diazonine-6(7H)-carboxylate **285**: The analyte was dissolved in 1140 µL of anhydrous d_6-DMSO. The following volumes of stock solutions were then added: 15 µL of *N,N*-dimethylaniline solution; 15 µL of pyridine solution; 10 µL of 2,6-lutidine solution; 10 µL of 1-methylimidazole solution and 10 µL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were **285** = 5.17 mmolL^{-1}; *N,N*-dimethylaniline = 7.5 mmolL^{-1}; pyridine = 7.5 mmolL^{-1}; 2,6-lutidine = 7.5 mmolL^{-1}; 1-methylimidazole = 5 mmolL^{-1}; HMDS = 275 µmolL^{-1}.

Benzyl 3,4,5,6-tetrahydro-2H-1,6-methanobenzo[b][1,5]diazecine-7(8H)-carboxylate **286**: The analyte was dissolved in 1140 µL of anhydrous d_6-DMSO. The following volumes of stock solutions were then added: 15 µL of *N,N*-dimethylaniline solution; 15 µL of pyridine solution; 10 µL of 2,6-lutidine solution; 10 µL of 1-methylimidazole solution and 10 µL of HMDS solution. The resulting concentrations of analyte and indicators in the measured sample were **286** = 5.20 mmolL^{-1}; *N,N*-dimethylaniline = 7.5 mmolL^{-1}; pyridine = 7.5 mmolL^{-1}; 2,6-lutidine = 7.5 mmolL^{-1}; 1-methylimidazole = 5 mmolL^{-1}; HMDS = 275 µmolL^{-1}.

To establish a pH gradient, solid acid was weighed directly into the NMR tube using a Mettler AE101 balance with a stated precision of ± 0.01 mg. Four 2 mm glass beads were placed on top of the solid acid in the NMR tube to prevent rapid mixing. 550 µL of basic solution was then gently layered on top of the glass beads and the tube left to stand vertically at ambient laboratory temperature (20 °C) until analysis. Basic analytes were investigated by titrating a solid acid of known pK_a (*p*-toluenesulfonic acid) against a solution containing the analyte and several basic indicators as specified. Limiting shifts of indicators were determined independently from the imaging experiments. An excess of strong acid or base was used to measure limiting shifts of all reagents. Water content across the samples was assessed by NMR and

established to be below 1.0 v% and as such low it would not have an impact on pK_aH value.[135]

7.6.2 Aqueous pK_aH calculations

All aqueous pK_aH calculations were performed by Krzysztof Baj:[141]

Jaguar Prediction Method was used to calculate pK_aH in water of **285**-**287** which calculates a reference value from the gas and water-solvated phase energies.[192,193,194,195,196] The conformational search was performed, and only conformers with the lowest energy were used for further calculations. Gas phase and water-solvated geometries were optimised using B3LYP/6-31G* density functional theory (DFT). Pseudospectral methods were turned off. Energies of each optimised geometry were obtained using single spot B3LYP/cc-pVTZ(+) DFT calculations. The solvation-free energy of the protonated and deprotonated species with empirical parameterisation being applied. The results were collected, and raw pK_aH was calculated. The Final pK_aH was obtained after applying empirical corrections.[192,193,194,195,196]

7.6.3 Geometric calculations

All geometric calculations were performed by Krzysztof Baj:[141]

Geometries of **285**-**287** were optimised using M06-2x/6-31G** with the Schrodinger optimisation tool which performs quantum mechanical Hessian matrix analysis to avoid convergence at a local minimum.[197,198,192] Pseudospectral methods were turned off. Geometries were optimised in the gas phase and also in the parallel runs in both DMSO and water using Poisson Boltzmann Finite (PBF) solvation model.[197,198,192]

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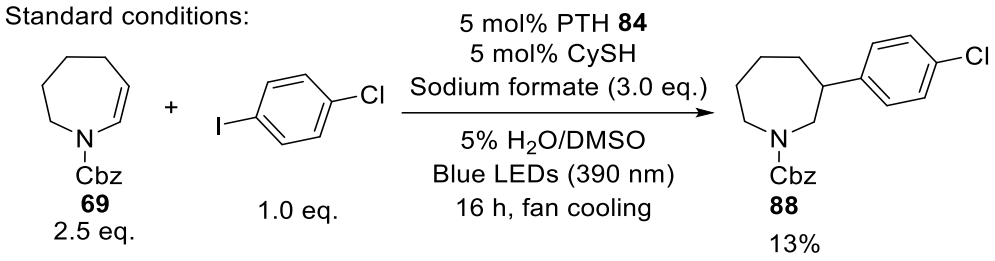
9 Appendix

9.1 Photocatalysed-arylation optimisation conditions

Table 9.1: The original standard conditions and the optimisation attempts of the β-arylation methodology.[73]



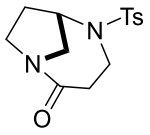
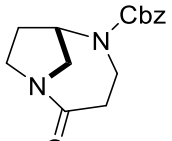
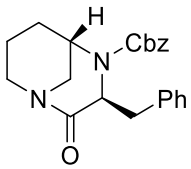
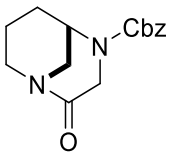
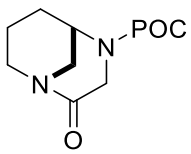
Entry	Deviation from standard conditions	Conversion of enecarbamate (%)	Yield of product based on aryl iodide (%)[a]
1	None	88	22
2	1:1 **69**:ArI	63	20
3	1:1.5 **69**:ArI	53	20
4	0.2 M	100	23
5	0.05 M	59	15
6	Different LEDs (450-455 nm)	77	20
7	No fan cooling	87	32
8	60 h	100	38
9	ArI = PhI	78	20

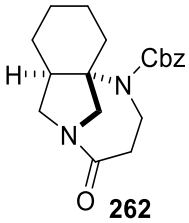
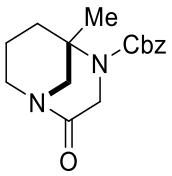
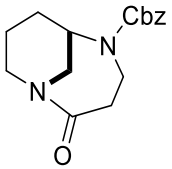
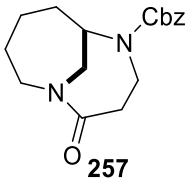
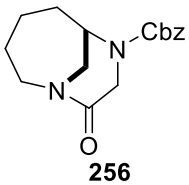
10	1 mol% CySH	85	25
11	10 mol% PTH	82	26
12	Alternative formate source: ammonium formate	76	22
13	1.5 eq. sodium formate	81	30
14	Bu_4NCl (3 eq.) used as phase-transfer reagent	69	28
15	2 x LEDs used (390 nm)	100	32
16	Blank (no ArI)	53	n/a
17	1:1.5 **69**:ArI, 0.05 N	43	15
18	1:1 **69**:ArI, 0.05 N	54	10
19	60 h, no fan cooling	100	30
20	60 h, 1.5 eq. sodium formate	100	32
21	60 h, no fan cooling, 1.5 eq. sodium formate	100	30

[a] Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard.

9.2 Physical properties of twisted lactams

Table 9.2: The C=O ^{13}C NMR and IR data for all twisted lactams reported in chapter 4.

Entry	Lactam	^{13}C NMR C=O δ (ppm)	IR C=O (cm^{-1})
1	 **263**	183.1	1682
2	 **259**	182.1, 182.0[a]	1680
3	 *(S,S)*-**254**	181.4	1684
4	 **253**	180.2	1686
5	 **255**	179.9	1691

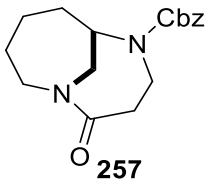
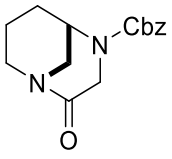
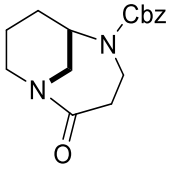
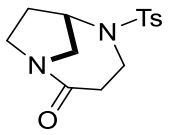
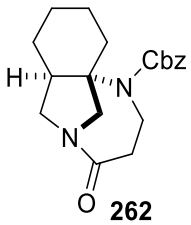
6	 **262**	179.9	1680
7	 **260**	179.7	1684
8	 **225**	176.8	1657
9	 **257**	172.80, 172.75[a]	1647
10	 **256**	170.9	1667

[a]Two values reported due to the presence of rotamers.

9.3 Growth inhibition calculations

9.3.1 Raw data

Table 9.3: Plate reader raw data for the twisted lactam series.

Sample	Replicate	Measured absorbance values as optical density for each concentration of sample				
		32 µg/mL	4 µg/mL	0.5 µg/mL	0.0625 µg/mL	0 µg/mL
 **257**	1	3.918	3.36	1.971	1.667	3.408
	2	5.466	4.247	3.204	2.95	5.054
 **253**	1	4.054	3.472	3.154	5.736	4.271
	2	4.886	5.404	4.934	2.102	2.582
 **225**	1	4.87	3.682	2.845	3.177	5.371
	2	5.583	4.146	4.798	3.664	4.019
 **263**	1	4.867	5.643	4.623	4.357	5.841
	2	4.879	4.466	5.67	4.125	5.663
 **262**	1	0.187	4.827	3.078	2.705	2.67
	2	0.188	4.796	2.356	2.308	3.376

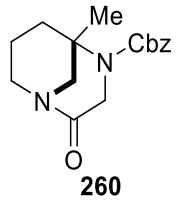
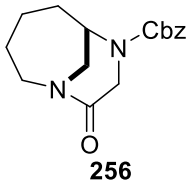
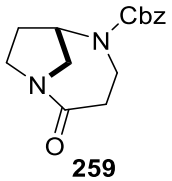
 **260**	1	3.445	2.639	2.841	3.343	3.103
	2	3.101	3.363	2.775	2.76	3.421
 **256**	1	3.268	3.237	3.317	3.095	2.819
	2	5.384	5.183	2.661	2.9	3.545
 **259**	1	3.825	3.511	3.327	2.991	3.393
	2	4.369	5.291	3.289	5.222	3.571

Table 9.4: Plate reader raw data for active twisted lactam **262** against control **253**. MIC = 32 µg/mL

Concentration (µg/mL)	Measured absorbance values as optical density for each concentration of sample							
	Colony 1		Colony 2		Colony 3		Colony 1 (Control, **253**)	
64	0.139	0.157	0.145	0.156	0.87	0.157	5.717	5.237
32	0.122	4.638	3.687	0.171	0.16	0.165	4.494	4.652
16	3.978	5.883	6.027	6.091	5.813	5.158	5.197	4.331
8	5.239	5.654	4.97	4.961	5.417	5.738	5.24	5.45
4	5.447	6.968	6.727	5.822	6.456	5.725	5.253	5.391

2	5.212	5.572	5.745	4.688	4.976	4.86	5.072	5.165
1	5.42	5.817	5.272	5.404	5.435	5.152	3.984	4.966
0.5	5.422	5.224	5.511	4.987	5.49	5.591	4.905	5.146
0.25	5.295	5.167	4.935	4.813	4.992	5.222	4.672	4.968
0.125	5.32	5.055	5.341	5.036	4.98	5.099	5.231	5.513

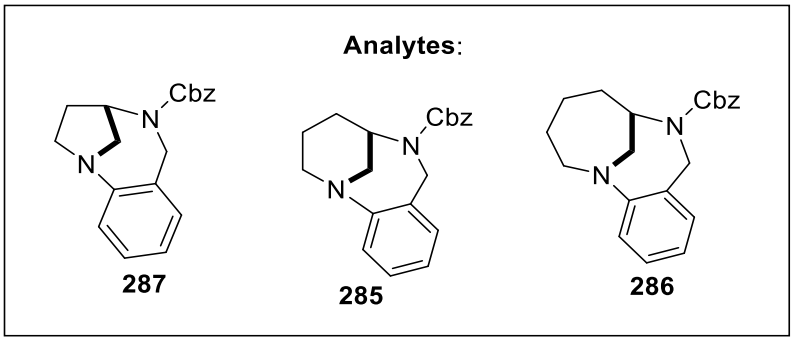
9.3.2 Growth inhibition

Growth inhibition values were calculated for lactam **262** within Excel using the optical density (OD) data obtained from the plate reader presented in table 9.4, using equation 3. Duplicates and colonies were averaged. Outlining values were excluded. Growth inhibition was calculated at 97.247% (64 µg/mL) and 96.621 (32 µg/mL).

$$Growth\ inhibition\ (\%) = \frac{\left(OD_{control} - OD_{sample}\right)}{OD_{control}} \times 100 \qquad (3)$$

9.4 Nonaqueous pK_aH determinations

9.4.1 NMR images



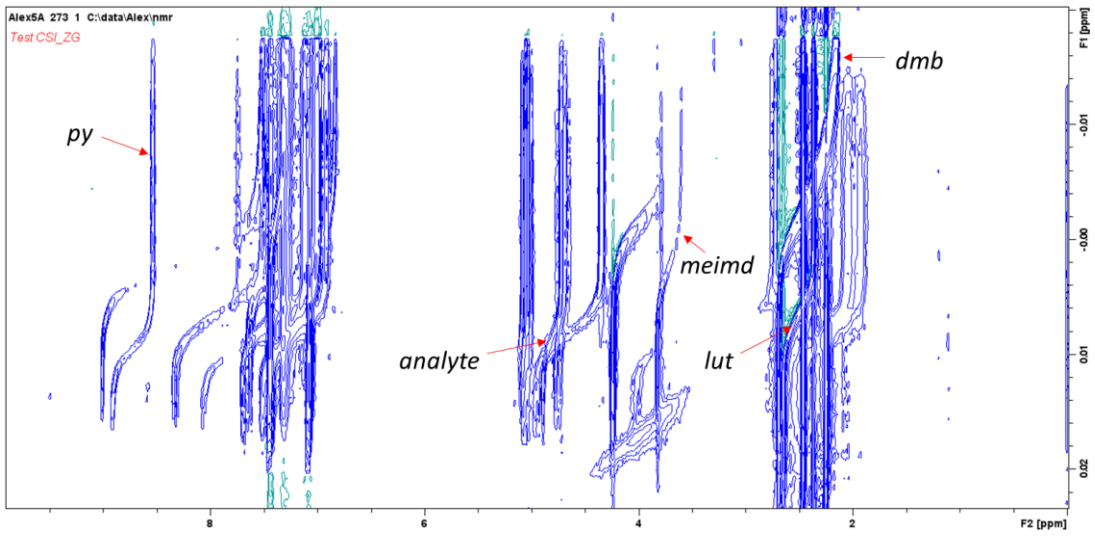


Figure 9.1: NMR image of bicyclic aniline **287**. Chemical shift reporters used for each indicator and analyte have been identified. Py = pyridine, meimd = 1-methylimidazole, lut = 2,6-lutidine, dmb = *N*,*N*-dimethylbenzylamine.

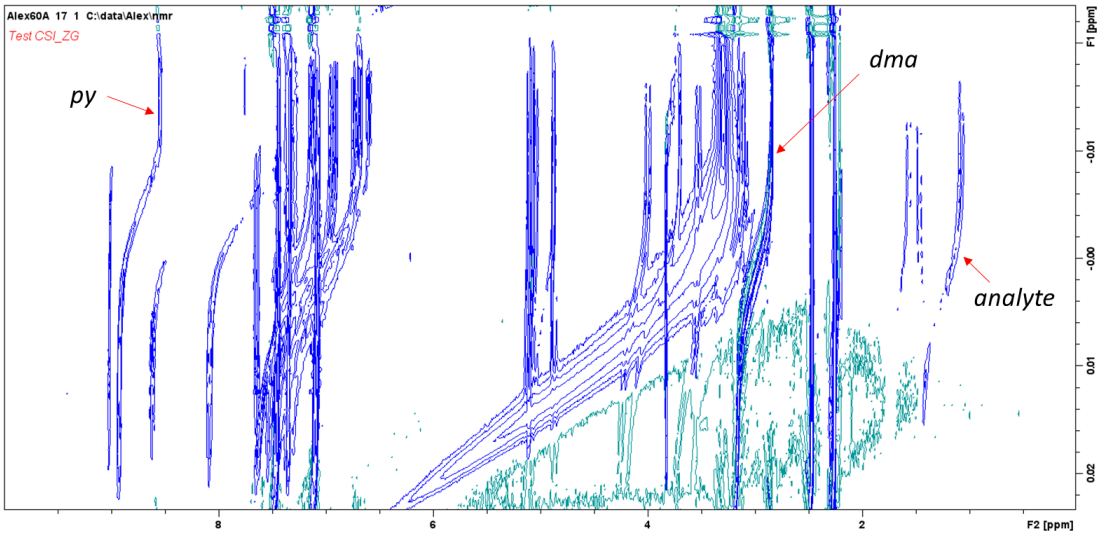


Figure 9.2: NMR image of bicyclic aniline **285**. Chemical shift reporters used for each indicator and analyte have been identified. Py = pyridine, dma = *N*,*N*-dimethylaniline.

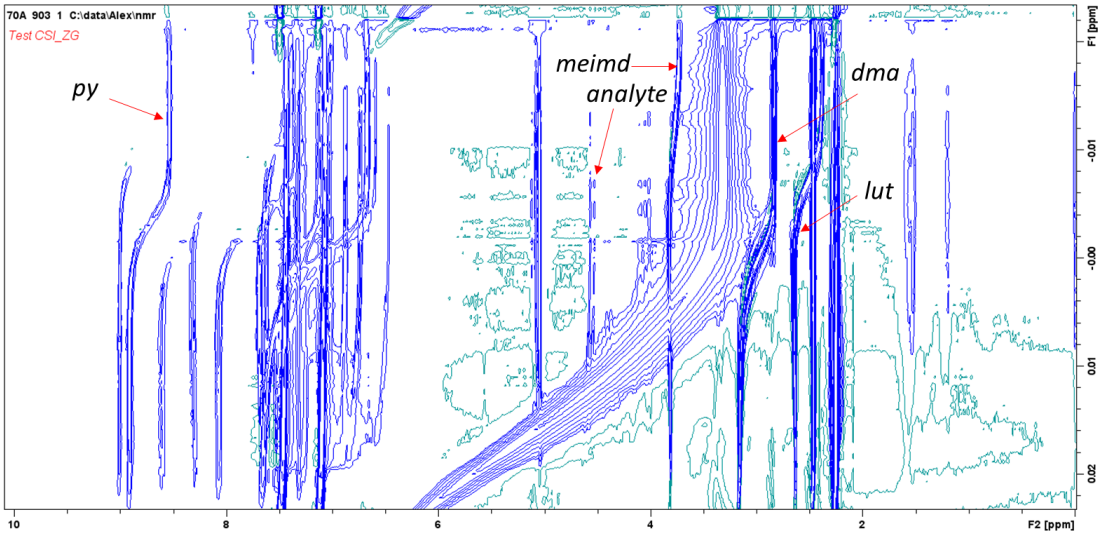


Figure 9.3: NMR image of bicyclic aniline **286**. Chemical shift reporters used for each indicator and analyte have been identified. Py = pyridine, meimd = 1-methylimidazole, lut = 2,6-lutidine, dma = *N*,*N*-dimethylaniline.

9.4.2 Titration curves

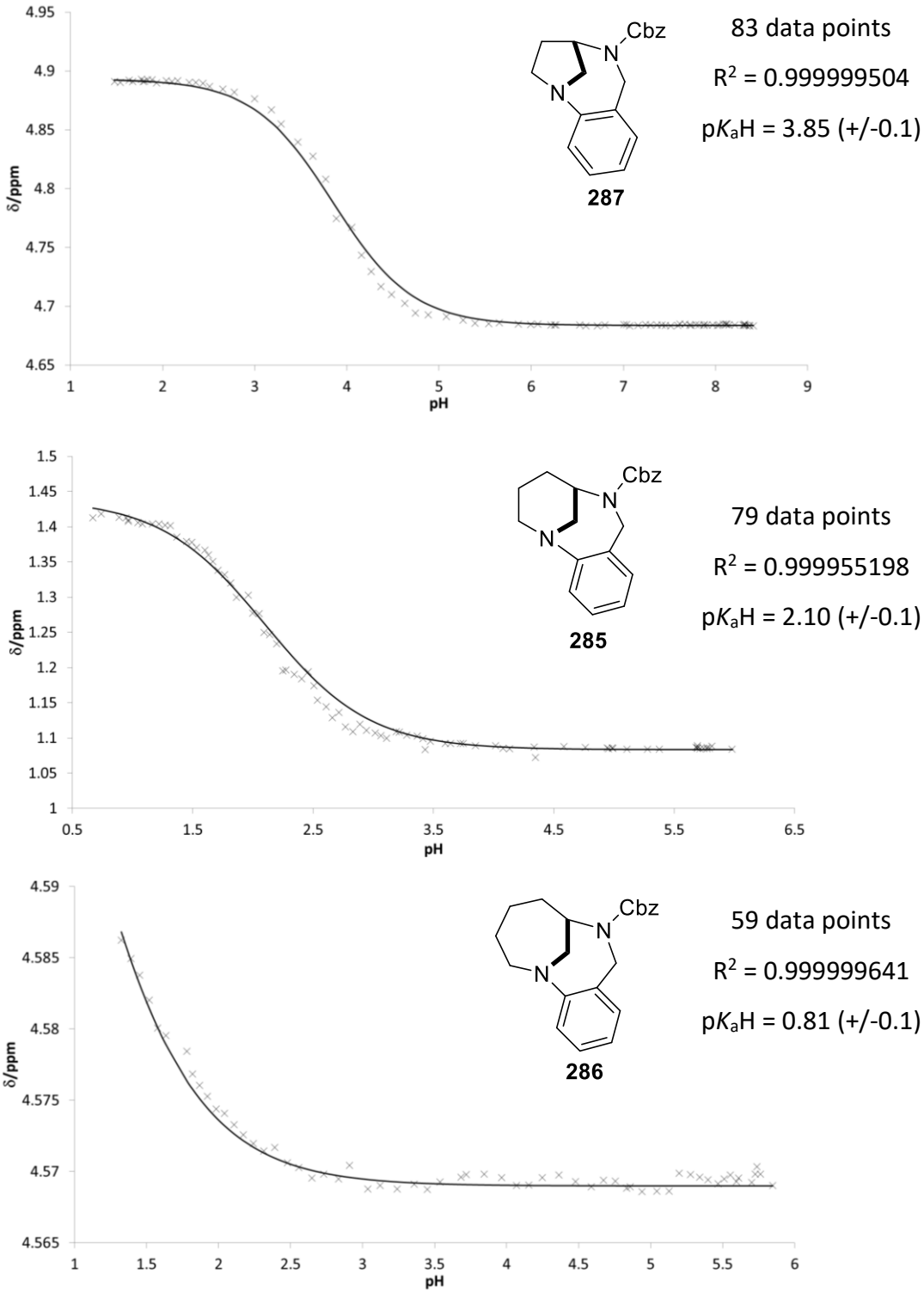


Figure 9.4: Titration curves corresponding to each analyte. Due to the unexpected acidity of bicyclic aniline **286**, a full titration curve was not generated. In this case, employing an excess of acid allowed the determination of an acidic limiting shift, providing confidence in the measured p*K*aH (+/- 0.1).