Synthesis of Substituted Azepanes
and Piperidines Using Organolithium Chemistry

Submitted by

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to the University of Sheffield as a thesis for the degree of Doctor of Philosophy in Chemistry

February 2018

The University Of Sheffield.
Abstract

α-Amino-organolithium compounds represent an important class of intermediates due to their excellent nucleophilic reactivity and importance in synthetic organic chemistry. This thesis describes some novel aspects of the n-BuLi mediated lithiation–substitution of N-Boc heterocycles, including N-Boc-2-substituted azepane, benzazepine and piperidine derivatives.

Chapter 2 details the optimization of the time required for the lithiation of N-Boc-2-phenylazepane and trapping of the lithiated intermediate. A variety of novel α-substituted and unusual ortho-substituted products were obtained in good to excellent yields.

Further novel α-substituted and ortho-substituted products were obtained by the lithiation of N-Boc-2-phenylbenzazepine and N-Boc-2-phenyl-7-methoxybenzazepine, as described in chapter 3. In addition, kinetic resolutions using the n-BuLi/(+)-sparteine chiral base have also been attempted on a number of N-Boc-azepane derivatives in chapters 2 and 3 but the starting materials were recovered from these reactions in low enantiomeric ratios.

In chapter 4, an investigation into the synthesis of 2-alkenyl or alkynyl substituted piperidines is reported such as D and E. Lithiation–substitution by using n-BuLi in THF gave a variety of products.
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Acknowledgements

First and foremost, thank you Allah, the lord, for giving me the support, strength, and knowledge in my life. Also, I would like to thank the Libyan government for the funding that allowed me to achieve my PhD degree.

I am grateful to my supervisor Professor Iain Coldham for his guidance, support, constant encouragement, advice and for stimulating my interest in the fields of organolithium chemistry throughout these years. I have been lucky to have a supervisor who cared so much about my work, my life in Sheffield and who responded to my questions and queries so promptly.

I would like to thank all the members of the Coldham Group, past and present. Firstly, I want to thank the first person with whom I researched Nicholas Carter for his help and guidance during experimental work and his friendship. Really, I do not find enough words with which I can express my feeling of thanks to which made me looked forward to coming into the lab’ each day due to the friendliness and companionship. Thank you, Nicholas, (again!), Ziad, Ashraf, Anthony, Zain and Ruaa for all the fun times and making the lab enjoyable. I would also like to thank Xiabing, Ed, Rachel, Arghya, Rungroj and thanks to the Level 4 student that I have supervised during my PhD, Callum for carrying out great work. In addition, many thanks must also go to the technical staff in the department.

My deepest gratitude goes to my family: my mother Karema, my brothers Salah, Naji, Abdul Salam, and Rafa and my sisters, Halima, Naima and Asma for their unflagging love, unflinching support throughout my life and encouragement to pursue my interests; this work is simply impossible without them.

Finally, I wished my father was alive to see this day when my dream came true.
Abbreviations

Ac acetyl
aq aqueous
Ar aryl
Bt benzotriazole
Bn benzyl
Boc t-butoxycarbonyl
Boc$_2$O di-tert-butyl dicarbonate
br broad
Bu butyl
Cby 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl
conc. concentrated
cm centimetre
conv. conversion
CSP HPLC Chiral stationary phase high performance liquid chromatography
CIPE complex induced proximity effect
d doublet
DFT density functional theory
DIBAL-H Diisobutylaluminium hydride
DMAP 4-Dimethylaminopyridine
DKR dynamic kinetic resolution
DMPU dimethylpropylideneurea
DME 1,2-dimethoxyethane
dr diastereomeric ratio
DTR dynamic thermodynamic resolution
E$^+$ electrophile
ES Electrospray
EI electron impact
ee enantiomeric excess
ent enantiomer
epi- epimer
eq. or equiv. equivalents
m.p. melting point
mmol millimole
mol mole(s)
mm millimeter
nm nanometre
MS mass spectrometry
NMR nuclear magnetic resonance
n-Bu normal butyl
Ph Phenyl
p- para
pro- proton
psi pounds per square inch
PhMe toluene
Piv pivaloyl
PMDTA pentamethyldiethylenetriamine
Pr Propyl
ppm parts per million
PTC phase transfer catalyst
rac racemic
Rf retention factor
RSM recovered starting material
Rt retention time
r.t. room temperature
ret. retention
sec second
s selectivity factor
SET single electron transfer
S_{E2} bimolecular electrophilic substitution
SM starting material
(+)-sp sur. (+)-sparteine surrogate
(−)-sp (−)-sparteine
(+)sp (+)-sparteine
ΔS^{‡} entropy of activation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-Bu</td>
<td>secondary butyl</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>t</td>
<td>time</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THQ</td>
<td>1,2,3,4-tetrahydroquinoline</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

1.1 Organolithium Chemistry

1.1.1 Organolithium Compounds in Modern Organic Synthesis

Organolithium chemistry is of great importance and has a broad utility in industry and chemical research. The central importance of organolithium reagents is in the synthesis of natural products and drug molecules, which remains the basis of modern organic synthesis. One of the most exciting synthetic uses of organolithium reagents is to create new σ carbon–carbon bonds with a high degree of selectivity. The nature of the structure, bonding and reactions of organolithium compounds still attracts chemists to investigate the reactivity of organolithium compounds and further work continues to be reported regularly.\(^1\)

1.1.2 The Structure and Reactivity of Organolithium Reagents

In 1917, organolithium reagents were first prepared by Schlenk\(^2\) by an exchange reaction from diethylmercury forming ethyl lithium and mercury amalgam (Figure 1a). This was developed in the following three decades by major contributions from Ziegler (who first prepared \(n\)-BuLi and other alkyllithiums from alkyl chlorides), Gilman and Wittig (who independently discovered aromatic metalation and the lithium–halogen exchange).\(^3\),\(^4\)

Generally, organic chemists synthesise an organolithium reagent via one of three ways; transmetallation or halogen metal exchange, reductive lithiation of alkyl halides with lithium metal, or deprotonation/lithiation (Figure 1b-d).

\[
\begin{align*}
\text{(a)} & \quad \text{Et}_2\text{Hg} \xrightarrow{3\text{Li}} 2\text{EtLi} + \text{Li(Hg)} \\
\text{(b) Transmetallation or Halogen-Metal Exchange} & \quad \begin{array}{c}
\text{R}^2\text{Li} \\
\text{R}^1\text{X} \\
\text{R}^2\text{X} \\
\text{R}^1\text{Li}
\end{array}
\quad \begin{array}{c}
\xrightarrow{2\text{Li} + 2\text{e}^-} \\
\text{L}i\text{X} \\
\text{R}^1\text{Li}
\end{array}
\quad \begin{array}{c}
\text{R}^2\text{Li} \\
\text{R}^1\text{H} \\
\text{R}^2\text{H} \\
\text{R}^1\text{Li}
\end{array}
\quad \text{Deprotonation/Lithiation}
\end{align*}
\]

\(X = \text{Sn}(\text{R}_3)^3, \text{SR}_4, \text{Br}, \text{I}\)

Figure 1
An organolithium reagent is an organometallic compound with a direct bond between a carbon and a lithium atom. As the electropositive nature of lithium puts more of the charge density of the bond on the carbon atom, the C–Li bond will be highly polar, effectively creating a carbanion. Therefore, organolithium compounds are extremely powerful bases and nucleophiles with $pK_a > 35$.

Organolithium reagents are surprisingly soluble and stable in hydrocarbon solvents. Such solutions can be kept for many months in the absence of water and air at low ($\leq 5$ °C) temperatures.

Organolithium reagents are often represented as monomeric species which contain a single Li atom and a single “R” group (for example, $n$-butyllithium as “$n$-BuLi”). However, the structure of these lithiated compounds is much more complex than this simple representation.

Organolithium reagents are typically aggregated. The lithium atom usually surrounds itself with more than one carbon atom, where carbon co-ordinates itself to more than one lithium atom. This aggregation can be affected by several factors; such as the electrostatic interaction between localized and delocalized counter charges, the coordination sphere of the lithium atom (which can either be solvent molecules or coordinating Lewis bases) and the steric hindrance of the hydrocarbon substituents. The lithium atoms tend to build oligomeric structures to form dimers and higher aggregates (Figure 2). A common use for commercially available organolithium compounds (like $n$-BuLi, sec-BuLi, $t$-BuLi, MeLi, PhLi) is as very strong bases.

X-ray crystallographic studies and $^7$Li solid state NMR spectroscopic studies of organolithiums show that they can be aggregated as hexameric, tetrameric or dimeric species. It was found that simple primary organolithiums are hexamers in hydrocarbon solvents, secondary and tertiary organolithiums are tetramers, while only benzyllithium and very bulky organolithiums, such as (Me$_2$PhSi)$_2$CHLi, are dimers (Table 1). This difference in
aggregation state is due to steric hindrance. Benzylolithium exists as dimers due to a bulky benzylic group while primary organolithiums such as \( n \)-butyllithium exist as hexamers.\(^1\)

<table>
<thead>
<tr>
<th>Hexameric</th>
<th>Tetrameric</th>
<th>Dimeric</th>
<th>Monomeric</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtLi</td>
<td>( s )-BuLi</td>
<td>PhCH(_2)Li</td>
<td>-</td>
</tr>
<tr>
<td>( n )-BuLi</td>
<td>i-PrLi</td>
<td>( t )-BuLi</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: The aggregation state of organolithiums in hydrocarbon solution**

The aggregation of organolithiums in apolar media form what are called Homo-Aggregates. This form is completely different upon the addition of either Lewis basic solvents such as diethyl ether and THF or nitrogen ligands such as TMEDA, PMDTA or sparteine, which tend to deaggregate organolithium compounds making them more soluble and more reactive. These compounds can stabilise the electron-deficient lithium atom forming an alternative source of electron density. These types of interactions lead to a new and more versatile class of aggregates called Hetero-Aggregates.\(^5,8^-11\) The most commonly used ligands in order of decreasing activating power are shown in Figure 3.\(^1\) HMPA > PMDTA > \((-\rangle\)-sparteine > DMPU > DME > TMEDA > THF > Et\(_2\)O

\[\text{HMPA} \quad \text{PMDTA} \quad \text{(-)}\)-sparteine \quad \text{DMPU} \quad \text{DME} \quad \text{TMEDA} \quad \text{THF} \quad \text{Et}_2\text{O}\]

**Figure 3**
In general, it is often considered that lower aggregation states result in more reactive organolithium reagents.\textsuperscript{12} Therefore, coordinating ligands and solvents, such as ethers or amines, can improve reactivity as they can deaggregate the organolithium. For instance, \textit{s}-BuLi in a hydrocarbon solvent exists as a tetramer, whereas in the presence of THF, the aggregation state shifts to a dimer.\textsuperscript{1}

TMEDA is one of the most commonly used ligands in organolithium chemistry and has been shown to have the capacity to reduce organolithium aggregation and increase reactivity.\textsuperscript{13} Collum had shown that TMEDA can reduce the organolithium aggregation of \textit{n}-BuLi in THF from a tetramer to a dimer.\textsuperscript{13}

\textit{(--)}-Sparteine [(\textit{--})-\textit{sp}], a naturally occurring chiral diamine, is one of the most powerful chiral ligands for organolithiums. In addition to being able to induce asymmetry, \textit{(--)}-sparteine can enhance the reactivity even when enantioselectivity is not required.\textsuperscript{14} In addition, it is the best alternative for very toxic HMPA.\textsuperscript{1}

\textbf{1.1.3 \textit{\alpha}-Amino Organolithium}

The lithiation of hydrocarbons is not an easy process under normal conditions, even when there are aromatic or vinylic sites of potential deprotonation. In general, deprotonation of a \textit{C}–\textit{H} bond is only possible if the organolithium intermediate has the following features: intramolecular coordination of the electron-deficient lithium atom to a nearby heteroatom or stabilisation of the electron-rich \textit{C}–\textit{Li} bond by a nearby empty orbital or electron-withdrawing group.\textsuperscript{1}

Typically, the presence of strongly acidifying groups such as arylsulfonyl, arylsulfinyl or dialkylphosphonyl groups enhance the lithiation adjacent to a heteroatom, but lithiation can also take place adjacent to oxygen or nitrogen-based functional groups.\textsuperscript{1} In this case, acidity is increased if the proton to be removed is benzylic, allylic, vinylic, or attached to a small ring saturated heterocycle. Many successful \textit{\alpha}-lithiations make use of allylic or benzylic stabilisation as well as the effect of the heteroatom.\textsuperscript{1} The removal of a proton from a carbon bearing a nitrogen atom gives an \textit{\alpha}-amino organolithium as an important intermediate, which reacts with electrophiles to produce substituted amines. \textit{\alpha}-Amino organolithium intermediates are classified into different types according to their stability as follows: unstabilised, dipole-stabilised, mesomerically stabilised, and dipole- and mesomerically stabilised.\textsuperscript{3}
Unstabilised (or non-stabilised) organolithium compounds: These are tertiary amines where the nitrogen's lone pair is able to co-ordinate powerfully to an incoming organolithium reagent (Coulombic attraction) which stabilises the lithium atom by forming a dimeric structure (Figure 4a). However, this co-ordination could destabilise the C–Li bond as a result of a filled-filled orbital interaction between the nitrogen lone pair and the C–Li bond. Tin-lithium exchange reactions and deprotonation of quaternary ammonium complexes have allowed the formation of non-stabilised α-amino-organolithiums but a degree of dipole stabilisation gives some extra stability to the organolithium species in the latter case (Figure 4b).

The chemistry of these compounds has limited progress not only because they have suffered from several failures, but also there has been difficulty to find a clear reason for the success or failure of these reactions (Figure 5).

Dipole-stabilised organolithium compounds: These are compounds in which the nitrogen atom lone pair is involved in conjugation with a carbonyl group such as an amide. In these compounds, the repulsion is lessened, and the lone pairs are lower in energy due to
delocalisation. This conjugation provides a new, electron-rich oxygen atom which can itself stabilise the organolithium by coordination (Figure 6). The delocalization of the nitrogen's lone pair into the amide carbonyl (or the dipoles of similar functional groups) is stabilised by the N(δ+)–C=O(δ-) dipole and this forms an important group of compounds which have been termed “dipole-stabilised carbanions”.  

![Figure 6](image_url)

**Figure 6**

Scheme 1 illustrates different activating groups, which can be used for dipole-stabilisation of α-amino-organolithiums. These will be described in more detail in the following sections.

![Scheme 1](image_url)

**Scheme 1**

**Mesomerically stabilised organolithium compounds:** These can be formed from two structural types; allylic or benzylic amines (Figure 7a,b) and 2-azaallyl anions (Figure 7c). Lithiation α- to the nitrogen atom in these cases gives delocalized organolithiums. As a result the lithium atom does not have a clear position. There are two types of bonding that can be generated from these organolithium compounds; η^1 or η^3. Figure 7b illustrates the dynamic equilibrium between η^1 and η^3 bonding of α-lithio N,N-dimethylbenzyl amine in solution. The position of the equilibrium is affected by the temperature: lower temperatures η^1 bonding is predominant and vice versa.
**Figure 7**

**Dipole and mesomerically stabilised organolithium compounds:** These can be formed from benzylic proton abstraction to give delocalized organolithiums. As shown in Figure 8 the stability of these compounds arises from conjugation with an aromatic ring in addition to the coordination with the activating group.$^{1}$

**Figure 8**
1.2 Directed Lithiation Using Organolithium Reagents

The generation of \(\alpha\)-amino-organolithiums relies on three routes (Figure 9). The first is deprotonation (path 1), the second is tin-lithium exchange (path 2), and the third is reductive lithiation (path 3).\(^3\)

![Figure 9](image)

Multi-step syntheses of organic compounds commonly include steps where a carbon-hydrogen bond is replaced chemoselectively, regioselectively, diastereoselectively, and/or enantioselectively by a carbon-carbon or carbon-heteroatom bond \textit{via} a carbanionic intermediate.\(^{21}\) This type of reaction is an attractive area of organic chemistry that can provide highly enantioenriched products starting from racemic or non-chiral substrates (also called asymmetric synthesis). Typically, such a strategy involves the formation of carbanions as intermediates by deprotonation of substrates that have conventional activating groups adjacent to the site of the proton that is to be removed. In 1986, Beak and Meyers noted that many of the novel carbanion formations by organolithium bases can be described using a two-step process in which the formation of a pre-lithiation complex brings reactive groups close in proximity for directed deprotonation.\(^{22,23}\) This phenomenon was termed the complex-induced proximity effect (CIPE).

As illustrated in Scheme 2, the general CIPE can be described as a lithiation-substitution sequence from 5 to 9. Co-ordination of 5 with an organolithium reagent provides the complex 6. This then holds the organolithium reagent in a suitable conformation for deprotonation to give the lithiated intermediate 8, which can react with an electrophile to provide the product 9. Examples that proceed by a CIPE include not only deprotonative mono- and dilithiations, but also heteroatom–lithium exchanges and additions.\(^{21,24-29}\)
Research into the CIPE found that it can be used to control the regioselectivity of directed ortho metalations by altering the balance of inductive and association effects. For example, the directed lithiation of 11 with s-BuLi-TMEDA provides 10, the product of lithiation adjacent to the strongly complexing carboxamide (Scheme 3).\textsuperscript{21} However, lithiation of 11 by \( \alpha \)-ethoxyvinyllithium-HMPA affords 12, the kinetic product of lithiation adjacent to the methoxy functionality. A reasonable rationale is that complexation, which drives the formation of 10 with s-BuLi-TMEDA, is suppressed with \( \alpha \)-ethoxyvinyl lithium-HMPA. Formation of 12 is then attributed to a favourable inductive effect of the methoxy group.\textsuperscript{21}

A further example (Scheme 4) of the importance of the CIPE for regioselectivity was reported by Beak and Meyers, who showed that a kinetic deprotonation of the benzyl protons to give the stable intermediate 15 was more favoured over the thermodynamic deprotonation of \( \alpha \)-methylene protons to form the amide enolate product 13.\textsuperscript{22}
A fundamental requirement for CIPE directing groups is that they are easy to add and remove. Also, they must have some Lewis basicity to allow complexation to the organometallic reagent. As a result they must have a low reactivity towards nucleophilic attack to allow deprotonation to occur.\textsuperscript{30}

It has been previously demonstrated that lithiation can be made possible by directing groups where direct lithiation was virtually impossible due to the presence of a nitrogen lone pair, which disfavoured formation of the C‒Li bond. Various sterically hindered directing groups have been used for stabilisation of organolithium compounds such as amide,\textsuperscript{24} formamidine,\textsuperscript{31} and nitroso\textsuperscript{32} groups (Scheme 5). All of these groups allow complexation of the organolithium reagent and have a low reactivity towards nucleophilic attack to allow $\alpha$-deprotonation to occur.
Amides, formamidines and the nitroso group are not the only directing groups that have been used. Further research has led to the discovery of the current most important class, tert-butyl carbamates. These were first used in the lithiation of heterocycles by Beak and Lee in 1989. The example in Scheme 6 shows the lithiation of N-Boc-azepane and trapping the organolithium intermediate by different electrophiles to produce azepanes 25a,b in different yields. The Boc can be readily added with Boc₂O and removed by mild acid treatment, which has made it the most prevalent directing group for the α-lithiation of amines.

Scheme 6

1.3 Reactions of Organolithium

α-Amino-organolithiums are advantageous intermediates to create new stereocentres with good enantioselectivity. There are two possible mechanisms in these reactions: polar and radical. The polar mechanism is a bimolecular electrophilic substitution process, which could proceed via retention (Sₑ₂ret) or inversion (Sₑ₂inv) to describe the steric course for stabilised organolithiums (compounds in which the lithium atom is found in an allylic or benzylic position). Both mechanisms are possible according to orbital symmetry, and sometimes they are in competition with each other (Figure 10).

These mechanisms were suggested by Gawley in 1999. Figure 10 illustrates the orbital symmetry analysis for an alkyllithium and an alkyl halide and describes the concerted formation of a new C–E bond and the breaking of C–Li and E–X bonds during both mechanisms (Sₑ₂ret or Sₑ₂inv). In both cases there is inversion at the electrophilic centre without the presence of an interaction between the lithium cation and the leaving group which requires like symmetry between the HOMO of the organolithium (the carbanionic orbital) and the LUMO of the electrophile (the σ* orbital of an alkyl halide).
A radical mechanism is the other possibility used to describe the electrophilic aliphatic substitutions of α-amino-organolithiums, represented as a single electron transfer mechanism (SET). In this case, the electrophile is able to oxidize the organolithium compound, generating radical intermediates that result in stereo-random coupling to give racemic products (Figure 11). It is possible to explain this mechanism and its competition with the polar mechanism (SE2ret and SE2inv) by looking at the redox potentials of both the nucleophile and the electrophile. When electrophiles that are easy to reduce are used the predominant mechanism is SET.

For stabilised organolithiums, especially benzylic, the presence of a π-system gives the C–Li bond more p-character. This increases the planarity of the organolithium and opens it up to a greater extent, both electronically and sterically meaning that there is a possibility for attack on the rear lobe of the C–Li σ bond (Figure 12).
In 1994, Hoppe and Carstens showed that the steric course of electrophilic aliphatic substitutions on α-amino-organolithiums could be classified according to the type of electrophile. When electrophiles, which have a leaving group able to coordinate to the lithium atom (such as RO− group) are used, retention of configuration is observed, but when there are non-coordinating electrophiles (such as NC−, X−) inversion of configuration occurs. Beak illustrated this for compounds 26a and 26b, in which the reactions of highly reactive and/or non-lithium coordinating electrophiles undergo inversion and less reactive and/or lithium coordinating electrophiles undergo retention (Scheme 7).
Gawley and co-workers have shown how the behaviour of different non-stabilised α-amino organolithiums could be affected by the type of electrophiles used (Scheme 8). The reactions that used carbonyl electrophiles gave the desired products in good yields with retention of configuration at the Li–bearing carbon. This was in accordance with a transition state where the carbonyl oxygen coordinates with the lithium atom before the reaction. SET appeared to be the predominant mechanism when the electrophile is easily reduced such was the case with benzophenone, as only racemic products were obtained.35

![Scheme 8](image)

### 1.4 Asymmetric Induction Using Organolithium Reagents

Organolithium compounds are one of the most attractive and relevant tools in asymmetric carbon–carbon bond formation for their capacity as reactive intermediates for a variety of applications. Scheme 9 shows the conversion of the achiral starting material 29 into one of two enantiomeric products 31 or epi-31. to induce asymmetry of a reaction with a chiral organolithium species, there are three key factors which determine the stereoselectivity.38

a) The selectivity of the formation of the stereoisomeric intermediates 30 and epi-30.

b) The rates of epimerization of 30 and epi-30 relative to their rate of reaction with electrophiles.

c) The stereochemical course of the electrophilic substitution (retention or inversion).
Four pathways are possible in order to transfer stereochemical information:

. **Asymmetric deprotonation**: A chiral base is used to abstract one of two enantiotopic protons selectively from achiral starting material 29 to generate a configurationally stable intermediate 30 or epi-30.

. **Kinetic Resolution (KR)**: One of the enantiomers of achiral starting material 29 is preferentially lithiated over the other. This give the possibility of enantioenriched products as well as enantioenriched recovered starting material.

. **Dynamic Thermodynamic Resolution (DTR)**: The configurational stability of the diastereomeric intermediates 30 and epi-30 is dependent on temperature, and the stereoselectivity is dependent on the ratio of the two complexes 30 and epi-30.

. **Dynamic Kinetic Resolution (DKR)**: The diastereomeric intermediates 30 and epi-30 are in equilibrium and stereoselectivity is dependent on the difference in the transition state energies of electrophilic substitution for each of the diastereomeric intermediates.

### 1.4.1 Asymmetric Deprotonation

In general, asymmetric deprotonation involves complexation of organolithium compounds to a chiral ligand to form a “chiral base”. This chiral base can abstract an enantiotopic proton from the achiral substrate 29 selectively to give diastereoenriched complex 30. This is followed by reaction with an electrophile to provide the chiral products 31 or epi-31 with retention or inversion of configuration at the carbon atom.\(^{39}\)

In 1990, Hoppe and co-workers were the first to achieve one of the best methods for
asymmetric deprotonation by using sec-BuLi with (−)-sparteine. They found that the deprotonation of the achiral primary alkyl carbamate 32 with s-BuLi/(−)-sparteine in Et₂O formed the enantioenriched lithium complex 33 which could be quenched with different electrophiles with retention of configuration (Scheme 10). This can be explained by the fact that the chiral base, s-BuLi/(−)-sparteine, prefers to abstract one of the two enantiotopic α-protons (the pro-S proton) on compound 32.

![Scheme 10](image)

Building on work by Hoppe, in 1991 Kerric and Beak reported methodology for the asymmetric deprotonation of N-Boc pyrrolidine 35 with s-BuLi and (−)-sparteine in Et₂O at −78 °C. In the asymmetric deprotonation, the s-BuLi/(−)-sparteine complex selectively abstracts one of the pro-S protons from one of the two pairs of enantiotopic protons in N-Boc pyrrolidine 35 to give configurationally stable lithiated intermediate (S)-36-L*(Scheme 11). Trapping with different electrophiles gave products in moderate to good yields ranging from 35 to 88% and high enantioselectivity (79:21–98:2 er). For instance, trapping the intermediate (S)-36-L* with TMSCl gave silylated product (S)-37a in 76% yield and 97:3 er.

![Scheme 11](image)

To confirm that the final product was formed via an asymmetric deprotonation pathway and not via an asymmetric substitution, tin–lithium exchange reactions were attempted. Firstly, as it was shown from scheme 12 that the racemic organolithium intermediate 36 was formed
both by deprotonation of 35 with s-BuLi and by tin–lithium exchange of the racemic stannane 38 with s-BuLi. Trapping this intermediate by TMSCl, followed by (−)-sparteine, the product 37a (E = TMSCl) in the two cases was formed as a racemate (very poor er) (Scheme 12). These results showed that (−)-sparteine did not affect the substitution step and the enantioselectivity of the reaction in Scheme 11 was therefore established during the deprotonation. Tin–lithium exchange of enantioenriched stannane (S)-38 gave the organolithium intermediate (S)-36 and hence (after adding TMSCl) gave the product (S)-37a in good er (Scheme 12). This proved that the organolithium intermediate (S)-36 was configurationally stable under the reaction conditions which further supported the asymmetric deprotonation hypothesis.

(+)-Sparteine surrogate 39 is another important diamine chiral ligand that allows access to the other enantiomeric form of the product after lithiation-substitution. This ligand is less hindered than (−)-sparteine so can show different enantioselectivity.

O’Brien and co-workers developed the (+)-sparteine surrogate 39 and demonstrated its use in asymmetric deprotonation. For example, asymmetric deprotonation of 35 followed by an electrophilic trapping with TMSCl gave the product (R)-37a as the major enantiomer (Scheme 13). This result showed that the (+)-sparteine surrogate was almost as effective as (−)-sparteine in the asymmetric lithiation.

Scheme 12
Scheme 13

The asymmetric deprotonation of N-Boc piperidine 40 has also been explored using s-BuLi and (−)-sparteine. This gave a surprising result compared to that of the analogous N-Boc pyrrolidine 35 as N-Boc piperidine was more difficult to lithiate. Beak showed in a computational study that the α-protons of N-Boc piperidine 40 are less acidic than those of N-Boc pyrrolidine 35. The yield of product (S)-42a was only 8% by lithiation of N-Boc piperidine 40 despite a reaction time of 16 h (Scheme 14). Furthermore, 43% yield of enamine 43 was produced as a by-product and this indicated that the attack by s-BuLi at the Boc group was in competition with deprotonation.

Scheme 14

In order to solve this problem, a collaboration between the O’Brien and Coldham groups led to the examination of fourteen chiral ligands for the enantioselective deprotonation of N-Boc piperidine 40. This study showed that the yield of the lithiation–trapping was dramatically reduced by increasing the steric bulk of the ligand. However, the enantioselectivity was reduced when using less sterically hindered ligands. They found that the highest enantioselectivity was achieved by using s-BuLi/(R,R)-44 to lithiate N-Boc piperidine 40. Trapping the intermediate with TMSCl gave silylated piperidine (S)-42a in 90:10 er but only 13% yield (Scheme 15).
Following on from this result, a high yielding asymmetric deprotonation of $N$-Boc piperidine 40 was reported by the O’Brien and Coldham groups using $s$-BuLi/(+)-sparteine surrogate, which lithiated compound 40 faster than $s$-BuLi/(-)-sparteine.\(^{47}\) For example, asymmetric deprotonation of 40 followed by an electrophilic trapping with TMSCl gave the product (R)-42a in a high yield when compared to (–)-sparteine (Scheme 16).

It is relatively rare for benzylic organolithiums to exhibit a significant configurational stability.\(^{48}\) However, in different solvents or in the presence of different kinds of ligands, benzylic organolithiums can exhibit configurationally stability. For example, transmetallation of the stannane 45 with n-BuLi in the presence of either TMEDA or (–)-sparteine was reported by Beak to generate the organolithium 46.\(^{43}\) The enantiomeric ratio was maintained after 30 min or even after 10 h in the presence of the chiral ligand (–)-sp, while the configurational stability was lower in the presence of TMEDA (Scheme 17).\(^{37}\)
Hoppe has reported different conditions of deprotonation for \((R)\) and \((S)\)-48. Good stereoselectivity was achieved by deprotonation of \((R)\)-48 with \(s\)-BuLi/TMEDA at \(-78^\circ C\) in hexane or pentane, and then trapping with TMSCl to give 50a with 94% yield and 98:2 enantiomeric ratio. In contrast, significant loss of enantiopurity was observed when using THF as the solvent (Scheme 18). The lithiation of \((S)\)-48 with \(s\)-BuLi/TMEDA in pentane, then adding allyl chloride formed product 50b in a yield of 88% with an enantiomeric ratio of 91.5:8.5. However, if the lithiation was carried out in THF both a lower yield and er were obtained.

A further study was carried out by Hoppe investigating the deprotonation of benzyl \(N,N\)-diisopropylcarbamate 51 using \(s\)-BuLi/(-)-sparteine in ether at \(-78^\circ C\). The organolithium intermediate was trapped after 4 h by introduction of carbon dioxide into the homogeneous...
reaction mixture (Scheme 19). After esterification with diazomethane only an er of 57:43 for the product in favour of (S)-53 was obtained. On the other hand, when using the same experimental conditions, but with hexane as the solvent, (S)-53 was formed with an er of 91:9. It was thought that there was a competition between the coordinating solvent Et<sub>2</sub>O and chiral ligand (−)-sparteine to complex with n-BuLi, which led to decrease in enantiomeric ratio. In this case, the non-polar solvent hexane is more better than other solvents since it won’t compete with the chiral ligand.

![Scheme 19](image)

Promising results with benzylic organolithiums have been discovered by our group. Investigation into the behaviour of configurational stability benzylic organolithiums plays an important role in inducing asymmetry and will be discussed in the next section.

1.4.2 Kinetic Resolution (KR)

In general, kinetic resolution is defined as a process where the two enantiomers of a racemate are transformed to products at unequal rates (Figure 13).51
One of the enantiomers of the racemic mixture is preferentially deprotonated by a 'chiral base' and transformed to the desired product, with the limitation of the theoretical yield being a maximum of 50%, while the other enantiomer is recovered unchanged.\textsuperscript{51} Trapping with an electrophile can give the product in higher er if the organolithium intermediate is configurationally stable.

To achieve high levels of enantioselectivity, many KR protocols have been developed and used in the synthesis of complex compounds\textsuperscript{52–56}, however there are few examples by using a chiral base.

In 1997, Beak and co-workers reported a moderate kinetic resolution by lithiation of \textit{rac-54} with \textit{n-BuLi}/(\textit{−}-sparteine) (Scheme 20).\textsuperscript{37} Lithiation of \textit{rac-54} with 0.5 equivalents of \textit{n-BuLi}/(\textit{−}-sparteine) and trapping with \textit{CO}_2 gave 55\% yield of the recovered starting material (\textit{R})-\textit{54} with 75:25 er and 22\% yield of (\textit{R})-\textit{55} with 87:13 er. However, increasing the number of equivalents of the chiral base to 0.8 provided (\textit{R})-\textit{54} (12\% yield, er 81:19) and (\textit{R})-\textit{55} (66\% yield, er 57:43) (Table 2). Although, these results didn’t give good enantioselectivity, it showed that KR could be extended to lithiation chemistry.

![Scheme 20](image)

<table>
<thead>
<tr>
<th>Equiv. of \textit{n-BuLi} \textit{/}(\textit{−})-sparteine</th>
<th>Yield (%) of RSM \textit{54}</th>
<th>er of RSM \textit{54}</th>
<th>Yield (%) of \textit{product 55}</th>
<th>er of \textit{product 55}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>55</td>
<td>75:25</td>
<td>22</td>
<td>87:13</td>
</tr>
<tr>
<td>0.8</td>
<td>12</td>
<td>81:19</td>
<td>66</td>
<td>57:43</td>
</tr>
</tbody>
</table>

Table 2

More recently, the Coldham group showed that by using 0.7 equivalents of the chiral base \textit{n-BuLi}/(\textit{−})-sparteine, a kinetic resolution of \textit{N}-\textit{Boc}-2-arylpyridines can be promoted at $–78$ °C.\textsuperscript{57} With these conditions, the enantioenriched starting material was recovered with yields of 39–48\% and ers up to 96:4 (Scheme 21). Lithiation followed by electrophilic quench of the
enantioenriched 56, 2,2-disubstituted piperidines 57 were obtained with excellent yields and high enantioselectivities (Scheme 22).

![Scheme 21](image)

Scheme 21

The optimised conditions involved adding n-BuLi last to a solution containing the N-Boc -2-phenylpiperidine 56a and (−)-sparteine in PhMe then after 3 h, ethyl chloroformate was added. Table 3 shows that the yield and er of the recovered starting material was affected by the number of equivalents of the chiral base and the best conditions were found with 0.7 equivalents of n-BuLi/(−)-sparteine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of n-BuLi / (−)-sparteine</th>
<th>Yield (%) and er of RS M 56a</th>
<th>Yield (%) and er of product 57a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.55</td>
<td>50%, (77:23)</td>
<td>42%, (92:8)</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>45%, (96:4)</td>
<td>51%, (86:14)</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>31%, (92:8)</td>
<td>56%, (77:23)</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>13%, (98:2)</td>
<td>74%, (57:43)</td>
</tr>
</tbody>
</table>

Table 3

In theory, kinetic resolution allows a single enantiomer of starting material to be retrieved, along with a single enantiomer of the quenched product. However, selectivity factors may not be very high, so it is often best to run reactions such that they allow recovery of starting
material with about 40‒50% yield. Slow reactions may require more than 0.5 equivalents of the chiral base for reasonable reaction timescales.

1.4.3 Dynamic Thermodynamic Resolution (DTR)

In the presence of a chiral ligand, if an intermediate organolithium complex is configurationally stable but the rate of interconversion of the diastereomeric complexes is slow on the timescale of the reaction of the organolithium with the electrophile, the enantiomeric ratio of the products will be reflected in the ratio of the diastereomeric organolithium complexes. To obtain a good enantioselectivity, the equilibrium between the complexes must lie heavily to one side. This process is known as a dynamic thermodynamic resolution (DTR) and this reaction is under thermodynamic control.\footnote{In 1996, Beak and co-workers reported a good example of a DTR to achieve high levels of enantioenrichment for the lithiation–substitution of N-pivaloyl-o-ethylaniline \textsuperscript{58,59}.

Anilide \textsuperscript{58} was deprotonated by s-BuLi in methyl tert-butyl ether (MTBE) at –25 °C to give the racemic organolithium reagent \textit{rac}-\textsuperscript{59}. The reaction mixture was cooled to –78 °C then \textit{rac}-\textsuperscript{59} was complexed with (−)-sparteine and electrophilic trapping with TMSCl gave silylated product (\textit{R})-\textsuperscript{60} with er 56:44 and 52% yield (Scheme 23).

However, if (−)-sparteine was added at –25 °C and the solution was left to stir at this temperature for 45 minutes before being cooled to –78 °C (warm-cool protocol) and trapping \textit{rac}-\textsuperscript{59} with TMSCl, (\textit{R})-\textsuperscript{60} was isolated in a dramatically improved 92:8 er and yield of 72% (Scheme 23).}

\textsuperscript{58}

\textsuperscript{59}

\textsuperscript{58}

\textsuperscript{59}

\textsuperscript{60}

\textsuperscript{60}

\textsuperscript{23}

Scheme 23
The need for a warm-cool cycle to accomplish high enantioselectivity demonstrated that the diasteroemeric lithiated intermediates were interconverting at −25 °C and not at −78 °C. The organolithium must have complexed to (−)-sp, then equilibrated to a 92:8 diastereomeric ratio at −25 °C. Cooling to −78 °C then freezes this ratio. Addition of an excess of electrophile then trapped the 92:8 mixture of diastereomeric organolithium complexes and this is reflected in the enantiomeric ratio of the product.

Beak also showed from this methodology that the enantiomeric ratio of the product could be improved by changing the number of electrophile equivalents. The addition of just 0.1 equiv. of TMSCl gave product (R)-60 in 99:1 er but the yield was restricted to 10% (Scheme 24). This improvement in enantioselectivity resulted from kinetic resolution as organolithium (R)-59·(−)-sp reacted faster with the electrophile than organolithium (S)-59·(−)-sp to give the product (R)-60 with a high enantioselectivity.

Coldham and co-workers reported that high yields and excellent enantiomeric ratios of 2-substituted piperidines could be achieved through dynamic thermodynamic resolution.60 N-Boc-piperidine 40 was first deprotonated with s-BuLi and TMEDA in diethyl ether at −78 °C for 3 hours. A chiral ligand such as 61 or 62, which was pre-treated with s-BuLi, was then added. The mixture was warmed to −40 °C to allow the equilibration of the diastereomeric lithiated intermediates, and after 90 min the mixture was cooled to −78 °C in order to prevent further interconversion. Finally, the reaction was quenched with TMSCl to give the product 42a with up to 85:15 er (Scheme 25).
The Coldham group applied their dynamic thermodynamic resolution methodology to N-Boc azepane 23. This gave low yields of products, but very good enantioselectivities (up to 92:8) for a range of electrophiles (Scheme 26). \(^6\)

1.4.4 Dynamic Kinetic Resolution (DKR)
In the presence of a chiral ligand, when the rate of interconversion between the two diastereomeric complexes is fast on the timescale of the reaction of the organolithium with the electrophile, the product ratio is reflected in the different rates of reaction that the complexes have with the electrophile.

The conversion of one enantiomer of a racemic mixture into a product more readily than the other in classical kinetic resolutions (KR) has the limitation of having a maximum theoretical
yield of 50%. This is acceptable if the aim is to produce highly enantiomerically pure compounds, but it is this essential selectivity that sets a low ceiling on the yield. Many attempts have been made to overcome this limitation, and at the same time afford compounds of high enantiomeric purity, but with much improved yields. It is a combination of these targets which has led to the progression from classical kinetic resolution into DKR. In such a process it is possible in principle to obtain a quantitative yield of one enantiomer. Effectively, DKR combines the resolution step of kinetic resolution, with an in-situ equilibration or racemisation of the chirally labile substrate.\(^5\)

In contrast to asymmetric deprotonation, the enantiodetermining step (EDS) is not the selective removal of one enantiotopic proton, but it arises from a kinetic preference for the reaction of one of the diastereomeric organolithium/chiral ligand complexes over the other with the electrophile.\(^3\) In this process, the lithiated intermediates 30 and epi-30 must be configurationally labile and equilibrate faster than they react with the electrophile (Scheme 9, see page 16).\(^3\)

A good example of a DKR to achieve high levels of enantioselectivity was reported by Beak in 1994.\(^6\) The lithiation of \(N,N\)-diisopropyl o-ethylbenzamide 63 with sec-BuLi/(−)-sparteine generated the rapidly interconverting diastereomeric organolithium intermediates (S)-64·(−)-sp and (R)-64·(−)-sp, which when quenched with alkyl halides formed the products 65a and 65b in good yields and enantiomeric ratios (Scheme 27).

![Scheme 27](image_url)
Beak illustrated that the leaving group of the electrophile had a dramatic effect on the enantioselectivity of the lithiation-trapping. Using $n$-BuCl gave the product (R)-65a while $n$-BuOTs gave the opposite configuration (S)-65a (Scheme 27). This difference was attributed to a difference in the substitution pattern of electrophilic attack, (i.e. retention or inversion). The non-complexing halide electrophile attacks the carbanion from the less sterically hindered face in an inversion process and the tosylate delivers the alkyl group to the carbanionic centre on the same face as the lithium to result in a net retentive substitution, presumably due to chelation of a tosylate oxygen atom with the lithium atom.

Tin-lithium exchange of the enantioenriched stannane (S)-65c with $n$-BuLi/TMEDA at −78 °C in the absence of (−)-sparteine, followed by allyl chloride quench gave the racemic product 65d, which indicated the configurational instability of intermediate 64 with respect to the rates of reaction with the electrophilic partner. In addition, the use of substoichiometric amounts of electrophile did not affect the er of the product and this proved a DKR pathway was the reaction mechanism (Scheme 28).61

In 2006, Coldham and co-workers carried out the DKR of N-Boc-2-lithiopyrrolidine by using different chiral ligands.62 They found that the enantioselectivity of the DKR was dependent on the electrophile and how fast it reacted with the two diastereomeric complexes (i.e. the rate of electrophilic quench needed to be slower than the rate of interconversion of the diastereomeric organolithium complexes). This could be achieved by adding the electrophile slowly at the temperature which equilibration occurred. The diamine derivative 66 was the best chiral ligand. N-Boc-pyrrolidine 35 was treated with $s$-BuLi (2.6 equiv.) in Et$_2$O at −78°C and after 6 h $n$-BuLi was added in a large excess (10 equiv.). Finally, slow addition of TMSCl (5 equiv.) over 30 minutes generated the product (S)-37a in excellent er (Scheme 29). Changing the number of equivalents of $n$-BuLi from 3.25 to 6.25 to 10 equivalents had a noticeable effect on selectivity and using 10 equivalents of $n$-BuLi gave the best selectivity.
1.5 Synthesis of 2,2-disubstituted saturated nitrogen heterocycles

Building on the work by Beak, that unsubstituted Boc-protected aza heterocycles may be effectively functionalized at the α-position through a lithiation/alkylation sequence, several researchers have extended the chemistry to the synthesis of α,α-disubstituted nitrogen heterocycles.63–69

In 2005, Xiao and co-workers reported the synthesis of 2,2-disubstituted pyrrolidines in which one substituent was an aryl group.66 This synthesis occurred readily through the increased acidity of the benzylic proton on the 2-arylpyrrolidine. Treatment of N-Boc-2-phenylpyrrolidine rac-67 with n-BuLi/TMEDA in THF at −78 ºC, followed by trapping of organolithium intermediate with methyl iodide afforded pyrrolidine rac-68a in 44% yield (Scheme 30).

The 2,5-disubstituted pyrrolidine was not obtained under these conditions and this confirmed that lithiation using n-BuLi as a base proceeded solely towards the benzylic position. More recently, Coldham’s group in collaboration with O’Brien’s group investigated the synthesis of N-Boc-2-substituted 2-phenylpyrrolidines through similar chemistry.65 The lithiation was monitored using in-situ ReactIR spectroscopy. In this study, full lithiation was not accomplished when rac-67 was treated with n-BuLi in THF at −78 ºC, but an initial partial rapid lithiation was observed. However, complete lithiation was accomplished after
approximately 2 minutes at 0 °C. This difference was attributed to the difference in the rate of interconversion of the Boc rotamers 67a and 67b of the substrate (Scheme 31).

**Scheme 31**

Variable temperature $^1$H NMR spectroscopy of 67 in $d$8-THF showed that the half-life ($t_{1/2}$) for rotation of the Boc group was ~10 h at −78 °C, but < 1 sec at 0 °C. Therefore, when the reactions were carried out at −78 °C low yields of the 2,2-disubstituted products were obtained. However, good yields were obtained at 0 °C. Unfortunately, the chiral organolithium was not configurationally stable at 0 °C and so the reaction with (R)-67 was optimized at −50 °C ($t_{1/2}$ for Boc rotation ~ 3.5 min) maintaining good enantioselectivities and yields of the products (Scheme 32).

**Scheme 32**

Coldham and co-workers found that lithiated (S)-N-Boc-2-phenylpiperidine 56a showed excellent configurationally stability even at −50 °C. Lithiation of (S)-2-phenylpiperidine 56a at −50 °C, followed by trapping with a range of electrophiles after 30 min provided disubstituted products with high enantioenrichment in good yields (Scheme 33). Variable
temperature $^1$H NMR spectroscopy and ReactIR spectroscopy showed that the Boc group rotates rapidly in 56a, even at $-78^\circ$C ($t_{1/2} \sim 4$ sec). Similar results were later reported by Gawley and co-workers.$^{70}$

![Scheme 33](image)

As previously mentioned, kinetic resolution, dynamic kinetic resolution and dynamic thermodynamic resolution of $N$-Boc-azaheterocycles have recently been attempted in our group.$^{57,62}$ The kinetic resolution chemistry was found to be effective for $N$-Boc-2-arylpyrrolidines (Scheme 34).$^{57}$ The recovered starting material ($R$)-56a could be isolated with high enantiomer ratios after electrophilic quench, especially if n-BuLi and the chiral ligand were not pre-mixed. The optimised conditions for kinetic resolution were determined by in-situ IR spectroscopy. After kinetic resolution, the recovered enantioenriched $N$-Boc-2-arylpyrrolidines could be deprotonated with n-BuLi in THF at $-78^\circ$C and quenched with electrophiles to provide highly enantiopure 2,2-disubstituted piperidine product 57d.$^{57}$ It was difficult to determine an er of product 57d therefore, tin–lithium exchange was carried out by treating 57d with n-BuLi at $-78^\circ$C. The intermediate was then protonated by addition of acetic acid. Product ($S$)-56 was isolated with er 82:18, suggesting that tin–lithium exchange and protonation occurred with retention of configuration. Interestingly, when the same procedure was performed at room temperature, rac-56 was recovered in 84% yield (Scheme 34).
As the N-Boc azepane work within the group gave some positive results, it seemed natural for N-Boc-2-phenylazepane to be investigated next using the group’s organolithium chemistry methodology. Therefore, investigating the chemistry of N-Boc-2-phenyl azepane has been the basis of the majority of this PhD work and this work will be explained in detail in Chapter 2 (Scheme 35).

Scheme 34

Scheme 35
Chapter 2

Synthesis and Lithiation–Substitution of \( N \)-Boc-2-phenylazepane

2.1 Saturated nitrogen heterocycles in chemistry

The asymmetric synthesis of pyrrolidines, piperidines, azepanes and their benzo-fused compounds form an interesting field of synthetic chemistry as they can be considered as key structural components of many biologically important natural alkaloids.\(^7\)

Functionalized azepanes play an important role in the synthesis of many medicinal heterocyclic compounds and biologically active alkaloids (Figure 14). For instance, azepanes are present in the structures of stemona (e.g. stenine),\(^7\) ergot (e.g. aurantioclavine and clavicipitic acid),\(^7\) kopsia (e.g. arboflorine),\(^7\) and securinega (e.g. securinine) alkaloids.\(^7\)

![Figure 14](image_url)

This chapter describes research on the synthesis of substituted azepanes and, in particular, a focus on the electrophilic quench of organolithium intermediates.

2.2 Previous methods used to prepare substituted azepanes

Natural and synthetic compounds containing a chiral azepane ring can display a range of potential or proven biological activities including gastropokinetic action and protein kinase C inhibitory effects.\(^7\) Despite extensive efforts, only a few methods exist to provide access to saturated substituted azepanes.

The reduction of caprolactams is the most utilised classical method in the synthesis of azepanes. Caprolactams are synthesised from either the Beckmann rearrangement of cycloalkanone oximes or from the Schmidt reaction of cycloalkanones. Although these are generally efficient reactions a mixture of constitutional isomers is often formed.\(^7\)
Lithiation-trapping of N-Boc allyl amines followed by cyclization is another method used to synthesise substituted azepanes. Beak and co-workers have recently reported a few interesting examples that can be considered an important source of azepane derivatives. 

2.2.1 The Beckmann Rearrangement

In 1886, Beckmann reported a rearrangement to prepare caprolactams from oximes by carrying out an acid mediated isomerisation (Scheme 36). 

![Scheme 36](image)

In general, the Beckmann rearrangement requires a strong acid such as sulfuric acid or the so-called Beckmann mixture containing acetic acid, acetic anhydride, and hydrogen chloride. The reaction mechanism involves an alkyl migration by initial protonation of the oxime oxygen to afford the oxonium cation. Migration of an alkyl group accompanied with departure of a water molecule gives a nitrilium cation, which undergoes base hydrolysis to form an amide.

This method was unfavoured in the case of unsymmetrical oximes where two pathways are possible, as this often forms a mixture of products (Scheme 37). The two pathways can occur, and the path taken will depend on the direction of OH group but path (a) is largely preferred because it is trans to the leaving group.

![Scheme 37](image)

2.2.2 The Schmidt Reaction

The Schmidt reaction provides an important method to prepare substituted azepanes by ring expansion. It involves an alkyl migration from a ketone to form a lactam (Scheme 38).
Scheme 38

The reaction gives a mixture of products when unsymmetrical ketones are used. Therefore, although these two methods were efficient and versatile, generation of a mixture of constitutional isomers created the need for a more specific process to synthesise substituted azepanes.

2.2.3 Lithiation-conjugate addition

Lee and Beak reported an asymmetric synthesis of polysubstituted azepanes that employed an enantioselective conjugate addition reaction using a lithiated allylamide, followed by lactamization. The highly diastereo- and enantioenriched enecarbamates 77a and 77b were obtained by treatment of N-Boc-allylamines 74 with n-BuLi at −78 °C followed by addition of an \( \alpha,\beta \)-unsaturated ester (Scheme 39, Table 4).

![Scheme 39](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>77a</td>
<td>CH₃</td>
<td>92</td>
<td>95:5</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>77b</td>
<td>Ph</td>
<td>86</td>
<td>93:7</td>
<td>&gt; 97:3</td>
</tr>
</tbody>
</table>

Table 4

Enantioenriched 77a and 77b were converted to the corresponding 3,4,5-trisubstituted N-Boc azepanes 82a and 82b in high yields via aminolysis, hydrolysis, reduction, debenzylation, and addition of the Boc group (Scheme 40).
The use of organolithium reagents is a very good way to achieve the synthesis of substituted azepanes. Investigating the chemistry of azepanes has been the basis of the majority of this PhD work and will be explained in detail in the next section.

2.3 Results and discussion

2.3.1 Synthesis of N-Boc-2-phenylazepane

N-Boc-2-phenylazepane was unavailable commercially and needed to be prepared. In 2008, the Coldham group reported a one-pot synthesis of N-Boc-2-phenylazepane 71 based on work by Dieter and co-workers. In this case, N-Boc-azepane 23 was lithiated α to the nitrogen atom using s-BuLi and TMEDA. A lithium-zinc exchange was then performed using zinc chloride, followed by a Negishi coupling with the required aryl halide (Scheme 41).
Scheme 41

This route was attractive as all the reaction steps could be carried out in one pot. However, the chemistry was challenging and needed expensive reagents, particularly the tri-tert-butylphosphonium tetrafluoroborate ligand used for the Negishi coupling.

An alternative method to synthesise \( N \)-Boc-2-phenylazepane 71 was reported by Gawley and co-workers in 2005.\(^{83}\) Gawley's protocol involved four steps to give the desired product with an overall yield of 58%. Beginning from \( \varepsilon \)-caprolactam 83, Boc protection, followed by reduction with diisobutylaluminium hydride (DIBAL-H) gave compound 85. A subsequent reaction with benzotriazole (Bt) and phenylmagnesium bromide gave \( N \)-Boc-2-phenylazepane 71 (Scheme 42).

Scheme 42

\( \varepsilon \)-Caprolactam 83 was found to be a cheap and readily available starting material, allowing work to begin on a relatively large scale. However, for the Boc protection, large quantities of butyllithium were required. It was found that by using 4-dimethylaminopyridine (DMAP), alongside Boc2O the protected compound 84 could be prepared with a yield of 85% (Scheme 43).\(^{84}\) It was not clear whether DMAP acted as a nucleophilic catalyst, or whether the tert-butoxide released from Boc2O deprotonated the amide. Both mechanisms would only require substoichiometric amounts of DMAP, but conditions in the literature used it stoichiometrically.\(^{84}\)
Scheme 43

The second step used DIBAL-H to partially reduce the amide moiety. Adding DIBAL-H (1.4 equiv.) dropwise to a solution of lactam 84 at –78 °C and stirring for 1 hour gave the desired product 85 in 86% yield, which was a slight increase when compared to the literature (Scheme 44). Two rotamers of unequal proportion were seen in the product 1H NMR spectrum.

Scheme 44

The next step was the reaction of 85 with benzotriazole, which was performed by heating the reaction mixture under reflux in toluene. This resulted in an 82% yield of product 86 once both isomers were combined. This yield was a noticeable increase on that achieved in the literature. As a matter of interest, the two isomers were initially isolated separately, but were believed to behave in the same manner when displaced in the next step (Scheme 45).

Scheme 45

The final step to reach the required N-Boc-2-phenylazepane 71 involved the reaction of 86 with phenylmagnesium bromide. It was carried out by adding phenylmagnesium bromide solution in Et₂O to a compound 86 in Et₂O and a small amount of THF to enhance the solubility. The isolated yield of 54% was slightly lower than that reported by Gawley.
It was noticed at this point that the $^1$H NMR spectrum of $N$-Boc-2-phenylazepane 71 clearly showed two rotamers. These were roughly in a 1:1 ratio and thought to be due to restricted rotation about the $N$-Boc bond.

![Scheme 46](image)

2.3.2 ReactIR spectroscopic monitoring of carbamate lithiation

To begin our investigations, it was necessary to optimise the conditions for full lithiation and this was achieved by carrying out *in-situ* infrared studies using Mettler Toledo ReactIR equipment. In 2012, Coldham, O’Brien and co-workers reported the lithiation of $N$-Boc-2-phenylpyrrolidine and piperidine by making use of *in-situ* ReactIR spectroscopy.\(^{65}\)

The lithiation of $N$-Boc-2-phenylazepane 71 would be affected by the interconversion of the two rotamers 71a and 71b (Scheme 47), both of which could be seen in the $^1$H and $^{13}$C NMR spectra. It was clear that the conjugation between the carbonyl group and the lone pair on nitrogen made the rotation of the C–N bond in this type of compound slower than in a normal single C–N bond. The direction of the carbonyl group controlled the lithiation by complexation to the base, so in this case only rotamer 71b was able to be deprotonated at the benzylic position.

![Scheme 47](image)
either did not interconvert or interconverted very slowly. If the rotamer interconversion was slow, it would have affected the lithiation of N-Boc-2-phenylazepane 71.

Figure 15: 3D and 2D plots of lithiation of 71 at −78 °C by in situ IR spectroscopy. (a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the C=O peak for 71 (blue) and for the lithiated intermediate 72 (red). The first and second red triangles indicate the additions of N-Boc-2-phenylazepane and n-BuLi, respectively.

Figure 16: 3D and 2D plots of lithiation of 71 at −30 °C by in situ IR spectroscopy. (a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the C=O for 71 peak (blue) and for the lithiated intermediate 72 (red). The first and second red triangles indicate the additions of N-Boc-2-phenylazepane and n-BuLi, respectively.
In contrast, the ReactIR plots at −5 °C (Figure 17) showed the complete appearance of the lithiated intermediate 72 after n-BuLi added to rac-71. Monitoring the lithiation using in-situ IR spectroscopy indicated that the rotation of the Boc group was slower at −78 °C and −30 °C than at −5 °C. Therefore, at −5 °C, rac-71 (νC=O = 1694 cm⁻¹) was fully converted into the lithiated intermediate 72 (νC=O = 1644 cm⁻¹) after n-BuLi was added (Scheme 47). This showed that complete lithiation was affected by the rate of interconversion of the N-Boc rotamers and so at −5 °C, full lithiation was achieved in just 4 minutes.

Figure 17: 3D and 2D plots of lithiation of 71 at −5 °C; Blue line represents intensity of C=O stretching frequency of 71 (1694 cm⁻¹) and red line of 72 (1644 cm⁻¹) over time.

2.3.3 Lithiation–substitution of N-Boc-2-phenylazepane

By applying the results obtained using in situ IR spectroscopy, N-Boc-2-phenylazepane 71 was deprotonated by adding 1.2 equiv. n-BuLi at −5 °C and leaving the reaction mixture for 4 min. Then, the corresponding organolithium was quenched with different electrophiles (Scheme 48).

![Scheme 48](image-url)
The first electrophile to be used was methyl iodide, which was known to be a reactive electrophile, and therefore should have worked well. The mixture was stirred for 4 minutes before the organolithium intermediate **72** was trapped with the electrophile, but the yield of the product was only moderate (**73a**, 45%). Therefore, different times were examined to find the best time for improving the yield. Increasing the reaction time to 10 minutes gave a better yield of 76% (Scheme 49). However, increasing the time to more than 15 minutes led to decomposition of organolithium intermediate.

![Scheme 49](image)

The racemic \(N\)-Boc-2-phenyl-2-substituted azepanes **73a–g** were obtained in varying yields (Scheme 50). In all cases, THF was used as the solvent. As previously discussed, THF is a very strong activating agent for organolithium reagents. Unfortunately, no product was isolated when using the electrophiles trimethylsilyl chloride, benzyl bromide or \(S\)-phenyl benzenethiosulfonate under these conditions. High yields of products were formed when using 1,3-dibromobutane, allyl bromide and 1,4-dibromobutane as electrophiles, while good yields were also obtained when using methyl iodide and tributyltin chloride to produce **73a** and **73e** (Scheme 50).
Using carbonyl electrophiles such as acetone and benzaldehyde did not proceed as expected to form alcohol products. Instead, the cyclic carbamates 73f and 73g were formed, where the intermediate alkoxide had cyclized on to the Boc group. In the latter case, a separable mixture of diastereomers (dr 3:1) was isolated, the stereochemistry of the major isomer (trans-phenyl groups) was determined by using X-Ray crystallography (Figure 18, Appendix 6.1a).

Figure 18
From these results we can see that electrophiles react with the organolithium intermediate 72 leading to the formation of \( \alpha \)-substituted products. However, an unusual interesting result was obtained where the regioselectivity for this reaction could be changed when we changed the electrophile. Surprisingly, under the same conditions the lithiation of \( N \)-Boc-2-phenylazepane 71, followed by the addition methyl cyanoformate or methyl chloroformate as electrophiles did not afford the expected \( \alpha \)-substituted products 73h (Scheme 51). Instead the \( ortho \)-substituted product 87a was formed in a moderate yield of 50–65%.

These results were confirmed by the presence of the peak for the benzylic proton in the \(^1\text{H} \) NMR spectrum at 5.62 ppm, together with a reduction in the number of aromatic protons that would be typical for a 1,2-disubstituted benzene ring. In this case, the binding of electrophiles could have change the structure of the organolithium intermediated by co-ordination to form an \( \eta^3 \) organolithium complex to give \( ortho \)-substituted products. This is discussed further below.

Using this methodology, different \( ortho \)-substituted products were synthesised by deprotonation of carbamate 71 with \( n \)-BuLi and then trapping the organolithium intermediate with alkyl chloro- or cyanoformate derivatives (Scheme 52).
It was difficult to explain the difference in regioselectivity in these cases. It was expected that the \textit{ortho} protons were slightly less acidic than the $\alpha$-protons. However, there was a possibility that the activation energy of \textit{ortho} deprotonation was less than $\alpha$-deprotonation, leading to the \textit{ortho}-lithiated intermediate being trapped by cyano- or chloroformate. This would seem unlikely gives the formation of products 73a-g. Looking in more depth in order to understand the reaction mechanism, it was hypothesized that the \textit{ortho} products could arise from the $\alpha$-lithiated intermediate 72 but with substitution at the \textit{ortho} position being more favoured than $\alpha$ to the nitrogen atom. Subsequent re-aromatization would then form the desired products. This would maintain the usual deprotonation protocol, where $\alpha$-deprotonation would give organolithium intermediate 72 which was able to co-ordinate to the carbonyl oxygen atom. From there, the lithium atom could co-ordinate in an $\eta^3$ arrangement to the \textit{alpha}, \textit{ipso} and \textit{ortho} carbons to give an $\eta^3$ intermediate 88, which after trapping with methyl chloro- or cyanoformate could provide the \textit{ortho}-substituted product 89. Aromatisation then gives the product 87a. This process could be described as a concerted thermal 1,3-hydride shift but these are not formally allowed by Woodward–Hoffmann rules and so the manner of proton transfer was assumed to be stepwise rather than concerted (Scheme 53).\textsuperscript{85} This was mentioned in Section 1.1.3, where mesomerically-stabilised organolithiums of allylic and benzylic organolithiums involve complexation by $\eta^1$ or $\eta^3$ (Figure 7c, chapter 1), so there is the possibility of co-ordination of lithium to both the $\alpha$ and the \textit{ortho} position.
A similar ortho-substituted product 92 was formed from the deprotonation of N-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline 90 with n-BuLi and trapping by methyl cyanoformate. This work was discovered by another member of the Coldham group.\(^\text{86}\) Interestingly, methyl chloroformate gave the \(\alpha\)-substituted product 91, not the ortho-substituted product (Scheme 54).

The \(\alpha\)-substituted product was the expected product in these types of reaction. In order to see whether the reaction was taking place via an ortho-lithiation pathway, THQ 90 was deprotonated with n-BuLi at \(-78\) °C in THF for 6 minutes then addition of \(\text{D}_2\text{O}\) gave the deuterated THQ \(\text{d}_1\)-90 in good yield with around 95% deuterium incorporation.\(^\text{86}\)
By following the same strategy of deprotonation, THQ d₁-90 was treated with n-BuLi (1.2 equiv.) at −78 ºC for 6 minutes in THF, then trapping the intermediate using methyl cyanoformate. Under these conditions no deprotonation of THQ d₁-90 occurred and only the starting material was recovered (Scheme 55). However, when a large excess of n-BuLi was used and the mixture was stirred for 1 hour at −78 ºC, the ortho-substituted product 92 was formed in very low yield after the addition of methyl cyanoformate. This was accompanied with disappearance of the deuterium in the α-position (Scheme 55). The loss of deuterium in the α-position of the product could support the suggested mechanism in Scheme 53 as this kinetic isotope effect showed that no ortho-lithiation was taking place.

Another experiment carried out by Carter used the pentadeuterated derivatives d₅-90a. Compound d₅-90a was deprotonated using 1.2 equivalents of n-BuLi in THF at −78 ºC. After 6 minutes, methyl chloroformate was added to the reaction to give product d₅-91a. The reaction was repeated, but methyl cyanoformate was used instead to give product d₄₅/₅₂a (Scheme 56).
According to Scheme 56, ds-90a gave the same products resulting from lithiation of 90 and this supported the mechanism illustrated in Scheme 53 where the migration of deuterium from the ortho-position to the α-position occurred in a non-concerted manner. Finally, it could be concluded that with THQs, the use of chloroformate gave α-substituted products, but with cyanoformate the ortho-substituted product was preferred with only α-lithiation taking place in both cases. This result was supported by DFT calculations, which was focussed on the lithiated intermediate. DFT calculations showed a difference in the position of the lithium atom in the minimum energy structures after addition of methyl chloroformate or methyl cyanoformate. This study illustrated that when methyl chloroformate was added, the lithium atom was closer to the α-carbon, whereas when methyl cyanoformate was added, the lithium was closer to the ortho-position of the aromatic ring with more of an η3 co-ordination. Thus, we can conclude that methyl cyanoformate was able to change the co-ordination of lithium, which explains the experimental result.

In contrast, with N-Boc-2-phenylazepane 71 both electrophiles gave the ortho-substituted products. This could be explained in the same manner, where the carbonyl oxygen atom co-ordinates to the lithium atom and favours an η3-intermediate organolithium.

The same investigation was carried out on N-Boc-2-phenylpiperidine 56a. Previously, our group has applied kinetic resolution to N-Boc-2-phenylpiperidine 56a by using n-BuLi/(−)-sparteine as a chiral base. Trapping with ethyl chloroformate gave α-substituted product 57a (Scheme 21, Chapter 1). In this research, racemic lithiation–substitution reactions were
done by deprotonation of N-Boc-2-phenylpiperidine 56a using 1.2 equivalents of n-BuLi in THF at −78 ºC. After 6 minutes, methyl chloroformate was added to the reaction to give α-substituted product 57f. However, when the intermediate was trapped with methyl cyanoformate instead, this gave ortho-substituted product 93 (Scheme 57). These results were identical with the lithiation of THQ 90.

It was doubtful that ortho-lithiation took place in the azepane as it was similar to the THQ. Therefore, it was probable that the energy of the transition states differed between α and ortho substitution and this was affected by the position of the lithium atom. When chloroformates or cyanoformates are coordinated, the position of the lithium favours ortho-substitution. After lithiation of N-Boc-2-phenylazepane 71, most electrophiles reacted in the α-position. However, coordination of the electrophile, such as a cyano- or chloroformate likely led to an η3 intermediate and provided ortho-substituted products. More investigations will be needed to determine the definitive mechanism of this transformation.

2.3.4 The rotation barrier of N-Boc-2-phenylazepane and DFT calculations

2.3.4.1 Variable temperature 1H NMR spectroscopy study
As illustrated in Scheme 50, the high yields of N-Boc-2-phenyl-2-substituted azepanes obtained indicated that the rotation of the Boc group was fast enough in N-Boc-2-phenylazepane 71 at −5 ºC. To estimate the rotation barrier of the Boc group, a variable temperature 1H NMR spectroscopy (VT NMR) study was performed. Previously, these studies were conducted by the Coldham group to calculate the rotation barrier of N-Boc-2-phenylpyrrolidine and piperidine, which were found to be ΔG‡ = 64.5 kJ mol⁻¹ at 46 ºC and ΔG‡ = 50.0 kJ mol⁻¹ at −28 ºC respectively (Figure 19).65
To determine the rotational barrier, a sample of $N$-Boc-2-phenylazepane 71 in DMSO-$d_6$ was examined at various temperatures to observe coalescence of the signals for the benzylic proton ($\delta = \sim 5.00$). The region $\delta = 5.50$–2.00 ppm is shown in Figure 20 with the ratio of rotamers being approximately 1:1.
The benzylic hydrogen of each rotamer appeared as a doublet of doublets, the expected splitting by the adjacent carbon's two distinct proton environments (pseudo-axial and pseudo-equatorial). These multiplets began to broaden when the temperature was increased and became broad singlets about 50 °C. A further increase of temperature made the two singlets merge together to become a single broad peak, which could be seen about 80 °C. Increasing the temperature further caused the broad peak to sharpen again. These changes in signal features could be interpreted in terms of the rotation rate when compared to the speed of NMR measurements. At room temperature, the two rotamers are locked in place for a long enough time to appear chemically different. Increasing the temperature increased the rate of rotation and so the two signals began to coalesce. Therefore, the distinction between the rotation states decreased. At the coalescence temperature, the rate of rotation of the N-Boc group was equal to the NMR timescale, which meant that the two separate states could not be picked out as chemically different. When the temperature was further increased then each rotational state had a shorter lifetime, and this explained the sharpening of this peak at 100 °C. Line-shape analysis was used to determine the parameters for the rotation of the Boc group based on the benzylic peaks at 4.83 and 5.04 ppm and an Eyring plot was formed (Appendix 6.2a). The activation parameters for N-Boc rotation were found to be: \( \Delta S^\ddagger = 8.8 \text{ J K}^{-1} \text{ mol}^{-1} \) and \( \Delta H^\ddagger = 73.2 \text{ kJ mol}^{-1} \), giving a barrier of rotation where \( \Delta G^\ddagger = 70.8 \text{ kJ mol}^{-1} \) at –5 °C. These activation parameters gave a rotation rate of \( 8.7 \times 10^{-2} \text{ s}^{-1} \) and a rotational half-life of \( t_{1/2} = 8 \text{ sec} \) at –5 °C. The half-life for rotation of the Boc group was estimated at –78 °C to be \( t_{1/2} = 28 \text{ days} \). Experimentally, these results agreed with the slow rotation and partial lithiation at –78 °C, as illustrated by the in-situ IR plots and the experimental data.

Similar coalescence studies were also carried out in toluene-d₈ for comparison (Figure 21 and Appendix 6.2a). The coalescence temperature of the benzylic peaks was not fully clear at 80 °C, so the energy barrier to the rotation of the Boc group was calculated by the triplet peaks at 2.53 and 2.63 ppm. Activation parameters of \( \Delta S^\ddagger = -1.2 \text{ J K}^{-1} \text{ mol}^{-1} \) and \( \Delta H^\ddagger = 68.1 \text{ kJ mol}^{-1} \), gave a rotational barrier of \( \Delta G^\ddagger = 67.8 \text{ kJ mol}^{-1} \) at –5 °C and 67.9 kJ/mol at –78 °C. The corresponding rate constants were worked out to be \( 3.4 \times 10^{-1} \text{ s}^{-1} \), leading to \( t_{1/2} = 2 \text{ sec} \) at –5 °C and \( 2.7 \times 10^{-6} \text{ s}^{-1} \), \( t_{1/2} = 72 \text{ h} \) at –78 °C. These values also supported the observed ReactIR studies, which showed full lithiation in around 10 min. There was not a big difference in activation parameter values by changing solvents, although the rate of rotation of the Boc group in toluene was slightly faster when compared to DMSO. Ideally, while THF-d₈ would have been the solvent of choice for the NMR spectroscopy investigation,
toluene was the solvent used for asymmetric deprotonations. Furthermore, THF had a low boiling point which meant the maximum temperature available would be 56 °C. This was hypothesised to be below the coalescence temperature for N-Boc-2-phenylazepane, therefore the higher boiling solvent DMSO-d$_6$ was used in this study due to its ability to reach the elevated temperatures required for coalescence of these signals.

![Figure 21](image)

**Figure 21**

### 2.3.4.2 Density functional theory (DFT) calculations

Variable-temperature NMR spectroscopy led to determination of the activation parameters for the rotation of the Boc group by carrying out line-shape analysis of VT-NMR data. It had been shown that there was a significant difference between the azepane and the corresponding five- and six-membered ring analogues. A more in-depth explanation relating to the high barrier of rotation (70.8 kJ mol$^{-1}$ in DMSO) was sought by carrying out DFT calculations, accomplished by Dr. Anthony Meijer from the Department of Chemistry at the University of Sheffield. Density functional theory (DFT) calculations were performed using Gaussian09, version D.01. Gaussian was compiled using Portland compiler v.8 with the 6-311G** basis set on all atoms. All the calculations performed on these systems were done using either THF or DMSO as the solvent via a polarizable continuum model (PCM) using the standard parameters as supplied by Gaussian.$^{87}$
In this study, the density functional theory method was used to optimize the conformations of N-Boc-2-phenylazepane rotamers in both THF and DMSO solvents. Four unique orientations of the N-Boc group were found corresponding to two different rotamers (Figure 22). The four different conformations were defined by the N-Boc position relative to the ring and whether the C=O was pointing towards or away from the phenyl group.

Figure 22: DFT structures of Transition states after studying clockwise and anticlockwise rotation of the Boc group, with the lowest Gibbs energy barrier
Firstly, from the four relatively low energy structures that were found (Figure 22), the lowest energy conformations were found to be the transition states 71a and 71b with the benzylic proton in the pseudo-equatorial position for both clockwise rotation 71a and anticlockwise rotation of the Boc group 71b. As mentioned before, the direction of the carbonyl group controls the lithiation by complexation to the base, so in this case only conformation 71a was able to be deprotonated at the benzylic position. DFT calculations showed as expected that the lowest Gibbs energy barrier (at 298 K) in DMSO was 72.9 kJ/mol (74.1 kJ/mol in THF) with a distribution ratio 1.0:0.8 between the two rotamers, which was a fairly good match with the Gibbs energy barrier at 298 K determined by VT-NMR spectroscopy in DMSO of 70.3 kJ/mol. On the other hand, the other conformations 71c and 71d place the benzylic proton in the pseudo-axial orientation and in this case the benzylic proton was far away from carbonyl group. These conformations 71c and 71d had a much higher Gibbs energy than the conformations 71a and 71b with a distribution ratio 0.12:0.09 between the two rotamers. The VT spectroscopic and DFT studies indicated that the optimum conditions for lithiation of N-Boc-2-phenylazepane would be at temperatures of at least –10 °C as this would allow for rotation of the Boc group and therefore subsequent higher yields after electrophilic quench (vide supra). We therefore allowed a lithiation period of several minutes at –5 °C in THF prior to adding an electrophile. We were pleased to find that this method allowed the formation of 2,2-disubstituted azepane products 73a–g in good to excellent yields (Scheme 51).

2.3.5 Kinetic Resolution of N-Boc-2-phenylazepane

Our group has previously reported studies of the dynamic thermodynamic resolution of 2-lithiated N-Boc-azepane (Scheme 26, Chapter 1). Although this gave low yields, excellent enantioselectivities (up to er 92:8) were achieved for a range of electrophiles.60 This methodology showed reported that N-Boc-azepane had a slower rate of lithiation than the corresponding five- and six-membered analogues. As a result, yields tended to be low. It was expected that N-Boc-2-phenylazepane 71 would be more reactive than N-Boc-azepane 23 due to the more acidic benzylic proton. We were therefore interested to do kinetic resolutions with the 2-phenyl derivatives. Kinetic resolutions were attempted with the aim to recover enantioenriched starting material. However, it was disappointing that poor enantiomeric ratios were obtained after treating N-Boc-2-phenylazepane 71 with n-BuLi/(+)/sparteine in PhMe using different conditions. For example, the lithiation of N-Boc-2-phenylazepane 71
was carried out by dissolving 71 and 1.5 equivalents of (+)-sparteine in PhMe at −5 °C, followed by the addition of 1.2 equivalents of n-BuLi. Then, after three hours, tri-n-butyltin chloride was added to give the recovered starting material 71 (42%, er 66:34), together with the product 73e (40%, er not determined) (Scheme 58 and Appendix 6.3).

Scheme 58

It was assumed that the absolute stereochemistry of recovered starting material could be the (S)-enantiomer based on the previous results in our group, in which (+)-sparteine preferred to abstract the R-proton. Therefore the (S)-enantiomer of starting material would be recovered.57,88

It appeared that N-Boc-2-phenylazepane 71 was less amenable to the kinetic resolution than the corresponding piperidine. The increase in the conformational freedom of the larger ring in comparison with the piperidine presumably led to reduced selectivity in the kinetic resolution with (+)-sparteine as the chiral ligand. Table 5 illustrates the different conditions that were used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.of n-BuLi</th>
<th>Equiv.of (+)-sp</th>
<th>E⁺</th>
<th>Yield (%) and er of RSM 71</th>
<th>Yield (%) of product</th>
<th>time</th>
<th>Temp.</th>
<th>Addition of n-BuLi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>1.8</td>
<td>Br(CH₂)₄Br</td>
<td>92%, (50:50)</td>
<td>0%</td>
<td>2 h</td>
<td>−5 °C</td>
<td>premix</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>1.5</td>
<td>Br(CH₂)₄Br</td>
<td>82%, (55:45)</td>
<td>10%</td>
<td>40 min</td>
<td>−5 °C</td>
<td>premix</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1.5</td>
<td>Bu₃SnCl</td>
<td>63%, (55:45)</td>
<td>16%</td>
<td>40 min</td>
<td>−5 °C</td>
<td>premix</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>1.5</td>
<td>Bu₃SnCl</td>
<td>70%, (55:45)</td>
<td>10%, 2 h</td>
<td>−5 °C</td>
<td>n-BuLi last</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>1.5</td>
<td>Bu₃SnCl</td>
<td>42%, (66:34)</td>
<td>57%</td>
<td>3 h</td>
<td>−5 °C</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
<td>1.5</td>
<td>Bu₃SnCl</td>
<td>70%, (58:42)</td>
<td>21%</td>
<td>3 h</td>
<td>−5 °C</td>
<td>premix</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.8</td>
<td>Bu₃SnCl</td>
<td>34%, (55:45)</td>
<td>59%</td>
<td>3 h</td>
<td>−5 °C</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>2.5</td>
<td>Bu₃SnCl</td>
<td>80%, (56:44)</td>
<td>12%</td>
<td>3 h</td>
<td>−78 °C</td>
<td>n-BuLi last</td>
</tr>
</tbody>
</table>

Table 5
Leaving the reaction for less than 3 h (entries 1-4) led to poor er's of the starting material being recovered in a high yield. There was no big change in the enantioselectivity when n-BuLi was added last or premixed with the chiral ligand (entries 5,6) although there was a slight increase when n-BuLi was added last. Even when < 50% of recovered starting material was isolated by increasing the number of chiral base equivalents, the er was low (entry 7). The yield of RSM was >50% when the reaction temperature was changed to –78 °C, however the starting material was recovered with poor er.

Changing the solvent to Et₂O gave nearly a similar result, where the recovered starting material 71 was obtained in 50% yield with reduction of the er (55:45). Increasing the time up to 5 h did not cause any improvements.

The DTR methodology was also used to check if it was possible to resolve the enantiomers using a warm-cool procedure but unfortunately this gave poor er as well (Scheme 59).

2.3.6 Removal of the Boc group

A key feature of the Boc group is its ability to be removed under acidic conditions to give a free amine. The most common removal reagent for the Boc group is TFA. Applying these conditions (1 equiv. TFA in CH₂Cl₂ at room temperature) to compound 73b did not give the desired product. ¹H NMR analysis of the crude mixture revealed the presence of the Boc group and alkene peaks at the same time, but this compound could not be isolated by column chromatography. Changing the number of equivalents of TFA did not give any improvement. Also, deprotection of 73b by using an ethereal HCl solution (2 M) at room temperature failed to give the desired product (Scheme 60).
Interestingly, deprotection of 73b was successful by using a different method previously used by Gawley.\textsuperscript{89} Compound 73b was reacted with TMSI, which was generated \textit{in-situ} from TMSCl and NaI. This promoted \textit{in-situ} cyclization to give the desired bicyclic product 94 (Scheme 61).

On the other hand, Boc deprotection of carbamate 87a using TFA did not suffer the same problem as 73b. It was interesting to find that treatment of 87a with TFA in CH$_2$Cl$_2$ at room temperature did not give the amine, but it gave instead lactam (isoindolinone) 95 in a good yield instead (Scheme 61). X-ray crystallography (Figure 23 and Appendix 6.1b) along with $^1$H NMR spectroscopy confirmed the structure of this product, which resulted from cyclization of the intermediate amine onto the carbonyl of the ester group.
2.4 Conclusions and future work

In conclusion, $N$-Boc-2-phenylazepane was synthesised in an overall yield of 54% in four steps starting from cheap and commercially available compounds. Different studies were used to determine the energy barrier of rotation for the Boc group such as VT-NMR and DFT calculations. The lithiation of $N$-Boc-2-phenylazepane 71 was optimized by in-situ ReactIR spectroscopy. Optimum conditions to give a full lithiation were found by using $n$-BuLi in THF at $-5 \, ^\circ C$ for 10 min. A range of 2,2-disubstituted azepanes had been synthesised with different regioselectivities according to the type of electrophile. Ortho-substituted products could be formed by using some carbonyl electrophiles, such as alkyl cyanoformates or chloroformates. However, the larger ring size of the azepanes when compared with the piperidines led to a reduction in the selectivity during the kinetic resolution reactions with (+)-sparteine. Bicyclic or tricyclic ring systems were obtained by removal of the Boc group. Attempting the kinetic resolution by using another chiral ligand or by using different substituents in the 2-position of the azepane ring could increase the reactivity towards asymmetric deprotonation. Ortho-substituted products were considered another good area for investigation in order to see whether $\alpha$-substituted products could be obtained when the ortho-positions were blocked. Finally, it may be useful to carry out in-situ NMR spectroscopic studies to investigate the structure of the lithiated intermediate.
Chapter 3

Synthesis and Lithiation–Substitution of N-Boc-2-phenylbenzazepine and N-Boc-2-phenyl-7-methoxybenzazepine

3.1 Importance of benzazepine derivatives

Benzazepines are 7-membered aza-heterocyclic compounds with an azepane ring fused to a benzene ring.\textsuperscript{90} In this chapter, two types of this wide class of compounds will be explored, \textit{N-Boc-2-phenylbenzazepine 96} and \textit{N-Boc-2-phenyl-7-methoxybenzazepine 97} (Scheme 63).

\textbf{Scheme 63}

Many benzazepine derivatives are found in alkaloid natural products.\textsuperscript{91} The benzazepine moiety is found in a wide number of interesting biologically active compounds.\textsuperscript{92} For example, benzazepine fragments are present in the structures of paullone derivatives (which have shown promising results in cancer treatment),\textsuperscript{93,94} Lotensin (Benzazepril) (which is used to treat high blood pressure)\textsuperscript{92} and mozavaptan (which plays a major role in the binding of arginine vasopressin (AVP) to vasopressin receptors located in the liver) (Figure 24).\textsuperscript{95}

This chapter describes research on the synthesis of substituted benzazepines and focuses on the electrophilic quench of organolithium intermediates.

\textbf{Figure 24}
3.2 Previous methods used to prepare substituted benzazepines

As discussed earlier in chapter 2, aza-seven-membered rings could be obtained by classical ring expansion methods which involve the Beckmann reaction and the Schmidt reaction. In a similar way, ring expansion is also considered the main route to synthesise benzazepine derivatives.

3.2.1 The Schmidt Reaction

Various substituted benzazepines could be synthesised by using the Schmidt reaction which was first reported in 1924. Different routes were used such as rearrangement of tetralones by the reaction of 1,2-dihydroquinoline with dibromocarbene followed by dehydrobromination, reaction with ethyl azidoformate and free-radical ring expansion of six-membered heterocycles to give benzazepines.

Scheme 64 illustrates the synthesis of 1-benzazepin-2-one by treatment of 1-tetralone with sodium azide in concentrated sulphuric acid. However, the same reaction when applied to 6-methoxy-1-tetralone produced 2-benzazepin-1-one derivative as the major product and only traces of 1-benzazepin-2-one derivative. An electronic effect influences whether the product is the benzamide or the acetanilide.

Ring expansion of an aza-six-membered ring by a free radical mechanism gave benzazepine firstly by Dieckmann condensation of the Michael adduct of ethyl anthranilate with ethyl acrylate to give β-keto ester (Scheme 65). β-Keto ester was alkylated with dibromomethane and sodium hydride under reflux in THF to give. This was finally
treated with tri-n-butyltin hydride in the presence of AIBN catalyst to obtain 84% yield of benzazepine 108 as the major product.  

\[
\begin{align*}
&\text{CO}_2\text{Et} & \text{CO}_2\text{Et} \\
&\text{NH}_2 & \text{BF}_3 \\
&\text{103} & \text{104} & \text{105} & \text{106} \\
&\text{NaH, HMPA} & \text{1. NaH, HMPA} & \text{2. CH}_2\text{Br}_2 \\
&\text{CO}_2\text{Et} & \text{CO}_2\text{Et} \\
&\text{N} & \text{O} \\
&\text{107} & \text{108, 84%} & \text{109, 16%} \\
&\text{Bu}_3\text{SnH, AIBN} & \text{benzene, reflux} \\
&\text{CO}_2\text{Et} & \text{CO}_2\text{Et} \\
&\text{N} & \text{O} \\
&\text{112} & \text{113} & \text{114}
\end{align*}
\]

\text{Scheme 65}

**3.2.2 Electrocyclic ring opening**

The reaction of indoles with dimethyl acetylene dicarboxylate\textsuperscript{103} or ethyl cyanoacetate\textsuperscript{104} has been used as a source to synthesise 1H-benzazepine derivatives \textit{via} electrocyclic ring-opening. The cycloaddition of 2-alkoxy-indole 110 to acetylene 111 gave benzazepine derivative 114 \textit{via} ring-opening of the intermediate 113 (Scheme 66).  

\[
\begin{align*}
&\text{OC}_2\text{H}_5 & \text{CO}_2\text{CH}_3 \\
&\text{H} & \text{H} \\
&\text{110} & \text{111} & \text{112} \\
&\text{CO}_2\text{CH}_3 & \text{CO}_2\text{CH}_3 \\
&\text{N} & \text{H} \\
&\text{113} & \text{114}
\end{align*}
\]

\text{Scheme 66}
3.2.3 Domino Reaction

A domino reaction, also known as a cascade reaction or tandem reaction, is a process involving two or more bond-forming reactions without the isolation of intermediates. Naito and co-workers have developed a synthetic method from \( N \)-alkoxy(arylmethyl)amines to \( N \)-alkyl-arylamines via a domino reaction.\textsuperscript{105} The treatment of 1-methoxyaminotetraline \textbf{115} with \( n \)-BuLi or PhLi in Et\(_2\)O gave the 2-butyl- or 2-phenylbenzazepines \textbf{116a} and \textbf{116b} in 66% and 63% yields respectively (Scheme 67).

\[
\text{MeO} \quad \begin{array}{c}
\text{HN} \\
\text{MeO}
\end{array} \\
\text{MeO} \\
\text{HN}
\]

\textbf{115} \quad \begin{array}{c}
3 \text{ equiv. Li-R}^1 \\
15 \text{ min, Et}_2\text{O, r.t.}
\end{array} \quad \begin{array}{c}
\text{MeO} \\
\text{HN} \\
\text{MeO}
\end{array} \\
\textbf{116a, 66\%, R}^1 = \text{Bu} \\
\textbf{116b, 63\%, R}^1 = \text{Ph}

\textbf{Scheme 67}

The mechanism of the reaction is proposed to involve the domino elimination of an alkoxide, rearrangement of the aryl group, and addition of an organolithium. It is assumed that \( N \)-methoxy (arylmethyl)amine \textbf{115} is firstly deprotonated by organolithium followed by elimination of methoxide to generate the nitrene intermediate \textbf{117}. This intermediate undergoes a rearrangement to form imine \textbf{118}. Finally, the addition of the organolithium to the imine \textbf{118} gives benzazepine derivatives \textbf{116} (Scheme 68).

\[
\begin{array}{c}
\text{MeO} \\
\text{HN} \\
\text{MeO} \\
\text{MeO}
\end{array} \\
\textbf{115} \\
\begin{array}{c}
\text{Elimination} \\
\text{R}^1-\text{Li}
\end{array} \\
\begin{array}{c}
\text{MeO} \\
\text{HN} \\
\text{MeO} \\
\text{MeO}
\end{array} \\
\textbf{117} \\
\begin{array}{c}
\text{Rearrangement}
\end{array} \\
\begin{array}{c}
\text{MeO} \\
\text{HN} \\
\text{MeO} \\
\text{MeO}
\end{array} \\
\textbf{118} \\
\begin{array}{c}
\text{Addition} \\
\text{then acidic work up}
\end{array}
\]

\textbf{Scheme 68}
3.3 Results and discussion

3.3.1 Synthesis and lithiation–substitution of N-Boc-2-phenylbenzazepine

Based on previous studies of azepanes and the power of n-BuLi to create carbon–carbon bonds, we aimed in this chapter to synthesise substituted benzazepines using the same methodology. Following our work with N-Boc-2-phenylazepane and the fact that the Boc group can be easily removed, methods to obtain substituted benzazepines from N-Boc protected derivative 96 were explored (Scheme 69). We attempted to synthesise 2,2-disubstituted benzazepine derivatives 120 by using n-BuLi in THF.

\[ \text{N-Boc, THF} \rightarrow \text{Li} \rightarrow \text{E}^+ \]

Scheme 69

3.3.1.1 Synthesis of N-Boc-2-phenylbenzazepine

N-Boc-2-phenylbenzazepine 96 was unavailable commercially and needed to be synthesised from readily available starting materials. Different protocols have been developed to synthesise this compound which utilise Schmidt and Beckmann reactions.\(^{101,102,106}\) It was necessary to find a simple synthetic route, especially as previously mentioned methods were unfavoured due to the fact that hazardous HN₃ is generated during the Schmidt reaction and the Beckmann rearrangement can generate a mixture of isomers. However, while there are other methods which are simpler such as the synthesis of 2-phenyl-1H-benzazepine 123 by oxidation of 121 using of \(m\)-chloroperbenzoic acid followed by reaction with phenylmagnesium bromide to give the product in modest yield (Scheme 70).\(^{107}\) A problem with this method was the commercial availability of the starting material 121 and also the production of a mixture of 123a and 123b.

\[ \text{m-chloroperbenzoic acid} \rightarrow \text{PhMgBr} \rightarrow \text{R} \]

Scheme 70
It was interesting to begin thinking about following the same synthetic route used for the synthesis of \( N\text{-Boc-2-phenylazepane} \) due to the easy availability of starting materials and simple reaction conditions (Gawley methodology).\textsuperscript{83} As mentioned before, this methodology involved four steps to give the desired product.

The first step was Boc protection of benzazepin-2-one \( 99 \) which was available commercially at a low price. A high yield of 93\% of protected product \( 124 \) was obtained by reaction of benzazepin-2-one \( 99 \) with Boc\(_2\)O in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 71). Attempting to do the reaction in the absence of DMAP did not give the product.

\[
\text{Scheme 71}
\]

The second step was treatment of \( 124 \) with DIBAL-H to reduce the lactam's amide moiety. Adding DIBAL-H (1.4 equiv.) dropwise to a solution of lactam \( 124 \) at \(-78\) °C gave a mixture of \( 125a \) and \( 125b \) in 89\% yield (Scheme 72). The reduction therefore led to the formation of two different isomers of the desired product in unequal proportion, in a 0.7:1.0 ratio of the aldehyde and alcohol isomers respectively. Purification by silica gel chromatography failed to give a perfect separation between the isomers, although it successfully separated some of the aldehyde isomer and gave a clear \(^1\)H NMR spectrum. However, the alcohol isomer was not pure and contained traces of the aldehyde isomer. As a matter of interest, even though we tried to isolate the two isomers separately, they were believed to behave in the same manner when displaced in the next step.

\[
\text{Scheme 72}
\]
Next, a substitution reaction using benzotriazole was performed by heating a 1.0:0.7 mixture of 125a and 125b under reflux in toluene, resulting in an 84% yield of the desired product 126 (Scheme 73).

Scheme 73

To form the desired target N-Boc-2-phenylbenzazepine, phenylmagnesium bromide as a solution in Et₂O was added to compound 126 in a mixture of Et₂O/THF (9:1) at 0 ºC (Scheme 74). A yield of 70% of 96 was obtained and this was better than that found in the synthesis of N-Boc-2-phenylazepane 71. Compound 96 was obtained as pure crystals following purification by flash silica chromatography. The X-ray crystal structure was able to be obtained in order to completely confirm the structure (Figure 25 and Appendix 6.1c). Dissolving N-Boc-benzotriazolylbenzazepine 126 in neat THF led to a lower yield of only 25%, therefore a mixture of Et₂O:THF was used to enhance the solubility of 126 which was less soluble in neat diethyl ether. The ¹H NMR spectrum of N-Boc-2-phenylbenzazepine 96 showed two rotamers with roughly a 1:0.8 ratio, which was attributed to restricted rotation about the N-Boc bond.

Scheme 74
3.3.1.2 ReactIR spectroscopic monitoring of carbamate lithiation

To begin our investigations, the lithiation conditions of the N-Boc-2-phenylbenzazepine 96 with n-BuLi/THF were monitored by using in-situ ReactIR spectroscopy. Rapid and full lithiation was achieved at -50 °C in the less than 10 minutes (Figure 26). The three-dimensional plot showed the appearance and disappearance of peaks which clearly shows that a reaction was progressing. The Boc carbonyl stretch of the starting material was observed at 1702 cm$^{-1}$, the intensity of this peak decreased rapidly after addition of n-BuLi, and a new peak was observed at 1644 cm$^{-1}$ which was attributed to the lithiated intermediate (Scheme 75).

![Scheme 75](image-url)
Figure 26: 3D and 2D plots of lithiation of 96 at −50 ºC by in situ IR spectroscopy. (a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the C=O for 96 (blue) and for the lithiated intermediate 119 (red). The first and second red triangles indicate the additions of N-Boc-2-phenylazepane and n-BuLi, respectively.

3.3.1.3 Lithiation–substitution of N-Boc-2-phenylbenzazepine

Based on the in-situ ReactIR results above, N-Boc-2-phenylbenzazepine 96 was deprotonated by adding 1.2 equiv. of n-BuLi at −50 ºC and the reaction mixture was left to stir for 10 minutes. Then, the resulting organolithium was quenched with different electrophiles. The racemic N-Boc-2-phenyl-2-substituted benzazepines 120a–f were obtained in good to excellent yields (Scheme 76).
An excellent yield of the product $120a$ was formed when using allyl bromide (85% yield), while good yields were observed when using 1,4-dibromobutane, tributyltin chloride and methyl iodide to produce $120b$, $120c$ and $120d$ with 78%, 75% and 60% yields respectively (Scheme 76).

Trapping with carbonyl electrophiles such as acetone and benzaldehyde did not form alcohol products. Instead, the cyclic carbamates $120e$ and $120f$ were formed in good yields respectively. The stereochemistry of compound $120f$ was determined by X-ray crystallography, after separating by column chromatography. This showed that the two phenyl groups of the major isomer were trans to each other (Figure 27 and Appendix 6.1d). The TLC and the $^1$H NMR spectrum showed that there were two isomers in a 15:1 ratio, however the minor isomer could not be isolated.
Interestingly, ortho-substituted products were formed when the organolithium intermediate was reacted with alkyl cyano- or chloroformates which was the same as that observed with N-Boc-2-phenylazepane 71. The lithiation of N-Boc-2-phenylbenzazepine 96 followed by the addition of methyl cyanoformate or methyl chloroformate as electrophiles gave ortho-substituted product 127a in a good yield of 63–68% (Scheme 77).

![Scheme 77](image)

Surprisingly, S-phenyl benzenethiosulfonate was another electrophile which gave the ortho-substituted product. The lithiation of N-Boc-2-phenylbenzazepine 96 with n-BuLi at −50 °C, followed by the addition of S-phenyl benzenethiosulfonate gave 85% yield of ortho-substituted product 127b (Scheme 78).

![Scheme 78](image)

As explained earlier in chapter 2, some electrophiles have different regioselectivity in the reaction with the organolithium intermediate to form α-substituted products or ortho-substituted products. The regioselectivity depends on the nature of lithium co-ordination. The lithium atom could co-ordinate in an η₁ arrangement to give complex 119, which would form α-substituted products. Alternatively, an η₃ complex could form where the lithium atom...
co-ordinates to the \textit{alpha}, \textit{ipso} and \textit{ortho} carbons forming \textit{ortho}-substituted products (Scheme 79).

![Scheme 79](image)

3.3.1.4 Variable temperature \textsuperscript{1}H NMR spectroscopy study

It was interesting to see if the energy barrier to the rotation of the Boc group could be determined for \textit{N}-Boc-2-phenylbenzazepine 96. A variable temperature NMR spectroscopic study was conducted to identify the barrier of rotation for the Boc group.

A sample of \textit{N}-Boc-2-phenylbenzazepine 96 in DMSO-$d_6$ was examined at various temperatures to observe coalescence of the signals for the benzylic proton which occurred at about 60 °C. The region $\delta = 5.50$–2.50 ppm is shown in Figure 28 with the ratio of rotamers being approximately 1:0.8.

![Figure 28](image)

\textbf{Figure 28: Variable temperature \textsuperscript{1}H NMR spectroscopy of \textit{N}-Boc-2-phenylbenzazepine 96}
The benzylic proton of each rotamer appeared as a broad doublet. The expected splitting should have been a doublet of doublets due to the adjacent carbon's two distinct proton environments (pseudo-axial and pseudo-equatorial) but coupling to the pseudo-equatorial proton likely has a small $J$ value. The coalescence of the benzylic signal took place at around 60 °C, at which temperature the rate of rotation of the N-Boc group was equal to the NMR timescale (Figure 28). Line-shape analysis was carried out to determine the parameters for the rotation of the Boc group based on the benzylic peaks at 4.90 and 5.10 ppm and an Eyring plot was formed (Appendix 6.2b). The activation parameters for N-Boc rotation were found to be: $\Delta S^\ddagger = -32.3 \text{ J K}^{-1} \text{ mol}^{-1}$ and $\Delta H^\ddagger = 55.8 \text{ kJ mol}^{-1}$, giving a barrier of rotation $\Delta G^\ddagger = 62.0 \text{ kJ mol}^{-1}$ at −78 °C and 62.9 kJ mol$^{-1}$ at −50 °C. These activation parameters gave a rotation rate of $1 \times 10^{-4} \text{ s}^{-1}$ and a rotational half-life of $t_{1/2} = 2 \text{ h}$ at −78 °C. The half-life for rotation of the Boc group was estimated at −50 °C to be $t_{1/2} = 2 \text{ min}$. Experimentally, these results agree with the quick rotation and full lithiation at −50 °C, as illustrated by the in-situ IR plots and the experimental data. In addition, the barrier of rotation of the Boc group of N-Boc-2-phenylbenzazepine 96 is lower than N-Boc-2-phenylazepane 71. Note that the NMR experiments were carried out in DMSO-d$_6$ to allow the high temperatures to observe post-coalescence and hence a good Eyring plot (Appendix 6.2b).

3.3.1.5 Kinetic resolution of N-Boc-2-phenylbenzazepine

Due to the variation in the N-Boc rotation rate between N-Boc-2-phenylbenzazepine 96 and N-Boc-2-phenylazepane 71, where the Boc group of 96 rotates faster at lower temperature (−50 °C), it was expected that N-Boc-2-phenylbenzazepine would exhibit more selectivity in kinetic resolutions than N-Boc-2-phenylazepane. Kinetic resolutions were attempted in order to try and recover enantioenriched starting material by using $n$-BuLi/(+-)sparteine in toluene as the chiral base. Different conditions were used in these reactions (Tables 6, 7). For example, the lithiation of N-Boc-2-phenylbenzazepine 96 was carried out by dissolving 96 and 1.3 equivalents of (+)-sparteine in PhMe at −50 °C, followed by the addition of 1.2 equivalents of $n$-BuLi. Then, after three hours, tri-$n$-butyltin chloride was added to give the recovered starting material 96 (57%, er 61:39), together with the product 120c (11%, er not determined) (Scheme 80). Also, it was assumed that the absolute stereochemistry of recovered starting material could be the (S)-enantioomer based on the previous results in our group, in which (+)-sparteine preferred to abstract the $R$-proton. Therefore the (S)-enantioomer of starting material would be recovered.$^{57,88}$
Scheme 80

In an attempt to improve the ers of the recovered starting material and product, different conditions have been used as illustrated in Tables 6 and 7. In general, at −50 °C (Table 6), the yield of recovered starting material was more than 50% in all attempts. Adding n-BuLi last to a solution of starting material and (+)-sparteine in PhMe or premixing n-BuLi with sparteine before adding starting material did not make a big difference. Poor ers (<57:43) and high yields of recovered starting material were obtained in both cases (entries 1,2). Leaving the reaction for a longer time (4-5 h) and increasing the number of chiral base equivalents gave the same poor level of enantioselectivity (entries 3,4). Entry 5 shows the best conditions compared to the other results, although the yield of the RSM was 57% with er 60:40. There was no improvement in enantiomeric ratio when the number of chiral base equivalents was reduced (entry 6).

![Scheme 80](image)

Table 6: Kinetic resolution conditions at −50 °C

Changing the temperature to −78 °C (Table 7) gave in general the same results as those obtained at −50 °C. Also, the yield of recovered starting material was more than 50% in all attempts with poor ers of around 55:45. The best er was 59:41 with a yield of 60% when
dissolving 96 and 1.3 equivalents of (+)-sparteine in PhMe at −78 ºC, followed by the addition of 1.2 equivalents of n-BuLi (entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of n-BuLi</th>
<th>Equiv. of (+)-sparteine in PhMe at −78 ºC, followed by the addition of 1.2 equivalents of n-BuLi</th>
<th>Yield (%) and er of RSM 107</th>
<th>Yield (%) of product</th>
<th>time</th>
<th>Addition of n-BuLi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>1.5</td>
<td>80%, (55:45)</td>
<td>10%</td>
<td>3 h</td>
<td>premix</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>1.5</td>
<td>70%, (52:48)</td>
<td>27%</td>
<td>5 h</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>2.5</td>
<td>65%, (61:39)</td>
<td>19%</td>
<td>5 h</td>
<td>premix</td>
</tr>
<tr>
<td>4</td>
<td>2.3</td>
<td>2.8</td>
<td>85%, (55:45)</td>
<td>10%</td>
<td>4 h</td>
<td>premix</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>1.3</td>
<td>60%, (59:41)</td>
<td>11%</td>
<td>3 h</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>1.0</td>
<td>87%, (54:46)</td>
<td>10%</td>
<td>3 h</td>
<td>n-BuLi last</td>
</tr>
</tbody>
</table>

Table 7: Kinetic resolution conditions at −78 ºC

It appeared that N-Boc-2-phenylbenzazepine 96 had the same amenability to the kinetic resolution as the corresponding N-Boc-2-phenylazepane 71. This would support the hypothesis that the increase in the conformational freedom of the larger ring reduced selectivity in the kinetic resolution with (+)-sparteine as the chiral ligand.

3.3.1.6 Removal of the Boc group

It was interesting to investigate the deprotection conditions of 2,2-disubstituted benzazepine derivatives. Previously, treating 2,2-disubstituted azepane 73b with 1 equiv. of TFA in CH₂Cl₂ at room temperature did not give the desired product. In contrast, the deprotection 2,2-disubstituted benzazepine 120b using 30% TFA in CH₂Cl₂ at room temperature gave 88% yield of the desired product without finding any problems in comparison with the analogous azepane derivatives (Scheme 81).

![Scheme 81]
It was interesting to see whether deprotecting ortho-carbamate products could give the cyclized lactam product similar to 87a (Scheme 62, chapter 2). Treating 127a with 30% TFA in CH₂Cl₂ at room temperature (Scheme 82) gave the amine product 130 in 86% yield which was not similar to the reaction pathway of the azepane derivatives. The inability of the amine to cyclize could be attributed to the nitrogen lone pair interacting with the delocalised electrons in the benzene ring which makes the subsequent cyclization more difficult.

![Scheme 82](image)

### 3.3.2 Synthesis and lithiation–substitution of N-Boc-2-phenyl-7-methoxybenzazepine

#### 3.3.2.1 Methods of synthesising N-Boc-2-phenyl-7-methoxybenzazepine

Attempts to prepare more benzazepine derivatives led to the successful lithiation–substitution reactions of N-Boc-2-phenyl-7-methoxybenzazepine 97. In this case, a different route was used to synthesise the starting material, which was different synthetic route of N-Boc-2-phenylazepane 71 and N-Boc-2-phenylbenzazepine 96. Three steps were required, starting from readily available starting material 6-methoxy-1-tetralone 100, as described in Scheme 83.

![Scheme 83](image)

The first two steps were the common synthetic route of amine synthesis by imine formation and reduction using a literature method. 6-Methoxy-1-tetralone 100 in methanol was treated with O-methylhydroxylamine hydrochloride in the presence of pyridine. This gave the corresponding N-methoxyimine (oxime) 131 in good yield. As a clean ¹H NMR spectrum was obtained, the product was able to be used directly in the next step without purification by
flash silica chromatography (Scheme 84). This step was carried out by a final year undergraduate student within the group.\textsuperscript{109}

\[
\begin{align*}
\text{MeO} & \quad \text{3.0 equiv. } \text{MeONH}_2\text{HCl} \\
\text{100} & \quad \text{1.1 equiv. pyridine, MeOH, r.t.} \\
& \quad \text{MeO} \\
& \quad \text{131, 91\%}
\end{align*}
\]

\textbf{Scheme 84}

No stereochemistry of product 131 was given in the literature about which isomer formed.\textsuperscript{108} It could not be a mixture of two isomers because the $^1\text{H}$ NMR showed only one isomer. It was assumed that the $E$-isomer was formed as drawn in scheme 84. The $E$-isomer was more likely to form because the methoxy group was anti to the migrating aromatic group according to the next step (Scheme 83). The $Z$-isomer was not preferred due to the steric clash with the \textit{ortho}-substituent.

By following the literature,\textsuperscript{108} oxime 131 could be reduced by sodium cyanoborohydride in acetic acid (Scheme 85). This method gave a low yield of crude product and so it was desirable to make the synthesis more efficient. Changing the number of sodium cyanoborohydride equivalents or the time of the reaction did not give any increase in the yield. The main problem in this method was the difficulty in fully evaporating the acetic acid and this led to a loss of product in the aqueous layer during the extraction. It was also difficult to remove the acetate salt from the crude product after the extraction and solvent removal. Thus, alternative methods were trialled to improve the yield, and these are summarised in Table 7.

\[
\begin{align*}
\text{MeO} & \quad \text{2.0 equiv. } \text{NaBH}_3\text{CN} \\
\text{131} & \quad \text{AcOH, r.t.} \\
& \quad \text{MeO} \\
& \quad \text{115, 28\%}
\end{align*}
\]

\textbf{Scheme 85}
As shown in Table 7, different reducing agents were used by a final year undergraduate student assisting with this project. Using sodium triacetoxyborohydride NaBH(OAc)$_3$ instead of sodium cyanoborohydride did not give a product in either acetic acid or ethanol (entries 1,2). The same problem was found when using sodium borohydride in ethanol or DIBAL in THF, in which no reaction took place even when leaving the mixture to stir for a long time (entries 3,4). Reduction using hydrogen gas in the presence of a Raney nickel catalyst failed to give the desired product forming a primary amine in high yield and this was confirmed by the disappearance of the methoxy group in the $^1$H NMR and $^{13}$C NMR spectrum (entry 5 and scheme 86).$^{109}$

Table 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent</th>
<th>Temp./ °C</th>
<th>Time/ h</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 eq. NaBH(OAc)$_3$, AcOH</td>
<td>24</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4 eq. NaBH(OAc)$_3$, AcOH</td>
<td>120</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4 eq. NaBH$_4$, EtOH</td>
<td>24</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.4 eq. DIBAL, THF</td>
<td>$-78$</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$, Raney Nickel, 1 atm, MeOH</td>
<td>24</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.25 eq. NaBH$_3$CN, MeOH, HCl</td>
<td>24</td>
<td>24</td>
<td>63</td>
</tr>
</tbody>
</table>

The best conditions were achieved when sodium cyanoborohydride was used as the reducing agent. As shown in entry 6, a 63% yield of amine 115 was obtained (Scheme 87) when oxime 131 was treated with sodium cyanoborohydride in methanol, followed by acidification of the solution with HCl. This method was much better than the original method using AcOH.
Scheme 87

Next, following a literature method, adding phenyl lithium to amine 115 gave 55% yield of 2-phenyl-7-methoxybenzazepine 133 (Scheme 88) via a rearrangement-addition reaction. The mechanism for this process was explained previously in section 3.2.3 (Scheme 68).

Scheme 88

The final step was incorporation of the Boc group by adding Boc$_2$O to 2-phenyl-7-methoxybenzazepine 133 in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 89). Unfortunately, this procedure did not form the desired product.

Scheme 89

Our target product was carbamate 97 not amine 133, therefore some changes were applied to the original procedure found in the literature. Instead of using a protic reagent to quench the reaction in Scheme 88, Boc$_2$O was added so that an in-situ reaction took place. This method was successful and 77% yield of the desired product 97 was obtained (Scheme 90).
With \(N\)-Boc-2-phenyl-7-methoxybenzazepine \(97\) in hand, the next step of the synthesis was deprotonation of the benzylic proton by \(n\)-BuLi to form 2,2-disubstituted-\(N\)-Boc-7-methoxybenzazepines.

### 3.3.2.2 Lithiation–substitution of \(N\)-Boc-2-phenyl-7-methoxybenzazepine

It was hypothesized that the methoxy group would not have a significant effect on the synthesis of organolithium compounds by deprotonation of the benzylic proton. If so, then \(N\)-Boc-2-phenyl-7-methoxybenzazepine \(97\) would have the same optimised lithiation conditions as \(N\)-Boc-2-phenylbenzazepine \(96\).

\(N\)-Boc-2-phenyl-7-methoxybenzazepine \(97\) was deprotonated by addition of 1.2 equiv. of \(n\)-BuLi at \(-50\ ^\circ\text{C}\) and the reaction mixture was left to stir for 10 minutes. Then, the corresponding organolithium was quenched with different electrophiles. The racemic \(N\)-Boc-2-phenyl-2-substituted-7-methoxybenzazepines \(135a\) and \(135b\) were obtained in good yields (Scheme 91) with the cyclized carbamate being formed when acetone was used as the electrophile.
The unusual ortho-substituted product was also formed with this substrate in the reaction with ethyl chloroformate to give 60% yield of compound 136 (Scheme 92). This supports the hypothesis that the change in regioselectivity arises from a change of the co-ordination of the lithium atom from an $\eta^1$ coordination, to form $\alpha$-substituted products, to an $\eta^3$ coordination (the alpha, ipso and ortho carbons) to form ortho-substitution products.

![Scheme 92](image)

**3.3.2.3 Kinetic Resolution of N-Boc-2-phenyl-7-methoxybenzazepine**

There was no big difference between $N$-Boc-2-phenyl-7-methoxybenzazepine 97 and $N$-Boc-2-phenylbenzazepine 96 in the lithiation–substitution reactions and so it was expected that $N$-Boc-2-phenyl-7-methoxybenzazepine 97 would exhibit the same poor selectivity (by using a chiral ligand) as the analogous azepane derivatives in the kinetic resolutions. An enantiomeric ratio of 57:43 with 46% yield of recovered starting material was found when 97 was stirred with 1.3 equivalents of (+)-sparteine in PhMe at $-50 \degree C$, followed by the addition of 1.2 equivalents of $n$-BuLi. After three hours, tri-$n$-butyltin chloride was added (Scheme 93).

![Scheme 93](image)

**3.4 Conclusions and future work**

In conclusion, $N$-Boc-2-phenylbenzazepine 96, a novel compound, was synthesised in an overall yield of 70% in four steps, starting from cheap, commercially available compounds using literature methods. The lithiation of $N$-Boc-2-phenylbenzazepine 96 was optimized by in-situ ReactIR spectroscopy. Optimum conditions to give a full lithiation were found by
using \(n\)-BuLi in THF at \(-50^\circ C\) for 10 minutes. A range of 2,2-disubstituted benzazepines have been synthesised with different regioselectivities according to the type of electrophile. *Ortho*-substituted products could be formed by using some carbonyl electrophiles, such as alkyl cyanoformates or chloroformates, and \(S\)-phenyl benzenethiosulfonate. The energy barrier of rotation for the Boc group was determined by VT-NMR calculations. However, the enantiomeric ratio of recovered starting material during the kinetic resolution reaction with (+)-sparteine as a chiral ligand was poor (similar to the analogous azepane). This result indicates that the conformation of the azepane ring affected the enantioselectivity. There is a possibility that other chiral ligands might be more suitable for these substrates. It appears that the activation energy required for the \(n\)-BuLi/sparteine to remove the proton from either face is very similar which leads to low selectivity.

Deprotection of the Boc group by TFA was used to form bicyclic compounds or amines from the corresponding carbamate. In a similar way to the benzazepine 96, the 7-methoxy analogue gave a range of 2,2-disubstituted benzazepines after lithiation then trapping with different electrophiles. The *ortho*-substituted product was formed by using methyl chloroformate as electrophile.

Attempting the synthesis of other benzazepine derivatives (Figure 29) would be a good area for investigation. If different aromatic groups were used then it would be possible to compare the rate of Boc rotation, lithiation and the enantioselectivity of deprotonation (in the presence of a chiral base) when the aromatic group is changed. Furthermore, finding other electrophiles which form *ortho*-substituted products would be another good area for investigation.

![Figure 29](image)
Chapter 4

Synthesis and Lithiation–Substitution of N-Boc-2-alkenylpiperidines and N-Boc-2-alkynylpiperidines

4.1 Importance of piperidine derivatives

The piperidine ring can be found in a large number of many complex polycyclic alkaloids. The piperidine derivatives are found not only in plants but also in insects and amphibians. The structural diversity of these alkaloids, with different substitution patterns, makes them attractive for synthetic methodology, both in racemic and in enantiopure form. Furthermore, piperidine-containing moieties are important for medical and pharmaceutical researchers to prepare. For example, methylphenidate (which is used for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy), and tadalafil (which is used for the treatment of pulmonary arterial hypertension (Figure 30).111,112

Various chiral piperidine alkaloids contain alkene or alkyne chains substituted in the 2-position and these have been challenging targets of total synthesis.113 This chapter describes research on the synthesis of 2-alkenyl or alkynyl substituted piperidines and in particular, a focus on electrophilic quench of organolithium intermediates.

4.2 Lithiation chemistry to synthesize 2,2-disubstituted N-Boc-piperidines

The last two and a half decades have witnessed the noticeable success of the lithiation chemistry protocol of piperidines which was initiated by the investigation of Beak, in which α-deprotonation of N-Boc-piperidine could be achieved by the action of sec-BuLi in the presence of a diamine (Scheme 14, Chapter 1).33,45

This early discovery led to the development of syntheses of functionalized piperidines by α-lithiation.114,115 Lithiation chemistry is one of the most established methods for the
functionalization of piperidines, although these methods usually only involve the introduction of a single substituent at the activated α-positions (i.e. C2 or C6). Our group has been using lithiation chemistry to synthesise 2,2-disubstituted N-Boc-piperidines. As shown earlier (Chapter 1, Section 1.5), different examples of 2,2-disubstituted piperidines were synthesised successfully. The incorporation of a carbonyl group attached to the nitrogen atom activates the compound by increasing the α-proton’s acidity. In addition, the acidity of the α-proton can be considerably enhanced by having a vinyl or aryl substituent in the α-position to make these attractive targets in order to form piperidine derivatives which contain unsaturated systems. In this chapter, different types of unsaturated, substituted piperidines will be explored: N-Boc-2-vinylpiperidine 136, N-Boc-2-(2-phenylethynyl) piperidine 137 and N-Boc-2-[((Z)-2-phenylethenyl)piperidine 138 (Scheme 94).

4.3 Results and discussion

4.3.1. N-Boc-2-vinylpiperidine 136

4.3.1.1 Synthesis of N-Boc-2-vinylpiperidine 136

N-Boc-2-vinylpiperidine 136 was unavailable commercially and needed to be synthesised from readily available starting materials. Various methods of synthesising N-Boc-piperidine derivatives have been reported over the years as a result of their potential use in synthesis. Wittig methylenation of N-Boc-2-formylpiperidine by treatment with potassium bis(trimethylsilyl)amide (KHMDS) and methyl triphenylphosphonium bromide was a common literature method, whether the reaction began with pipecolinic acid or 2-piperidinemethanol as starting material (Scheme 95 and 96). As outlined in scheme 96, this method was reported to be successful to give an excellent yield of 95%. Pipecolinic acid 139 was firstly reduced with borane. Then, the resulting amino alcohol was protected by Boc₂O in a one pot reaction to give 140 which was oxidized by the Swern procedure (by using dimethyl sulfoxide activated by oxalyl chloride) to provide aldehyde 141. Finally, Wittig methylenation was applied on aldehyde 141 to give N-Boc-2-vinylpiperidine 136.
In a similar way, by using pipecolinic acid as starting material, this gave N-Boc-2-vinylpiperidine 136 in a lower yield of 54\% via a three step synthetic route.\textsuperscript{120} The first step was an esterification to form methyl ester 142 which was then reduced by DIBAL to form aldehyde 141. Finally, Wittig methylenation gave the desired product 136 (Scheme 96).

An efficient protocol (Scheme 97) towards different 2-substituted N-Boc-piperidines by reaction of N-Boc-benzotriazolylpiperidine 146 with different types of Grignard reagents was reported by Gawley and co-workers, although they did not prepare the desired product 136.\textsuperscript{83} Therefore, it was decided to follow this methodology to check whether N-Boc-2-vinylpiperidine 136 could be formed by this method or not. An advantage of this route was that it should allow a variety of Grignard reagents to be tested in the final step to prepare vinyl and alkynyl derivatives.

![Scheme 95](image.png)

**Scheme 95**

![Scheme 96](image.png)

**Scheme 96**

![Scheme 97](image.png)

**Scheme 97**
Boc protection of δ-valerolactam 143 (commercially available) was attempted using 4-dimethylaminopyridine (DMAP) alongside Boc₂O to give the protected compound 144 with a yield of 86% which was a slight increase compared to the literature (Scheme 98).  

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{Boc} & \quad \text{Boc} \\
143 & \quad 144, 86%
\end{align*}
\]

Scheme 98

Reduction of the amide moiety of lactam 144 was achieved by treating it with DIBAL-H at –78 °C to give the desired product 145 in 83% yield, which was slightly lower than the yield obtained in the literature (Scheme 99).  

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{OH} \\
\text{Boc} & \quad \text{Boc} \\
144 & \quad 145, 83%
\end{align*}
\]

Scheme 99

The third step was a substitution reaction of lactamol 145 with benzotriazole to give an excellent yield of 146 as a mixture of two isomers in ratio 1.0:0.6 according to the \(^1\)H NMR spectrum. This yield was an increase on that achieved in the literature and the two isomers were not isolated separately as they both behave in the same manner when displaced in the next step (Scheme 100).  

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{Boc} & \quad \text{Boc} \\
145 & \quad 146a, 97% \\
& \quad + \quad 146b
\end{align*}
\]

Scheme 100

Synthesis of the desired compound N-Boc-2-vinylpiperidine 136 was achieved by the reaction of vinylmagnesium bromide solution with N-Boc-benzotriazolylpiperidine 146 in THF. However, while the method was successful, a poor yield of product 136 was obtained (Scheme 101).
Different conditions were applied to try and improve the yield, but all attempts were futile. For example, using a mixture of Et₂O:THF 9:1 as mentioned in the literature did not give any increase in the yield. Also, using neat Et₂O gave a lower yield of 10%. Furthermore, changing the number of equivalents of Grignard reagent did not give any improvement, also leaving the reaction mixture to stir at room temperature for more than 24 h or warming it to 66 °C failed to give a good yield. The main target for this project was studying racemic lithiation–substitution reactions, therefore this low yielding reaction was still useful and enough of compound 136 was obtained in order to carry out experiments to check the ability of this molecule to lithiate.

4.3.1.2 Lithiation–substitution of \(N\)-Boc-2-vinylpiperidine 136

With \(N\)-Boc-2-vinylpiperidine 136 in hand, a racemic lithiation–substitution was attempted by using tributyltin chloride as the electrophile. \(N\)-Boc-2-vinylpiperidine 136 was deprotonated at –78 °C with \(n\)-BuLi in THF and stirred for 10 minutes before tributyltin chloride was added. The Boc group rotation was rapid at –78 °C and the lithiation was complete within a few minutes.

It was thought that the lithiation would give 2,2-disubstituted piperidines as a result of the lithiation at the \(\alpha\)-proton to form compound 147 but according to the \(^1\)H NMR spectrum, there is one alkene proton at \(\delta = 5.44–5.16\) ppm and this did not coincide with the expected product 147 (Scheme 102).
As shown in Scheme 102, the \((Z)\)-isomer of the piperidine 148 was the product that resulted from this reaction. The stereochemistry for this product was interpreted from the suggested mechanism (Scheme 103). Based on the complexing intermediate, the lithium atom could co-ordinate to the allyl structure to give an \(\eta^3\) intermediate 149, which after trapping with tributyltin chloride should provide the \(Z\)-substituted product 148. This is attributed to the possibility of co-ordination of lithium to both the \(\alpha\) position and the double bond as mentioned before in chapter 1 (Section 1.1.3).

Unfortunately, while the mass spectra indicated that the desired products were present when using electrophiles such as methyl cyanoformate and \(S\)-phenyl benzenethiosulfonate, the crude reaction mixtures obtained from reactions with 136 were unstable to column chromatography. This was indicated by the observation of many spots on the TLC plate.

As the lithiation–substitution was successful with tributyltin chloride to form 69% yield of product 148, this motived us to study the enantioselectivity of the kinetic resolutions of \(N\)-Boc-2-vinylpiperidine 136 by using \(n\)-BuLi/(+)-sparteine in PhMe (Scheme 104). It was firstly necessary to separate \(rac\)-\(N\)-Boc-2-vinylpiperidine 136 by HPLC, but it was difficult to
find a suitable chiral stationary phase to separate the racemic starting material. This was a disappointing issue, especially as the yield of recovered starting material was 43% in the kinetic resolution.

![Scheme 104](image)

Therefore, it was difficult to carry out further investigations on this substrate because it was synthesised in a poor yield and it was difficult to separate the enantiomers by chiral HPLC.

4.3.2 N-Boc-2-(2-phenylethynyl)piperidine 137

4.3.2.1 Synthesis N-Boc-2-(2-phenylethynyl)piperidine 137

Even though the lithiation‒substitution on the substrates discussed above gave mostly disappointing results, it was still considered that other 2-unsaturated substituted piperidines could have reactivity towards lithiation‒substitution chemistry.

The next molecule investigated in this chapter was N-Boc-2-(2-phenylethynyl)piperidine 137. By following Gawley’s methodology, in this case N-Boc-benzotriazolylpiperidine 146 was reacted with phenylethynylmagnesium bromide solution in THF at 0 ºC to give 45% yield of product 137 (Scheme 105).

![Scheme 105](image)

This compound was not prepared by Gawley and in contrast to N-Boc-2-vinylpiperidine 136, the yield was improved to 70% when the reaction mixture was heated under reflux at 66 ºC for 48 h (Scheme 106). These conditions were optimised after many attempts to carry out the reaction at 0 ºC or room temperature.
4.3.2.2 Lithiation–substitution of N-Boc-2-(2-phenylethynyl)piperidine 137

With N-Boc-2-(2-phenylethynyl)piperidine 137 in hand, the initial lithiation–substitution was carried out using n-BuLi in THF at −78 °C and stirred for 10 minutes before the electrophile was added. These conditions yielded promising results with moderate to good yields of product being obtained.

Tributyltin chloride was the first electrophile used in lithiation–substitution reactions and it was surprising that the expected 2,2-disubstituted piperidine 150 was not formed (Scheme 107).

The $^1$H NMR spectrum of the formed product was shown to have two alkene protons, one of them appeared as a singlet at around 6.7 ppm while the other was a triplet at around 5.1 ppm. The $^{13}$C NMR spectrum showed a number of CH peaks in the chemical shift area characterized by unsaturated carbons which suggested the presence of an alkene. As a result of this NMR analysis, it was confirmed that the diene 151a was formed in good yield from deprotonation of N-Boc-2-(2-phenylethynyl)piperidine 137 by n-BuLi in THF at −78 °C after trapping by tributyltin chloride (Scheme 108).
In the beginning, it was difficult to understand and interpret what happened during the reaction. The same type of product was formed when the reaction mixture was trapped with other electrophiles such as methyl iodide and acetone to give products 151b and 151c in good yields (Scheme109). The $^1$H NMR spectrum of these compounds showed a mixture of two isomers where, in every product, there was one isomer that was predominant. Compounds 151b and 151c were both formed in 9:1 ratio but 151a was only formed as $E$-isomer. The stereochemistry of these products will be discussed later in this section.

![Scheme 109](image)

Interestingly, when checking the $^1$H NMR spectrum of the crude reaction mixture of the reaction that formed compound 151a, it was found that there were no proton peaks between 6.7 and 5.1 ppm as found in pure 151a. However, when the reaction mixture was purified by column chromatography, this gave the conjugated diene 151a. Based on these observations, it could be suggested that the conjugated diene 151a was formed after rearrangement of the original compound which, according to the crude $^1$H NMR spectrum, was allene 152 (Scheme 110). From the outlined scheme, the allene 152 was formed firstly before this rearranged to give 151a.
This suggested that the conjugated diene 151a was more stable than allene 152. In an attempt to separate the allene 152, it was decided to basify the silica gel used as the stationary phase in column chromatography by adding triethylamine. This method was successful and allene 152 was obtained as a pure compound. Although it was pleasing to get a full analysis for this compound, it was unstable and after 24 h, rearranged to diene 151a.

It is assumed that the formation of conjugated diene 151a was according to the mechanism of proton transfer as outlined below (Scheme 112). Firstly, silica gel is slightly acidic due to the silanol group on the surface. Therefore, silica was likely to protonate the allene 152 to form the intermediate 154. Then subsequent deprotonation of 154 would form the suggested diene product 151.
Interestingly, deprotonation of N-Boc-2-(2-phenylethynyl)piperidine 137 by n-BuLi in THF at –78 °C then after 10 minutes trapping by methanol (Scheme 113) was able to help the interpretation of the stereochemistry of the diene compounds 151a-c. The major isomer that resulted from this reaction was the Z isomer, this was clear from the $^1$H NMR spectrum (Figure 31) which showed a mixture of E:Z in a ratio of nearly 1:12. The $J$ value (12.0 Hz for the major isomer, 16.0 Hz for the minor) was used as the main indicator to determine the stereochemistry of the product.

Scheme 112

Scheme 113
A tin–lithium exchange reaction was carried out on compound 151a by using n-BuLi in THF at –78 °C, then after 10 minutes trapping by methanol to give the Z isomer of compound 151d (Scheme 114).

According to the $^1$H NMR spectrum, this method effected the synthesis of Z-isomer 151d as the major product. Based on the expected reaction of the organolithium with retention of configuration, the product 151a would be the E-isomer$^{35,125}$ and this suggested that the
stereochemistry of 151a was as drawn. If assuming the tin-lithium exchange proceeds with retention and the protonation proceeds with retention, then 151a would have the stereochemistry as drawn in Scheme 114.

However, the stereochemistry of other products was not verified, but based on this interpretation, we assumed that (Z)-151b and (E)-151c would be the major isomers.

4.3.2.3 Kinetic Resolution of N-Boc-2-(2-phenylethynyl)piperidine 137

Although reactions of N-Boc-2-(2-phenylethynyl)piperidine 137 with n-BuLi did not provide α-substituted products or even stable allene compounds (which also are chiral molecules), kinetic resolution reactions were attempted because an important part of the kinetic resolutions is the er of the recovered starting material and this should not be affected by the product of the reaction. Therefore, kinetic resolutions were carried out using n-BuLi/(+) sparteine as the ‘chiral base’ (Scheme 115 and Table 9).

![Scheme 115](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.of n-BuLi</th>
<th>Equiv.of (+)-sparteine</th>
<th>Yield (%) and er of RSM 137</th>
<th>Yield (%) of product 151a</th>
<th>time</th>
<th>Addition of n-BuLi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>0.9</td>
<td>35%, (80:20)</td>
<td>40%</td>
<td>3 h</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.3</td>
<td>10%, (52:48)</td>
<td>75%</td>
<td>1 h</td>
<td>premix</td>
</tr>
<tr>
<td>3</td>
<td>0.6</td>
<td>0.9</td>
<td>62%, (58:42)</td>
<td>25%</td>
<td>1 h</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
<td>0.9</td>
<td>50%, (62:38)</td>
<td>42%</td>
<td>3 h</td>
<td>n-BuLi last</td>
</tr>
<tr>
<td>5</td>
<td>0.7</td>
<td>1.1</td>
<td>21%, (65:35)</td>
<td>62%</td>
<td>3 h</td>
<td>n-BuLi last</td>
</tr>
</tbody>
</table>

Table 9
Generally, the enantioselectivities were disappointing. The best enantiomeric ratio of recovered starting material was 80:20 with 35% yield, by adding \( n\text{-BuLi} \) last to a mixture of \( \text{137} \) and \((+)-\text{sparteine}\) in toluene (entry 1 and Scheme 115). Attempts were made to improve this enantioselectivity by using different conditions. As illustrated in Table 9, using pre-mixed \( n\text{-BuLi}/(+)\text{-sparteine} \) as the ‘chiral base’ gave 10% yield of RSM with poor enantioselectivity (entry 2). Reducing the number of \( n\text{-BuLi} \) equivalents from 0.8 to 0.6 raised the yield of RSM but gave a poorer er whether the reaction mixture was left to stir for 1 hour (entry 3) or 3 hours (entry 4). Increasing the chiral ligand equivalents to 1.1 with 0.7 equiv. of \( n\text{-BuLi} \) led to low yield and poor enantioselectivity (entry 5).

It was disappointing that the enantioselectivity of the kinetic resolutions of \( N\text{-Boc-2-alkynylpiperidine} \) were not as good as \( N\text{-Boc-2-phenylpiperidine} \). The er of the kinetic resolutions depends on the difference in energy between \( n\text{-BuLi/sparteine} \) removing the \( \alpha \)-proton of the \((R)\) enantiomer and \((S)\) enantiomers. The smaller the energy difference between the two, the lower the er will be. In Scheme 115, the starting material \( \text{137} \) was effectively deprotonated, as the yield of the recovered starting material was 35%, but the proton was not being removed in a selective way. This could be thought due to the substituent at the \( \alpha \)-position being linear, so this might mean the molecule prefers to be in a conformation where \( n\text{-BuLi/sparteine} \) is able to remove the \( \alpha \)-proton of either enantiomer. Also, it could be that the lithium co-ordinates to the alkyne linkage and this could co-ordinate from either side. Therefore, the \( n\text{-BuLi}/(+)\text{-sparteine} \) might be able to remove the proton from either enantiomer which would lower the enantioselectivity.

### 4.3.3 \( N\text{-Boc-2-[(Z)-2-phenylethenyl]piperidine} \) \( \text{138} \)

#### 4.3.3.1 Synthesis \( N\text{-Boc-2-[(Z)-2-phenylethenyl]piperidine} \) \( \text{138} \)

It was interesting to try and synthesise more 2-substituted piperidine derivatives to use in lithition–substitution reactions. \( N\text{-Boc-2-[(Z)-2-phenylethenyl]piperidine} \) \( \text{138} \) was chosen because the \( \alpha \)-carbon in this substrate is connected to a \( \text{C=}\text{C}, \text{sp}^2 \) hybridised carbon which was similar to the 2-arylpiperidines. We thought that the presence of a bulky \( \beta \)-arylethenyl group would promote better selectivity than the alkynyl group. Also, this type of linkage was attractive because \( \beta \)-arylethyl groups are in natural products like sedamine.

It was thought that we should be able to follow the same method as used to synthesise compounds \( \text{136} \) and \( \text{137} \) by adding 2-phenylethenylmagnesium bromide \( \text{156} \) to \( N\text{-Boc-2-} \)
benzotriazolylpiperidine 146 (Scheme 117). Firstly, it was necessary to prepare the Grignard reagent because it was not commercially available. This was achieved by adding β-bromostyrene 155 to magnesium (Scheme 116).

\[
\begin{align*}
\text{Ph} - \text{Br} & \quad + \quad \text{Mg} \quad \xrightarrow{\text{THF, reflux 1 h}} \quad \text{Ph} - \text{MgBr} \\
\text{155} & \quad \text{156}
\end{align*}
\]

**Scheme 116**

Then N-Boc-2-benzotriazolylpiperidine 146 was added to Grignard reagent 156 to give the desired product 138 (Scheme 117). Unfortunately, only about 10% yield was formed of a mixture of isomers of 138 with ratio E:Z 3:1. This low yield could be attributed to the formation of Grignard reagent 156 which was poor, therefore the reaction to form 138 gave a low yield. This low yield of 138 would not be enough to carry out the next step, therefore we needed to find a more efficient method.

\[
\begin{align*}
\text{N} & \quad \text{Bt} \quad + \quad \text{Ph} - \text{MgBr} \quad \xrightarrow{\text{THF, 0 °C}} \quad \text{N} - \text{Boc} \\
\text{146} & \quad \text{156} & \quad \text{138}, \ 10\% \\
& & \text{E:Z, 3:1}
\end{align*}
\]

**Scheme 117**

Reducing N-Boc-2-(2-phenylethynyl)piperidine 137 by Lindlar’s catalyst successfully provided the Z-isomer of the desired product. By adding a few drops of quinoline to a solution of 137 in methanol followed by Lindlar’s catalyst, then stirring the mixture under a hydrogen atmosphere for 16 h gave 73% yield of N-Boc-2-[(Z)-2-phenylethenyl]piperidine 138 (Scheme 118). Attempts to carry out the reaction without quinoline did not provide a product, only the starting material was recovered.

\[
\begin{align*}
\text{N} - \text{Boc} & \quad \xrightarrow{\text{H}_2, \text{Lindlar cat./ quinoline, MeOH, r.t., 16 h}} \quad \text{N} - \text{Boc} \\
\text{137} & \quad \text{138}, \ 73\%
\end{align*}
\]

**Scheme 118**
4.3.3.2 Lithiation–substitution and Kinetic Resolution of \(N\)-Boc-2-[(Z)-2-phenylethenyl]piperidine 138

The initial lithiation–substitution was carried out by adding \(n\)-BuLi to carbamate 138 in THF at \(-78 \, ^\circ\text{C}\). The reaction mixture was stirred for 10 minutes before trapping the organolithium intermediate with tributyltin chloride to give product 158 in 58% yield. Similar to \(N\)-Boc-2-vinylpiperidine 136, the lithium atom could co-ordinate to the allyl structure to give an \(\eta^3\) intermediate 157, which after trapping with tributyltin chloride could provide the \(Z\)-substituted product 158 (Scheme 119).

![Scheme 119]

In order to test whether this compound had enantioselectivity in kinetic resolutions, just one trial kinetic resolution was attempted by adding \(n\)-BuLi to a mixture of 138 and (+)-sparteine in toluene at \(-78 \, ^\circ\text{C}\). After 3 hours, tributyltin chloride was added. The starting material was recovered in 45% yield with er 79:21 (Scheme 120).

![Scheme 120]

Furthermore, it is important to mention that another 2-substituted piperidine derivative 159 was synthesised by using Gawley’s protocol (Scheme 121). Unfortunately, the yield was less than 10% and this caused an impediment in using this compound as a substrate in the lithiation chemistry. However, we carried out one trial to check the lithiation–substitution reaction of 159 at \(-78 \, ^\circ\text{C}\) by adding \(n\)-BuLi in THF but this did not give any product, just recovered starting material, and so work on this substrate was discontinued (Scheme 121).
Finally, due to the high utility of the olefinic moiety in subsequent functional transformations, it would be interesting if N-Boc-2-[(Z)-2-phenylethenyl]piperidine 138 was applied to synthesise a piperidine alkaloid such as sedamine. The same chemistry was successful with THQ derivative 160 to synthesis (±)-galipinine 161 (Scheme 122).\textsuperscript{126}

\begin{align*}
\text{N-Me} & \quad \text{N-Me} \\
\text{(±)-galipinine, 80\%} & \quad \text{H}_2, 10\% \text{ Pd/C} \\
\text{MeOH, r.t., 12 h} &
\end{align*}

\textbf{Scheme 122}

This chemistry could be carried out by Boc group reduction, then a regioselective hydroboration–oxidation reaction of the double bond as indicated in Scheme 123. However, reduction of the Boc group by using LiAlH\textsubscript{4} was disappointing and amine 162 was not formed.\textsuperscript{127} Although, the reaction was repeated with different conditions such as leaving the reaction mixture to stir at room temperature for more than 24 h or warming it to 66 °C failed to give a desired product, only the starting material was recovered.

\begin{align*}
\text{N-Me} & \quad \text{N-Me} \\
\text{Me} & \quad \text{Me} \\
\text{Boc} & \quad \text{Boc} \\
\text{138} & \quad \text{161} 0\% \\
\text{Me} & \quad \text{Me} \\
\text{162} & \\
\end{align*}

\textbf{Scheme 123}
4.4 Conclusions and future work

In conclusion, 2-alkenyl and alkylnypiperidine derivatives were synthesised in four steps, starting from cheap, commercially available compounds using literature methods. N-Boc-2-vinylpiperidine 136 was successfully synthesised but a poor yield of product 136 was obtained. A racemic lithiation–substitution was attempted by using n-BuLi at –78 °C in THF to give N-Boc (2Z)-2-[2-(tributylstannyl)ethylidene]piperidine 148 via η3 intermediate 149 (Scheme 124). The limitation for this substrate was inability to separate the formed products after the reaction with different electrophiles, Bu3SnCl was the only electrophile used where the product was able to be separated after trapping the organolithium intermediate. The other limitation was the difficulty in finding a suitable chiral stationary phase to separate the racemic starting material, therefore no further investigation on this substrate.

\[
\begin{align*}
136 & \xrightarrow{n\text{-BuLi, THF}} 149 & 148 \\
\end{align*}
\]

Scheme 124

N-Boc 2-(2-ethynylphenyl)piperidine 137 was the other substrate investigated in this chapter. The starting material was synthesised following a literature method in a good yield. The lithiation–substitution did not give α-substituted product and diene compounds 151a-d were formed instead. Diene compounds were produced as a result of rearrangement of the allene product 152 which was unstable and easily protonated. Different electrophiles were used to trap organolithium intermediate 153 to give a mixture of isomers (Scheme 125).

\[
\begin{align*}
137 & \xrightarrow{n\text{-BuLi, THF}} 153 & 152 & 151a-d \\
\end{align*}
\]

(E)-151a, \(E^+ = \text{SnBu}_3\text{Cl}, 74\%
\]

151b, \(E:Z 1:9, E^+ = \text{MeI}, 82\%
\]

151c, \(E:Z 9:1, E^+ = \text{Acetone}, 81\%
\]

151d, \(E:Z 1:12, E^+ = \text{MeOH}, 91\%
\]

Scheme 125
However, the stereochemistry of the products resulting from quenches by methyl iodide 151b and acetone 151c were not verified. The product resulting from quenching by tributyltin chloride 151a was proven by a different method. Two experiments were attempted to confirm that the E-isomer of product 151a was the major isomer. The first experiment was trapping the organolithium intermediate 153 with methanol to give Z-151d and it was clear from the $^1$H NMR spectrum and $J$ values that the Z-isomer was the major product. The product Z-151d was also formed by tin-lithium exchange of 151a and based on the expected reaction of the organolithium with retention of configuration, the product 151a would be the E-isomer (Scheme 125). A kinetic resolution was attempted with 137 by using n-BuLi/(+)-sparteine as the ‘chiral base’ to give 35% of recovered starting material with er 80:20. This result reflects that binding of the $\alpha$-carbon to a linear group like the alkynyl group can reduce the selectivity of the abstraction of the $\alpha$-proton by a ‘chiral base’ compared with 2-arylpiperidines.

Reduction of 137 by Lindlar’s catalyst was an elegant procedure used to form N-Boc-2-[(Z)-2-phenylethenyl]piperidine 138 which was another substrate used in lithiation chemistry. It was expected to have better selectivity in kinetic resolutions due to the presence of a $sp^2$ C=C bond connected to the $\alpha$-carbon like in the 2-arylpiperidines. The initial lithiation–substitution by using n-BuLi gave a product which formed via an $\eta^1$ intermediate 157 like N-Boc-2-vinylpiperidine 136 (Scheme 125). The kinetic resolution was disappointing to give 45% of recovered starting material with er 79:21 by using n-BuLi/(+)-sparteine as the ‘chiral base’.
N-Boc 2-(2-methylprop-1-en-1-yl)piperidine 159 was another 2-alkenylpiperidine substrate. The synthetic route did not give a good yield and also the lithiation–substitution with n-BuLi at −78 °C was unsuccessful, just starting material was recovered. There was not enough time to do more investigation on this molecule and so more reactions could be carried out on this substrate in the future.

As we observed that the enantioselectivity was not poor in all cases, maybe by using another chiral ligand with bulky group, the enantioselectivity will be improved in the kinetic resolution of these compounds. It would be interesting to separate the allene products that resulted from lithiation of 137 as it could then be possible to get enantioenriched products in the kinetic resolutions of 137 and 138.
Chapter 5

Experimental procedures

5.1 General Experimental Details

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Solvents were obtained from Grubbs dry solvent system (model: SPS-200-6 or SPS-400-6). Methyl chloroformate, ethyl chloroformate, allyl bromide, benzaldehyde, 1,4-dibromobutane and 1,3-dibromopropane were freshly distilled from CaH₂, n-BuLi was titrated before use.¹²⁸ (+)-Sparteine was freshly distilled by Kugelrohr distillation. Thin layer chromatography was performed on Merck silica gel 60F₂₅₄ plates and visualised by UV irradiation at 254 nm or by staining with an alkaline KMnO₄ dip. Flash column chromatography was performed using DAVISIL or Geduran silica gel (40-63 micron mesh). ¹H NMR spectra were recorded on a Bruker AC400 (400 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Coupling constants (J values) are quoted to nearest 0.5 Hz with values in Hertz (Hz) and were corrected.¹³C NMR spectra were recorded on the above instrument at 100 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walters LCT instrument for Electro–Spray (ES). Infra–Red spectra were recorded on Perkin Elmer Spectrum RX Fourier Transform – IR System. Only selected peaks are reported, and absorption maxima are given in cm⁻¹. Melting points were recorded on a Gallenkamp hot stage and were uncorrected. Resolution between the enantiomers was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 column (250 mm × 4.60 mm i.d.), a Phenomenex Lux Cellulose-2 column (250 mm × 4.60 mm i.d.). In situ ReactIR infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC 4000 spectrometer equipped with a diamond-tipped (DiComp) probe.
5.2 General Experimental procedures

General procedure A for racemic lithiation-quench reactions of tert-butyl 2-phenyl-1-azepanecarboxylate 71 in THF

To a solution of tert-butyl 2-phenyl-1-azepanecarboxylate 71 (100 mg, 0.363 mmol) in dry THF (2 mL) at −5 ºC under nitrogen, was added n-BuLi (0.189 mL, 0.436 mmol, 2.4 M in hexane). After stirring for 10 minutes, the electrophile (1.089 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated, and the mixture was absorbed onto silica then purified by flash column chromatography, as described below.

General procedure B for racemic lithiation-quench reactions of tert-butyl 2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 96 in THF

To a solution of tert-butyl 2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 96 (100 mg, 0.309 mmol) in dry THF (2 mL) at −50 ºC under nitrogen, was added n-BuLi (0.154 mL, 0.370 mmol, 2.4 M in hexane). After stirring for 10 minutes, the electrophile (0.927 mmol) was added. The mixture was allowed to warm, gradually warming to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated, and the mixture was absorbed onto silica then purified by flash column chromatography, as described below.

General procedure C for racemic lithiation-quench reactions of tert-butyl 2,3,4,5-tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate 97 in THF

To a solution of tert-butyl 2,3,4,5-tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate 97 (100 mg, 0.280 mmol) in dry THF (2 mL) at −50 ºC under nitrogen, was added n-BuLi (0.150 mL, 0.330 mmol, 2.4 M in hexane). After stirring for 10 minutes, the electrophile (0.840 mmol) was added. The mixture was allowed to warm, gradually warming to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated, and the mixture was absorbed onto silica then purified by flash column chromatography, as described below.
5.3 Experimental Details

tert-Butyl 2-Oxoazepane-1-carboxylate (84)

To a solution of ε-caprolactam 83 (11.3 g, 100 mmol) and N,N-dimethylpyridin-4-amine (13.4 g, 110 mmol) in dry THF (120 mL) at room temperature was added di-tert-butyl dicarbonate (24.0 g, 110 mmol) in dry THF (60 mL). The reaction mixture was stirred at room temperature under nitrogen for 3 h. The reaction mixture was concentrated under vacuum and diluted with EtOAc (150 mL), before being washed with 0.5 M HCl (3 × 100 mL), saturated brine solution (3 × 25 mL) and saturated NaHCO₃ solution (3 × 25 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with CH₂Cl₂–MeOH (95:5), gave the carbamate 84 (21.0 g, 85%) as a clear oil; R f 0.39 [petrol–EtOAc (75:25)]; FT-IR ν max ATR/cm⁻¹ 2980, 2935, 2865, 1765 (C=O), 1700 (C=O), 1140; ¹H NMR (400 MHz, CDCl₃) δ = 3.77–3.72 (2H, m, NCH₂), 2.65–2.60 (2H, m, 2 × CH), 1.79–1.68 (6H, m, 6 × CH), 1.51 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃) δ = 174.7 (C=O), 151.8 (C=O), 81.6 (C), 45.1 (CH₂), 38.4 (CH₂), 28.2 (CH₂), 27.6 (CH₂), 27.0 (CH₃), 22.4 (CH₂); HRMS (ES) Found: MNa⁺, 236.1260. C₁₁H₁₉NO₃Na requires MNa⁺, 236.1257; LRMS m/z (ES) 236 (15%, MNa⁺), 158 (100, MNa⁺–Boc+H). Data in accordance with the literature.¹²⁹

tert-Butyl 2-Hydroxyazepane-1-carboxylate (85)

To a solution of carbamate 84 (10.0 g, 46.9 mmol) in dry THF (100 mL) at –78 °C was added DIBAL-H (59.7 mL, 59.7 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at –78 °C under nitrogen for 1 h, before gradually warming to room temperature over a further 1 h. The reaction was carefully quenched with saturated aqueous potassium acetate
solution (20 mL). The solids were filtered off and washed with EtOAc (3 × 25 mL). The organic layers were combined, washed with saturated brine solution (4 × 25 mL), dried over MgSO₄ and the solvent was removed under vacuum to afford the crude product as an off-white solid. The crude product was washed with petrol (30 mL) to give the carbamate 85 (10.0 g, 86%) as an amorphous white solid; m.p. 74–76 ºC, lit.¹²⁹ m.p. 75.5–78.5 ºC; Rf 0.32 [CH₂Cl₂–MeOH (90:10)]; FT-IR νmax ATR/cm⁻¹ 3430, 2980, 2935, 2855, 1675 (C=O), 1160; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 5.57–5.50 (0.67H, m, NCH), 5.46–5.40 (0.33H, m, NCH), 3.80–3.70 (0.33H, m, NCH), 3.64–3.56 (1.33H, m, NCH), 3.14–3.00 (1H, m, NCH, CH), 2.92–2.70 (0.33H, m, CH), 2.18 (1H, td, J = 14.5, 8.0 Hz, CH), 1.83–1.50 (3H, m, 3 × CH), 1.49 (3H, s, t-Bu), 1.46 (6H, s, t-Bu) 1.40–1.15 (3H, m, 3 × CH); ¹³C NMR (100 MHz, CDCl₃, rotamers) δ = 155.3 (C=O), 154.0 (C=O), 79.3 (C), 79.2 (C), 78.9 (CH), 78.6 (CH), 40.3 (CH₂), 39.8 (CH₂), 33.4 (CH₂), 33.1 (CH₂), 28.6 (CH₂), 28.5 (CH₂), 28.3 (CH₂), 28.2 (CH₂), 27.4 (CH₃), 27.3 (CH₃), 21.9 (CH₂), 21.8 (CH₂); HRMS (ES) Found: MNa⁺, 238.1418. C₁₁H₂₁NO₃Na requires MNa⁺, 238.1414; LRMS m/z (ES) 238 (5%, MNa⁺), 142 (100, MH⁺–t-Bu+H, OH). Data in accordance with the literature.¹²⁹

tert-Butyl 2-(1H-Benz[d][1,2,3]triazol-1-yl)azepane-1-carboxylate (86a,b)

To a solution of carbamate 85 (4.0 g, 18.5 mmol) in toluene (100 mL) was added benzo-triazole (3.3 g, 28.0 mmol) and MgSO₄ (1.0 g). The reaction mixture was heated to reflux for 18 h then allowed to cool to room temperature, before washing with saturated aqueous NaCO₃ solution (3 × 20 mL) and saturated brine solution (3 × 20 mL). The organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (75:25) to give the carbamate 86a,b (4.81 g, 82%) for a mixture of isomers (ratio 2:1), as an amorphous white solid; m.p. 124–126 ºC; Rf 0.64, 0.68 [petrol-EtOAc (75:25)]; FT-IR νmax ATR/cm⁻¹ 2970, 2930, 2860, 1690 (C=O), 1160, 1110; ¹H NMR (400 MHz, CDCl₃, mixture of isomers and
rotamers) δ = 8.09–7.63 (2H, m, 2 × CH), 7.52–7.32 (2H, m, 2 × CH), 7.03–6.88 (0.65H, m, CH), 6.77–6.62 (0.35H, m, CH), 2.97 (0.35H, dt, J = 11.5, 11.0 Hz, CH), 2.78–2.26 (1.65H, m, CH), 2.09–1.75 (3H, m, 3 × CH), 1.70–1.49 (3H, m, 3 × CH), 1.46 (2.35H, s, t-Bu), 1.45 (3.65H, s, t-Bu), 1.40 (1H, s, t-Bu), 1.34 (2H, s, t-Bu); 13C NMR (100 MHz, CDCl3, only major isomer reported) δ = 154.6 (C=O), 144.6 (C), 131.8 (C), 125.1 (CH), 122.9 (CH) 117.4 (CH), 110.0 (CH), 79.5 (C), 66.3 (CH), 41.6 (CH2), 31.7 (CH2), 28.5 (CH2), 27.2 (CH3), 27.1 (CH2), 22.8 (CH2); HRMS (ES) Found: MNa+, 339.1791. C17H24N4O2Na requires MNa+, 339.1791; LRMS m/z (ES) 339 (10%, MNa+), 142 (100, MH+‒t-Bu+H, −C6H3N3).

tert-Butyl 2-Phenylazepane-1-carboxylate (71)

To a solution of carbamate 86a,b (4.2 g, 15.2 mmol) in dry Et2O (90 mL) and dry THF (10 mL) at 0 ºC was added phenylmagnesium bromide solution (20.3 mL, 20.3 mmol, 3 M in Et2O) dropwise. The reaction mixture was stirred under argon for 20 h, slowly warming to room temperature, then diluted with a saturated solution of NH4Cl (10 mL) and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated brine solution (4 × 25 mL), dried over MgSO4 and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol–EtOAc (97:3), gave the carbamate 71 (3.60 g, 54%) as an amorphous white solid, m.p. 41–42 ºC, (reported as oil lit.)83; Rf 0.56 [petrol–EtOAc (75:25)]; FT-IR νmax ATR/cm−1 2970, 2925, 2850, 1690 (C=O), 1750; 1H NMR (400 MHz, CDCl3, rotamers) δ = 7.35–7.25 (2H, m, 2 × CH), 7.27–7.18 (3H, m, 3 × CH), 5.22 (0.5H, dd, J = 12.0, 6.0 Hz, NCH), 4.94 (0.5H, dd, J = 12.0, 6.0 Hz, NCH), 4.20–4.12 (0.5H, m, NCH), 3.93–3.85 (0.5H, m, NCH), 3.05–2.87 (1H, m, NCH), 2.46–2.37 (0.5H, m, CH), 2.33–2.24 (0.5H, m, CH), 2.01–1.54 (5H, m, 5 × CH), 1.51 (4.5H, s, t-Bu), 1.48–1.39 (1H, m, CH), 1.33 (4.5H, s, t-Bu), 1.30–1.22 (1H, m, CH); 13C NMR (100 MHz, CDCl3, rotamers) δ = 155.0 (C=O), 154.8 (C=O), 143.7 (C), 142.6 (C), 127.3 (CH), 127.2 (CH), 125.4 (CH), 125.4 (CH), 124.7 (CH), 124.5 (CH), 78.3 (C), 78.2 (C) 59.3 (CH), 57.2 (CH), 42.2 (CH2), 42.0 (CH2), 35.3 (CH2), 34.5 (CH2), 28.7 (CH2), 28.6 (CH2), 28.5 (CH2),
28.4 (CH₂), 27.5 (CH₃), 27.3 (CH₃), 25.4 (CH₂), 24.5 (CH₂); HRMS (ES) Found: MH⁺, 276.1958. C₁₇H₂₅NO₂ requires MH⁺, 276.1958; LRMS m/z (ES) 276 (5%, MH⁺), 220 (100, MH⁺–t-Bu+H). Data in accordance with the literature.⁸³

**ReactIR monitoring of the lithiation of tert-butyl 2-phenyl-1-azepane carboxylate 71 by n-BuLi in THF (Scheme 47, Figure 17)**

Solvent background of dry THF (10 mL) was taken at –5 °C. A solution of tert-butyl 2-phenyl-1-azepanecarboxylate 71 (552 mg, 2.0 mmol) in dry THF (2 mL) was added, and data acquisition was initiated. After 2 min, n-BuLi (0.96 mL, 2.4 mmol, 2.5 M in hexane) was added dropwise. The reaction mixture was stirred for 10 min (until full disappearance of the peak at 1694 cm⁻¹ and a new peak at 1644 cm⁻¹ observed which was assigned to νC=O of lithiated intermediate 72). The reaction was quenched with MeOH (1 mL), then purified by flash column chromatography, eluting with petrol–EtOAc (97:3), to afford pure starting material (452 mg, 82%).

**tert-Butyl 2-Methyl-2-phenylazepane-1-carboxylate (73a)**

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and iodomethane (0.07 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 73a (80 mg, 76%) as a yellow oil; Rf 0.56 [petrol–EtOAc (75:25)]; FT-IR νmax ATR/cm⁻¹ 2970, 2930, 2855, 1680 (C=O), 1155; ¹H NMR (400 MHz, CDCl₃) δ = 7.34–7.22 (4H, m, 4 × CH), 7.20–7.15 (1H, m, CH), 4.01–3.86 (1H, m, NCH), 3.61–3.50 (1H, m, NCH), 2.00–1.90 (1H, m, CH), 1.88–1.75 (6H, m, CH₃, 3 × CH), 1.66–1.52 (4H, m, 4 × CH), 1.05 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃) δ = 156.8 (C=O), 149.6 (C), 127.6 (CH), 125.3 (CH), 125.0 (CH), 79.3 (C), 63.3 (C), 45.8 (CH₂), 44.9 (CH₂), 31.0 (CH₂), 29.1 (CH₂), 28.0 (CH₃), 27.0 (CH₃),
23.5 (CH$_2$); HRMS (ES) Found: MH$^+$, 290.2113. C$_{18}$H$_{28}$NO$_2$ requires MH$^+$, 290.2115; LRMS m/z (ES) 290 (5%, MH$^+$), 234 (100, MH$^+$$-$$t$-Bu+H).

**tert-Butyl 2-(3-Bromopropyl)-2-phenylazepane-1-carboxylate (73b)**

![Chemical structure](image)

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.189 mL, 0.44 mmol, 2.4 M in hexanes) and 1,3-dibromopropane (0.11 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 73b (131 mg, 92%) as an amorphous white solid; m.p. 88–90 ºC; R$_f$ 0.58 [petrol–EtOAc (75:25)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2975, 2935, 2860, 1685 (C=O), 1230, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.32–7.23 (4H, m, 4 × CH), 7.21–7.15 (1H, m, CH), 4.54–4.40 (1H, m, NCH), 3.49 (2H, t, $J$ = 6.0 Hz, BrCH$_2$), 3.02–2.89 (1H, m, NCH), 2.70 (1H, td, $J$ = 13.0, 4.0 Hz, CH), 2.34–2.25 (1H, m, CH), 2.17 (1H, td, $J$ = 13.0, 4.0 Hz, CH), 2.12–2.01 (1H, m, CH), 2.00–1.91 (1H, m, CH), 1.90–1.79 (1H, m, CH), 1.71–1.60 (3H, m, 3 × CH), 1.49–1.35 (3H, m, 3 × CH), 1.05 (9H, s, $t$-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.1 (C=O), 148.5 (C), 127.4 (CH), 125.8 (CH), 125.4 (CH), 79.7 (C), 65.4 (C), 46.4 (CH$_2$), 42.8 (CH$_2$), 39.8 (CH$_2$), 34.3 (CH$_2$), 30.7 (CH$_2$), 29.1 (CH$_2$), 27.9 (CH$_3$), 27.6 (CH$_2$), 23.4 (CH$_2$); HRMS (ES) Found: MH$^+$, 396.1527. C$_{20}$H$_{31}$BrNO$_2$ requires MH$^+$, 396.1533; Found: MH$^+$, 398.1515. C$_{20}$H$_{33}$BrNO$_2$ requires MH$^+$, 398.1515; LRMS m/z (ES) 398 (5%, MH$^+$), 396 (5, MH$^+$), 342 (100, MH$^+$$-$$t$-Bu+H), 340 (100, MH$^+$$-$$t$-Bu+H).
**tert-Butyl 2-Allyl-2-phenylazepane-1-carboxylate (73c)**

![Diagram](image)

Using general procedure A, carbamate 71 (100 mg, 0.363 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and allyl bromide (0.09 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 73c (90 mg, 82%) as a clear oil; R_f 0.58 [petrol–EtOAc (75:25)]; FT-IR ν_max ATR/cm⁻¹ 2970, 2929, 2855, 1680 (C=O), 1385, 1150; ^1^H NMR (400 MHz, CDCl_3) δ = 7.33–7.23 (4H, m, 4 × CH), 7.22–7.15 (1H, m, CH), 5.98–5.84 (1H, m, CH=CH_2), 5.23–5.15 (2H, m, CH=CH_2), 4.45–4.34 (1H, m, NCH), 3.31 (1H, dd, J = 13.0, 8.0 Hz, NCH), 2.99–2.87 (1H, m, CH), 2.76 (1H, dd, J = 13.0, 8.0 Hz, CH), 2.40–2.27 (1H, m, CH), 2.00–1.82 (1H, m, CH), 1.76–1.56 (3H, m, 3 × CH), 1.33–1.25 (3H, m, 3 × CH), 1.05 (9H, s, t-Bu); ^13^C NMR (100 MHz, CDCl_3) δ = 155.2 (C=O), 147.5 (C), 133.0 (CH), 126.4 (CH), 124.7 (CH), 124.3 (CH), 117.6 (CH_2), 78.5 (C), 64.5 (C), 45.3 (CH_2), 43.6 (CH_2), 41.6 (CH_2), 29.8 (CH_2), 28.0 (CH_3), 26.8 (CH_2), 22.1 (CH_2); HRMS (ES) Found: MH⁺, 316.2271. C_{20}H_{30}NO_2 requires MH⁺, 316.2271; LRMS m/z (ES) 260 (100%, MH⁺–t-Bu+H).

**tert-Butyl 2-(4-Bromobutyl)-2-phenylazepane-1-carboxylate (73d)**

![Diagram](image)

Using general procedure A, carbamate 71 (100 mg, 0.363 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and 1,4-dibromobutane (0.13 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 73d (131 mg, 89%) as a clear oil; R_f 0.43 [petrol–EtOAc (75:25)]; FT-IR ν_max ATR/cm⁻¹ 2975, 2935, 2860, 1685 (C=O), 1230, 1155; ^1^H NMR (400 MHz, CDCl_3) δ = 7.32–7.21 (4H, m, 4 ×
CH), 7.19–7.14 (1H, m, CH), 4.55–4.42 (1H, m, NCH), 3.52–3.41 (2H, m, BrCH₂), 3.07–2.94 (1H, m, NCH), 2.57–2.46 (1H, m, CH), 2.38–2.29 (1H, m, CH), 2.04 (1H, td, J = 12.5, 4.0 Hz, CH), 1.99–1.87 (3H, m, CH), 1.76–1.55 (4H, m, 4 × CH), 1.48–1.36 (3H, m, 3 × CH), 1.34–1.27 (1H, m, CH), 1.04 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃) δ = 155.2 (C=O), 147.8 (C), 126.3 (CH), 124.8 (CH), 124.3 (CH), 78.5 (C), 64.8 (C), 45.4 (CH₂), 41.7 (CH₂), 39.2 (CH₂), 32.5 (CH₂), 32.3 (CH₂), 29.8 (CH₂), 28.1 (CH₂), 26.9 (CH₃), 22.4 (CH₂), 21.6 (CH₂); HRMS (ES) Found: MH⁺, 412.1668. C₂₁H₃₃⁸¹BrNO₂ requires MH⁺, 412.1671; Found: MH⁺, 410.1681. C₂₁H₃₃⁷⁹BrNO₂ requires MH⁺, 410.1689; LRMS m/z (ES) 412 (100%, MH⁺), 410 (100, MH⁺).

tert-Butyl 2-(Tributylstannyl)-2-phenylazepane-1-carboxylate (73e)

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and tributyltin chloride (0.29 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate 73e (153 mg, 75%) as a clear oil; Rf 0.74 [petrol–EtOAc (75:25)]; FT-IR νmax ATR/cm⁻¹ 2955, 2925, 2855, 1660 (C=O), 1155; ¹H NMR (400 MHz, CDCl₃) δ = 7.29–7.22 (2H, m, 2 × CH), 7.08–7.01 (1H, m, CH), 6.98–6.92 (2H, m, 2 × CH), 3.80–3.71 (1H, m, NCH), 2.91–2.82 (1H, m, CH), 6.98–6.92 (2H, m, 2 × CH), 3.80–3.71 (1H, m, NCH), 2.91–2.82 (1H, m, NCH), 2.71–2.61 (1H, m, CH), 1.96–1.56 (6H, m, 6 × CH), 1.53 (9H, s, t-Bu), 1.48–1.42 (1H, m, CH), 1.37–1.16 (12H, m, 6 × CH₂), 0.85 (9H, t, J = 7.0 Hz, 3 × CH₃), 0.75–0.58 (6H, m, 3 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ = 156.9 (C=O), 147.3 (C), 127.0 (CH), 123.0 (CH), 122.7 (CH), 78.4 (C), 61.3 (C), 42.3 (CH₂), 37.1 (CH₂), 28.4 (CH₂), 28.0 (CH₂), 27.9 (CH₂), 27.4 (CH₃), 26.7 (CH₂), 23.6 (CH₂) 12.8 (CH₂), 12.7 (CH₃); HRMS (ES) Found: MNa⁺, 588.2864. C₂₉H₅₁¹²⁰SnNO₂Na requires MNa⁺, 588.2839; Found: MNa⁺, 586.2872. C₂₉H₅₁¹⁸SnNO₂Na requires MNa⁺, 586.2860; LRMS m/z (ES) 588 (100%, MNa⁺), 586 (80, MNa⁺), 508 (45, MH⁺–t-Bu+H), 452 (50, MH⁺–C₄H₉+H).
1,1-Dimethyl-9a-phenyl-tetrahydro-5H-[1,3]oxazolo[3,4-a]azepin-3-one (73f)

Using general procedure A, carbamate 4 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and acetone (0.07 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate 4e (60 mg, 67%) as a clear oil; Rf 0.4 [petrol–EtOAc (75:25)]; FT-IR νmax ATR/cm⁻¹ 2980, 2935, 2865, 1735, 1065; ¹H NMR (400 MHz, CDCl₃) δ = 7.43–7.12 (5H, m, 5 × CH), 3.92 (1H, ddd, J = 9.0, 5.5, 3.5 Hz, NCH), 3.01–2.92 (1H, m, NCH), 2.54–2.45 (1H, m, CH), 2.17–2.08 (1H, m, CH), 1.97–1.84 (1H, m, CH), 1.77–1.60 (3H, m, 3 × CH), 1.50 (3H, s, CH₃), 1.42–1.30 (2H, m, 2 × CH), 0.80 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 157.2 (C=O), 139.8 (C), 127.7 (CH), 127.4 (CH), 126.5 (CH), 125.6 (CH), 125.1 (CH), 83.0 (C), 71.2 (C), 42.5 (CH₂), 35.4 (CH₂), 27.8 (CH₂), 25.8 (CH₃), 25.0 (CH₂), 22.9 (CH₂), 22.6 (CH₃); HRMS (ES) Found: MH⁺, 260.1642. C₁₆H₂₂NO₂ requires MH⁺, 260.1645; LRMS m/z (ES) 260 (100%, MH⁺).

trans-Hexahydro-1,9a-diphenyloxazolo[3,4-a]azepan-3(1H)-one (trans-73g) and cis-Hexahydro-1,9a-diphenyloxazolo[3,4-a]azepan-3(1H)-one (cis-73g)

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.189 mL, 0.44 mmol, 2.4 M in hexanes) and benzaldehyde (0.11 mL, 1.09 mmol) gave a mixture of isomers (dr 3:1), after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate trans-73g (82 mg, 75%) and the carbamate cis-73g (25 mg, 23%).
Carbamate trans-73g was isolated as needles; m.p. 93–94 °C; R_f 0.45 [petrol–EtOAc (75:25)]; FT-IR v_{max} ATR/cm^{-1} 3065, 2925, 2850, 1750, 1390, 1040; ^1H NMR (400 MHz, CDCl_3) δ =7.51–7.44 (2H, m, 2 × CH), 7.42–7.34 (4H, m, 4 × CH), 7.32–7.28 (2H, m, 2 × CH), 7.20–7.15 (2H, m, 2 × CH), 5.27 (1H, s, OCH), 3.97–3.90 (1H, m, NCH), 3.03–2.94 (1H, m, NCH), 1.97–1.86 (2H, m, 2 × CH), 1.73–1.65 (1H, m, CH), 1.62–1.52 (1H, m, CH), 1.44–1.32 (4H, m, 4 × CH); ^13C NMR (100 MHz, CDCl_3) δ = 157.0 (C=O), 141.7 (C), 133.3 (C), 128.2 (CH), 127.5 (CH), 127.2 (CH), 126.8 (CH), 125.0 (CH), 124.9 (CH), 86.2 (CH), 69.5 (C), 41.8 (CH_2), 33.9 (CH_2), 27.0 (CH_2), 24.8 (CH_2), 22.2 (CH_2); HRMS (ES) Found: MH^+, 308.1654. C_{20}H_{22}NO_2 requires MH^+, 308.1645; LRMS m/z (ES) 330 (5%, MNa^+), 308 (100, MH^+).

Carbamate cis-73g (25 mg, 23%) was isolated as needles; m.p. 97–98 °C; R_f 0.42 [petrol–EtOAc (70:30)]; FT-IR v_{max} ATR/cm^{-1} 3090, 2940, 2850, 1735, 1400, 1020; ^1H NMR (400 MHz, CDCl_3) δ =7.18–6.68 (10H, m, 10 × CH), 5.35 (1H, s, OCH), 4.15–4.08 (1H, m, CH), 2.81–2.68 (2H, m, NCH, CH), 2.10–1.71 (6H, m, 6 × CH), 1.37–1.29 (1H, m, CH); ^13C NMR (101 MHz, CDCl_3) δ = 156.9 (C=O), 139.1 (C), 133.1 (C), 127.2 (CH), 127.0 (CH), 126.6 (CH), 126.2 (CH), 125.6 (CH), 125.2 (CH), 83.4 (CH), 69.6 (C), 41.7 (CH_2), 37.8 (CH_2), 29.4 (CH_2), 27.6 (CH_2), 22.0 (CH_2); HRMS (ES) Found: MH^+, 308.1654. C_{20}H_{22}NO_2 requires MH^+, 308.1645; LRMS m/z (ES) 330 (5%, MNa^+), 308 (100, MH^+).

**tert-Butyl 2-(2-(methoxycarbonyl)phenyl)azepane-1-carboxylate (87a)**

![tert-Butyl 2-(2-(methoxycarbonyl)phenyl)azepane-1-carboxylate (87a)](image)

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.08 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate 87a (78 mg, 65%) as an amorphous white solid; m.p. 82–84 °C; R_f 0.41 [petrol–EtOAc (75:25)]; FT-IR v_{max} ATR / cm^{-1} 2975, 2925, 2850, 1715 (C=O), 1685 (C=O), 1155; ^1H NMR (400 MHz, CDCl_3, rotamers) δ = 8.08–7.76 (1H, m, CH), 7.55–7.41 (1H, m, CH), 7.31–7.22 (2H, m, 2 × CH), 5.90 (0.2H, dd, J = 12.0, 5.0 Hz, NCH), 5.63 (0.8H, dd, J = 12.0, 5.0 Hz, NCH), 5.27 (1H, s, OCH), 3.97–3.90 (1H, m, NCH), 3.03–2.94 (1H, m, NCH), 1.97–1.86 (2H, m, 2 × CH), 1.73–1.65 (1H, m, CH), 1.62–1.52 (1H, m, CH), 1.44–1.32 (4H, m, 4 × CH); ^13C NMR (100 MHz, CDCl_3) δ = 157.0 (C=O), 141.7 (C), 133.3 (C), 128.2 (CH), 127.5 (CH), 127.2 (CH), 126.8 (CH), 125.0 (CH), 124.9 (CH), 86.2 (CH), 69.5 (C), 41.8 (CH_2), 33.9 (CH_2), 27.0 (CH_2), 24.8 (CH_2), 22.2 (CH_2); HRMS (ES) Found: MH^+, 308.1654. C_{20}H_{22}NO_2 requires MH^+, 308.1645; LRMS m/z (ES) 330 (5%, MNa^+), 308 (100, MH^+).
4.38 (0.8H, dd, J = 14.0, 5.0 Hz, NCH), 4.14–4.06 (0.2H, m, NCH), 3.90 (0.6H, s, CH$_3$), 3.89 (2.4H, s, CH$_3$), 3.31–3.11 (1H, m, NCH), 2.43–2.27 (1H, m, CH), 2.06–1.80 (3H, m, 3 × CH), 1.58–1.46 (3H, m, 3 × CH), 1.44 (2.2H, s, t-Bu), 1.37–1.26 (1H, m, CH), 1.16 (6.8H, s, t-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$, rotamers) δ = 167.8 (C=O), 167.6 (C=O), 155.8 (C=O), 155.7 (C=O), 149.0 (C), 147.1 (C), 132.3 (CH), 132.2 (CH), 130.9 (CH), 130.1 (CH), 127.8 (C), 127.4 (C), 126.1 (CH), 126.0 (CH), 125.3 (CH), 124.9 (CH), 79.2 (C), 77.2 (C), 58.6 (CH), 57.8 (CH), 52.0 (OCH$_3$), 51.9 (OCH$_3$), 44.5 (CH$_2$), 44.1 (CH$_2$), 35.9 (CH$_2$), 35.6 (CH$_2$), 31.0 (CH$_2$), 30.5 (CH$_2$), 29.3 (CH$_2$), 29.1 (CH$_2$), 28.5 (CH$_3$), 28.0 (CH$_3$), 27.8 (CH$_2$) 27.7 (CH$_2$); HRMS (ES) Found: MH$^+$, 334.2016. C$_{19}$H$_{28}$NO$_4$ requires 334.2013; LRMS m/z (ES) 334 (10%, MH$^+$), 278 (20, MH$^+-$t-Bu+H), 234 (100, MH$^+$–Boc+H).

Alternatively, compound 87a was prepared as follows: Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and methyl chloroformate (0.08 mL, 1.09 mmol) gave the carbamate 87a (72 mg, 60%) as an amorphous white solid; data as above.

**tert-Butyl 2-(2-(Ethoxycarbonyl)phenyl)azepane-1-carboxylate (87b)**

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and ethyl cyanoformate (0.107 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate 87b (80 mg, 64%) as an amorphous white solid; m.p. 71–72 ºC; R$_f$ 0.42 [petrol–EtOAc (75:25)]; FT-IR $\nu_{\text{max}}$ ATR / cm$^{-1}$ 2975, 2930, 2855, 1715 (C=O), 1680 (C=O), 1160; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) δ = 7.92–7.83 (1H, m, CH), 7.57–7.41 (1H, m, CH), 7.32–7.22 (2H, m, 2 × CH), 5.91 (0.2H, dd, J = 12.0, 5.0 Hz, NCH), 5.63 (0.8H, dd, J = 12.0, 5.0 Hz, NCH), 4.42–4.32 (2.8H, m, NCH, OCH$_2$), 4.14–4.07 (0.2H, m, NCH), 3.27–3.12 (1H, m, NCH), 2.44–2.30 (1H, m, CH), 2.07–1.79 (3H, m, 3 × CH), 1.62–1.47 (3H, m, 3 × CH), 1.44 (2H, s, t-Bu), 1.40 (3H, t, J = 7.0 Hz, CH$_3$), 1.35–1.29 (1H, m, CH), 1.16 (7H, s, t-Bu); $^{13}$C NMR
(100 MHz, CDCl₃, rotamers) \(\delta = 167.4\) (C=O), 166.3 (C=O), 155.8 (C=O), 155.7 (C=O), 148.7 (C), 146.9 (C), 132.2 (CH), 132.0 (CH), 130.9 (CH), 130.2 (CH), 128.7 (C), 128.2 (C), 126.1 (CH), 126.0 (CH), 125.2 (CH), 124.8 (CH), 79.2 (C), 77.2 (C), 68.1 (CH₂), 60.8 (CH₂), 58.7 (CH), 57.8 (CH), 44.5 (CH₂), 44.1 (CH₂), 35.9 (CH₂), 35.6 (CH₂), 31.0 (CH₂), 29.7 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 28.5 (CH₃), 28.0 (CH₃), 27.8 (CH₂), 27.7 (CH₂), 14.3 (CH₃), 14.0 (CH₃); HRMS (ES) Found: MH⁺, 348.2175. C₂₀H₃₀NO₄ requires MH⁺, 348.2169; LRMS m/z (ES) 348 (10%, MH⁺), 248 (100, MH⁺–Boc+H).

Alternatively, compound 87b was prepared as follows: Using general procedure A, carbamate 71 (100 mg, 0.363 mmol), n-BuLi (0.189 mL, 0.436 mmol, 2.4 M in hexanes) and ethyl chloroformate (0.104 mL, 1.089 mmol) gave the carbamate 87b (63 mg, 50%) as an amorphous white solid; data as above.

tert-Butyl 2-(2-((Benzyloxy)carbonyl) phenyl)azepane-1-carboxylate (87c)

Using general procedure A, carbamate 71 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and benzyl cyanoformate (0.15 mL, 1.09 mmol) gave, after flash column chromatography on silica, gel eluting with petrol–EtOAc (95:5), the carbamate 87c (90 mg, 64%) as an amorphous white solid; m.p. 94–96 °C; Rf 0.43 [petrol–EtOAc (75:25)]; FT-IR \(\nu_{\text{max}}\) ATR/cm⁻¹ 2980, 2920, 2855, 1705 (C=O), 1672 (C=O), 1151; \(^1\)H NMR (400 MHz, CDCl₃, rotamers) \(\delta = 8.05–7.89\) (1H, m, CH), 7.51–7.34 (6H, m, 6 × CH), 7.35–7.29 (1H, m, CH), 7.27–7.22 (1H, m, CH), 5.94 (0.2H, dd, \(J = 12.0, 4.0\) Hz, NCH), 5.65 (0.8H, dd, \(J = 12.0, 4.0\) Hz, NCH), 5.42–5.28 (2.2H, m, NCH, PhCH₂), 4.38 (0.8H, dd, \(J = 14.0, 4.0\) Hz, NCH), 3.26–3.10 (1H, m, NCH), 2.30 (1H, tt, \(J = 9.0, 4.0\) Hz, CH), 2.00–1.78 (3H, m, 3 × CH), 1.70–1.48 (3H, m, 3 × CH), 1.45 (2H, s, t-Bu), 1.41–1.34 (1H, m, CH), 1.14 (7H, s, t-Bu); \(^{13}\)C NMR (100 MHz, CDCl₃, rotamers) \(\delta = 167.0\) (C=O), 166.3 (C=O), 155.8 (C=O), 155.7 (C=O), 148.9 (C), 147.2 (C), 136.9 (C), 135.8 (C), 132.4 (CH), 132.3 (CH), 131.0
Kinetic Resolution of tert-Butyl 2-Phenylazepane-1-carboxylate 71 in Presence of (+)-Sparteine (Scheme 58)

\( n\text{-BuLi} \) (0.17 mL, 0.45 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (127 mg, 545 mmol) and \( N\text{-Boc-2-phenylazepane} 71 \) (100 mg, 0.36 mmol) in dry toluene (6 mL) at \(-5 {\degree}C\). After 3 h, tributyltin chloride (0.29 mL, 1.09 mmol) was added. The mixture was allowed to warm to room temp. over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with petrol/EtOAc (99:1), gave the recovered starting material (S)-71 (42 mg, 42%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 66:34 by CSP HPLC using a Beckman system fitted with a phenomenex Lux Cellulose-1 column (250 mm \( \times \) 4.60 mm i.d.) as the stationary phase with a mixture of \( n\text{-hexane:isopropanol} \) (99:1 v/v) as the mobile phase at a flow rate of 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 \( \mu\)L of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the major component eluted at 12.1 min; \([\alpha]_{D}^{22} = -23.4 \) (3.2, CHCl\(_3\)), 66:34 er.

Octahydro-9a-Phenyl-1H-pyrrolo[1,2-a]azepane (94)

A mixture of tert-butyl 2-(3-bromopropyl)-2-phenylazepane-1-carboxylate 73b (100 mg, 0.25 mmol), NaI (113 mg, 0.76 mmol) and chlorotrimethylsilane (0.09 mL, 0.51 mmol) in dry acetonitrile (3 mL) was heated under reflux for 2 h. The mixture was allowed to cool to room temperature and methanol (1 mL) saturated with HCl was added. The reaction mixture was
stirred for 30 min. The solvent was evaporated, and the residue was dissolved in methanol (5 mL), the solution was made alkaline with aqueous NaOH (3 mL, 2 M). The methanol was evaporated, and the residue was extracted with ether (5 mL) and the combined organic layer was washed with water (3 × 2 mL), sodium thiosulfate solution (10%, 2 mL), and brine. The organic layers were dried over MgSO₄ and the solvent was evaporated. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (98:2), to give the bicyclic product 94 (39 mg, 78%) as a brown oil; R_f 0.59 [petrol–EtOAc (80:20)]; FT-IR ν_max ATR/cm⁻¹ 2980, 2890, 2750, 1150; ¹H NMR (400 MHz, CDCl₃) δ = 7.53–7.15 (5H, m, 5 × CH), 3.18–3.06 (3H, m, 3 × CH), 3.03–2.95 (1H, m, CH), 2.27–2.18 (1H, m, CH), 2.03–1.97 (2H, m, 2 × CH), 1.96–1.88 (1H, m, CH), 1.86–1.78 (1H, m, CH), 1.70–1.53 (3H, m, 3 × CH), 1.52–1.34 (4H, m, 4 × CH); ¹³C NMR (100 MHz, CDCl₃) δ = 151.7 (C), 127.6 (CH), 126.6 (CH), 125.2 (CH), 68.7 (C), 54.0 (CH₂), 50.0 (CH₂), 43.4 (CH₂), 40.5 (CH₂), 30.6 (CH₂), 26.5 (CH₂), 24.0 (CH₂), 23.5 (CH₂); HRMS (ES) Found: MH⁺, 216.1751. C₁₅H₂₂N requires MH⁺, 216.1747; LRMS m/z (ES) 216 (100%, MH⁺).

7,8,9,10,11,11a-Hexahydroazepino[2,1-a]isoindol-5-one (95)

To a solution of tert-butyl 2-(2-(methoxycarbonyl)phenyl)azepane-1-carboxylate 87a (60 mg, 0.18 mmol) in CH₂Cl₂ (1 mL) was added trifluoroacetic acid (0.13 mL, 1.8 mmol) and the mixture was allowed to stir for 2 h at room temperature. After this time, the acid was evaporated and the crude mixture was diluted with CH₂Cl₂ (2 mL). Aqueous NaOH (2 mL, 2 M) was added and the mixture was stirred vigorously for 15 min. The organic layer was separated, dried over MgSO₄ and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (95:5), to give the tricyclic lactam 95 (31 mg, 86%) as needles; m.p. 70–72 °C; R_f 0.15 [petrol–EtOAc (70:30)]; FT-IR ν_max ATR/cm⁻¹ 2930, 2920, 2850, 1660 (C=O); ¹H NMR (400 MHz, CDCl₃) δ = 7.88–7.80 (1H, m, CH), 7.58–7.51 (1H, m, CH), 7.49–7.38 (2H, m, 2 × CH), 4.62 (1H, dd, J = 7.0, 4.0 Hz, CH), 4.03–3.95 (1H, m, CH), 3.46 (1H, ddd, J = 11.0, 8.0, 3.0 Hz, CH),
2.34–2.25 (1H, m, CH), 2.02–1.90 (1H, m, CH), 1.84–1.72 (3H, m, 3 × CH), 1.67–1.51 (3H, m, 3 × CH); 13C NMR (100 MHz, CDCl₃) δ = 168.7 (C=O), 146.3 (C), 132.6 (C), 131.2 (CH), 128.0 (CH), 123.1 (CH), 121.9 (CH), 61.4 (CH₂), 43.5 (CH₂), 34.6 (CH₂), 29.5 (CH₂), 26.9 (CH₂), 26.1 (CH₂); HRMS (ES) Found: MH⁺, 202.1229. C₁₃H₁₆NO requires MH⁺, 202.1226; LRMS m/z (ES) 202 (100%, MH⁺).

tert-Butyl 2,3,4,5-Tetrahydro-2-oxobenzo[b]azepine-1-carboxylate (124)

To a solution of 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 99 (3.0 g, 18.6 mmol) and N,N-dimethylpyridin-4-amine (2.5 g, 20.4 mmol) in dry THF (50 mL) at room temperature was added di-tert-butyl dicarbonate (4.7 g, 20.4 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature under nitrogen for 3 h. The reaction mixture was concentrated under vacuum and diluted with EtOAc (50 mL), before being washed with 0.5 M HCl (3 × 50 mL), saturated brine solution (3 × 25 mL) and saturated NaHCO₃ solution (3 × 25 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with CH₂Cl₂–MeOH (95:5), gave the carbamate 124 (4.5 g, 93%) as an amorphous white solid; m.p. 110–112 °C; Rf 0.26 [petrol–EtOAc (70:30)]; FT-IR νmax ATR/ cm⁻¹ 2980, 2930, 2860, 1765 (C=O), 1715 (C=O), 1145; 1H NMR (400 MHz, CDCl₃) δ = 7.39–7.20 (3H, m, 3 × CH), 7.19–7.05 (1H, m, CH), 2.81 (2H, t, J = 7.0 Hz, 2 × CH), 2.28 (2H, t, J = 7.0 Hz, 2 × CH), 2.19–2.05 (2H, m, 2 × CH), 1.47 (9H, s, t-Bu); 13C NMR (100 MHz, CDCl₃) δ = 172.6 (C=O), 151.4 (C=O), 138.8 (C), 135.4 (C), 129.0 (CH), 127.8 (CH), 127.1 (CH), 126.0 (CH), 83.4 (C), 34.6 (CH₂), 29.3 (CH₂), 27.8 (CH₃), 27.5 (CH₂); HRMS (ES) Found: MH⁺, 262.1443. C₁₃H₂₀NO₃ requires MH⁺, 262.1438; LRMS m/z (ES) 262 (5%, MH⁺), 206 (100, MH⁺–t-Bu+H).
**tert-Butyl 2,3,4,5-Tetrahydro-2-hydroxybenzo[b]azepine-1-carboxylate (125a,b)**

To a solution of carbamate 124 (4.0 g, 15.3 mmol) in dry THF (50 mL) at −78 °C was added DIBAL-H (21.4 mL, 21.4 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at −78 °C under nitrogen for 1 h, before gradually warming to room temperature over a further 1 h. The reaction was carefully quenched with saturated aqueous potassium acetate solution (20 mL). The solids were filtered off and washed with EtOAc (3 × 25 mL). The organic layers were combined, washed with saturated brine solution (4 × 25 mL), dried over MgSO₄, and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with CH₂Cl₂–MeOH (95:5), gave the carbamate 125a,b (3.6 g, 89%) as a brown oil of a mixture of two isomer (ratio 0.7:1); Rf 0.50 (alcohol), 0.75 (aldehyde) [CH₂Cl₂–EtOAc (90:10)]; FT-IR νmax ATR/cm⁻¹ 3450, 3360, 2970, 2980, 2940, 2870, 1710 (C=O), 1680 (C=O), 1160; ¹H NMR (400 MHz, CDCl₃, 1:0.7 mixture of two isomer) δ = 9.82 (0.7H, t, J = 1.0 Hz, CHO), 7.82 (0.7H, d, J = 8.0 Hz, CH), 7.25–7.19 (2.7H, m, CH), 7.17–7.11 (2.7H, m, CH), 7.04–7.01 (0.7H, m, CH), 6.80 (0.7H, br s, NH), 5.71–5.54 (1H, m, CH), 3.92 (1H, s, OH), 2.75 (1H, td, J = 13.0, 7.0 Hz, CH), 2.62–2.54 (4H, m, 4 × CH), 1.95–1.87 (1.7H, m, CH), 1.86–1.77 (2.1H, m, CH), 1.55 (6.3H, s, t-Bu), 1.54–1.52 (1.4H, m, CH), 1.40 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃, mixture of two isomer) δ = 202.3 (C=O), 155.5 (C=O), 153.6 (C=O), 137.1 (C), 136.5 (C), 136.0 (C), 131.0 (C), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.1 (CH), 126.5 (CH), 123.9 (CH), 122.2 (CH), 80.7 (C), 80.3 (C), 78.9 (CH), 42.9 (CH₂), 30.5 (CH₂), 29.6 (CH₂), 29.4 (CH₂), 28.3 (CH₃), 28.2 (CH₃), 21.9 (CH₂), 21.1 (CH₂); HRMS (ES) Found: MNa⁺, 286.1417. C₁₅H₂₁NO₃Na requires MNa⁺, 286.1414; LRMS m/z (ES) 286 (5%, MH⁺), 190 (100, MH⁺–t-Bu+H, OH), 146 (85, MH⁺–Boc+H).

It was possible to separate 125b from this mixture and its data are as follows: ¹H NMR (400 MHz, CDCl₃) δ = 9.83 (1H, br s, CHO), 7.84 (1H, d, J = 8.0 Hz, CH), 7.25–7.20 (1H, m, CH), 7.13 (1H, d, J = 7.0 Hz, CH), 7.07–7.01 (1H, m, CH), 6.80 (1H, br s, NH), 2.63–2.54 (4H, m, 4 × CH), 1.95–1.84 (2H, m, 2 × CH), 1.55 (9H, s, t-Bu); ¹³C NMR (100 MHz,
CDCl₃ δ = 202.3 (C=O), 153.5 (C=O), 136.0 (C), 131.0 (C), 129.4 (CH), 127.1 (CH), 123.9 (CH), 122.0 (CH), 80.3 (C), 43.0 (CH₂), 30.5 (CH₂), 28.3 (CH₃), 22.0 (CH₂).

ter-Butyl-2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate (126)

To a solution of carbamate 125a and 125b (3.0 g, 11.4 mmol) in toluene (70 mL) was added benzotriazole (2.03 g, 17.1 mmol) and MgSO₄ (0.5 g). The reaction mixture was heated to reflux for 18 h then allowed to cool to room temperature, before washing with saturated aqueous NaCO₃ solution (3 × 20 mL) and saturated brine solution (3 × 20 mL). The organic layers were dried (MgSO₄), and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol‒EtOAc (75:25), to give the carbamate 126 (3.50 g, 84%), as a brown oil; Rf 0.45 [petrol‒EtOAc (70:30)]; FT-IR ν_maximum ATR/cm⁻¹ 3025, 2970, 1690 (C=O), 1360, 1210; ¹H NMR (400 MHz, CDCl₃) δ = 8.08–7.43 (3H, m, 3 × CH), 7.42–7.30 (2H, m, 2 × CH), 7.26–7.02 (3H, m, 3 × CH), 7.00–6.12 (1H, m, NCH), 3.06–2.93 (1H, m, CH), 2.83–2.68 (1H, m, CH), 2.54–1.84 (4H, m, 4 × CH), 1.33 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃, one C=O missing) δ = 143.9 (C), 137.6 (C), 136.8 (C), 136.5 (C), 128.6 (CH), 128.1 (CH), 127.2 (CH), 126.0 (CH), 123.8 (CH), 119.7 (CH), 118.4 (CH), 110.6 (CH), 79.0 (C), 66.8 (CH), 29.9 (CH₂), 29.5 (CH₂), 29.0 (CH₂), 28.0 (CH₃); HRMS (ES) Found: MNa⁺, 387.1793. C₂₂H₂₄N₄O₂Na, requires MNa⁺, 387.1791; LRMS m/z (ES) 387 (15% MNa⁺), 190 (28), 146 (100).
**tert-Butyl 2,3,4,5-Tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (96)**

To a solution of carbamate 126 (4.0 g, 10.9 mmol) in dry Et₂O (90 mL) and dry THF (10 mL) at 0 °C was added phenylmagnesium bromide solution (14.6 mL, 43.9 mmol, 3 M in Et₂O) dropwise. The reaction mixture was stirred under argon for 20 h, slowly warming to room temperature, then diluted with a saturated solution of NH₄Cl (10 mL) and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated brine solution (4 × 25 mL), dried over MgSO₄, and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol‒EtOAc (95:5), gave the carbamate 96 (2.48 g, 70%) as needles, m.p. 110‒112 ºC; Rₓ 0.65 [petrol‒EtOAc (80:20)]; FT-IR νₓ ATR/cm⁻¹ 2980, 2945, 2855, 1690 (C=O), 1160; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 7.54‒7.19 (9H, m, 9 × CH), 5.17 (0.55H, br d, J = 12.0 Hz, NCH), 4.94 (0.45H, br d, J = 12.0 Hz, NCH), 3.08‒2.89 (1H, m, CH), 2.65 (1H, dd, J = 13.0, 8.0 Hz, CH), 2.04‒1.90 (1H, m, CH), 1.84‒1.62 (2H, m, 2 × CH), 1.58‒1.42 (1H, m, CH), 1.31 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃, rotamers, one CH missing) δ = 154.8 (C=O), 154.6 (C=O), 146.5 (C), 144.9 (C), 138.9 (C), 138.7 (C), 137.3 (C), 137.1 (C), 130.0 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 126.5 (CH), 126.4 (CH), 126.0 (CH), 80.4 (C), 79.7 (C), 61.0 (CH), 59.3 (CH), 32.1 (CH₂), 31.1 (CH₂), 29.7 (CH₂), 29.5 (CH₂), 28.2 (CH₃), 28.1 (CH₃), 23.6 (CH₂), 23.0 (CH₂); HRMS (ES) Found: MNa⁺, 346.1779. C₂₁H₂₅NO₂Na requires MNa⁺, 346.1778; LRMS m/z (ES) 346 (>5%, MNa⁺), 268 (100%, MH⁺–t-Bu+H).

**ReactIR monitoring of the lithiation of tert-butyl 2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 96 by n-BuLi in THF (Scheme 75, Figure 26)**

Solvent background of dry THF (10 mL) was taken at −50 ºC. A solution of tert-butyl 2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 96 (409 mg, 1.26 mmol) in dry THF (2 mL) was added, and data acquisition was initiated. After 2 min, n-BuLi (0.63 mL, 1.5 mmol, 2.5 M in hexanes) was added dropwise. The reaction mixture was allowed to stir for 10 min (until full disappearance of the peak at 1702 cm⁻¹ and a new peak at 1644 cm⁻¹...
observed which was assigned to $\nu_{\text{C=O}}$ of lithiated intermediate 119). The reaction was quenched with MeOH (1 mL), then purified by flash column chromatography, eluting with petrol–EtOAc (97:3), to afford pure starting material (250 mg, 61%).

**tert-Butyl 2-Allyl-2,3,4,5-Tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (120a)**

![Chemical Structure of 120a]

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), $n$-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and allyl bromide (0.08 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 120a (94 mg, 85 %) as a clear oil; $R_f$ 0.68 [petrol–EtOAc (70:30)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2965, 2925, 2850, 1695 (C=O), 1260, 1090; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 7.77–7.53 (1H, m, CH), 7.41–7.19 (8H, m, $8 \times$ CH), 5.36–5.00 (1H, m, CH=CH$_2$), 4.99–4.58 (2H, m, CH=CH$_2$), 3.03–2.83 (1H, m, CH), 2.73–2.62 (1H, m, CH), 2.54–2.12 (3H, m, $3 \times$ CH), 2.03–1.86 (1H, m, CH), 1.74–1.65 (1H, m, CH), 1.31 (2H, s, $t$-Bu), 1.28 (1H, s, $t$-Bu) 1.12 (6H, s, $t$-Bu), 0.99–0.88 (1H, m, CH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 155.4 (C=O), 143.0 (C), 141.2 (C), 134.7 (C), 130.6 (CH), 129.0 (CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 126.6 (CH), 125.7 (CH), 125.4 (CH), 118.2 (=CH$_2$), 80.4 (C), 68.0 (C), 29.7 (CH$_2$), 27.9 (CH$_3$), 23.6 (CH$_3$), 23.0 (CH$_2$), 22.1 (CH$_2$); HRMS (ES) Found: MH$^+$, 364.2272. C$_{24}$H$_{31}$NO$_2$ requires MH$^+$, 364.2271; LRMS $m/z$ (ES) 364 (5%, MH$^+$), 308 (100, MH$^+$–$t$-Bu+H), 264 (23, MH$^+$–Boc+H).
**tert-Butyl 2-(4-Bromobutyl)-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (120b)**

![Chemical Structure](image)

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and 1,4-dibromobutane (0.11 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 120b (109 mg, 78%) as a clear oil; R<sub>f</sub> 0.34 [petrol–EtOAc (80:20)]; FT-IR ν<sub>max</sub> ATR/cm<sup>−1</sup> 2950, 2925, 2860, 1700 (C=O), 1160; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.71–7.12 (9H, m, 9 × CH), 3.17–3.05 (2H, m, BrCH<sub>2</sub>), 2.89–2.77 (1H, m, CH), 2.74–2.65 (1H, m, CH), 2.62–2.34 (2H, m, 2 × CH), 2.06–1.90 (1H, m, CH), 1.73–1.56 (2H, m, 2 × CH), 1.54 –1.43 (2H, m, 2 × CH), 1.34–1.25 (3H, m, 3 × CH), 1.10 (9H, s, t-Bu); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, one CH<sub>2</sub> missing) δ = 153.4 (C=O), 141.3 (C), 134.1 (C), 133.7 (C), 130.5 (CH), 129.1 (CH), 128.4 (CH), 127.5 (CH), 126.6 (CH), 125.8 (CH), 125.3 (CH), 80.1 (C), 66.0 (C), 39.6 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 33.3 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 27.9 (CH<sub>3</sub>), 22.4 (CH<sub>2</sub>); HRMS (ES) Found: MNa<sup>+</sup>, 480.1507. C<sub>25</sub>H<sub>31</sub>BrNO<sub>2</sub>Na requires MNa<sup>+</sup>, 480.1509; Found: MNa<sup>+</sup>, 482.1489. C<sub>25</sub>H<sub>31</sub>BrNO<sub>2</sub>Na requires MNa<sup>+</sup>, 482.1492; LRMS m/z (ES) 482 (10%, MNa<sup>+</sup>), 480 (10, MNa<sup>+</sup>), 404 (100, MH<sup>+</sup>–t-Bu+H), 402 (100, MH<sup>+</sup>–t-Bu+H).

**tert-Butyl 2-(Tributylstannyl)-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (120c)**

![Chemical Structure](image)

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and tributyltin chloride (0.25 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate 120c (142 mg, 75%) as a clear oil; R<sub>f</sub> 0.75 [petrol–EtOAc (80:20)]; FT-IR ν<sub>max</sub> ATR/cm<sup>−1</sup> 2955,
2920, 2860, 1670 (C=O), 1135; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.24–6.94 (9H, m, 9 × CH), 2.99–2.86 (1H, m, CH), 2.60 (1H, dt, $J = 9.0, 4.5$ Hz, CH), 2.55–2.45 (1H, m, CH), 1.92–1.82 (2H, m, 2 × CH), 1.47–1.19 (22H, m, t-Bu, CH, 3 × CH$_2$CH$_2$), 0.87 (9H, t, $J = 7.0$ Hz, 3 × CH$_3$), 0.83–0.65 (6H, m, 3 × CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.8 (C=O), 139.5 (C), 138.3 (C), 131.2 (C), 130.3 (CH), 128.2 (CH), 127.7 (CH), 126.8 (CH), 126.0 (CH), 124.9 (CH), 123.7 (CH), 79.8 (C), 61.8 (C), 35.1 (CH$_2$), 32.5 (CH$_2$), 29.0 (CH$_2$), 28.2 (CH$_3$), 27.7 (CH$_2$), 22.5 (CH$_2$), 13.7 (CH$_3$), 13.4 (CH$_2$); HRMS (ES) Found: MNa$^+$, 636.2841. C$_{33}$H$_{51}$NO$_2$Sn Na requires MNa$^+$, 636.2839; Found: MNa$^+$, 634.2863. C$_{33}$H$_{51}$NO$_2$Sn Na requires MNa$^+$, 634.2860; LRMS m/z (ES) 636 (72%, MNa$^+$), 634 (50, MNa$^+$), 500 (35, MH$^+$–t-Bu+H, –Bu), 498 (25, MH$^+$–t-Bu+H, –Bu), 212 (100).

**tert-Butyl 2,3,4,5-Tetrahydro-2-methyl-2-phenylbenzo[b]azepine-1-carboxylate (120d)**

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and iodomethane (0.06 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate 120d (62 mg, 60%) as a yellow oil; R$_f$ 0.65 [petrol–EtOAc (80:20)]; FT-IR $\nu$_max ATR/cm$^{-1}$ 2960, 2930, 2860, 1695 (C=O), 1160; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 7.56–7.15 (9H, m, 9 × CH), 3.20–2.87 (1H, m, CH), 2.72–2.60 (1H, m, CH), 2.12–1.89 (1H, m, CH), 1.81–1.43 (3H, m, 3 × CH), 1.31 (4H, s, t-Bu), 1.28 (1H, s, CH$_3$), 1.26 (2H, s, CH$_3$), 1.31 (5H, s, t-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$, rotamers) $\delta$ = 156.2 (C=O), 154.6 (C=O), 145.1 (C), 144.9 (C), 138.9 (C), 138.7 (C), 137.2 (C), 136.6 (C), 129.9 (CH), 129.4 (CH), 129.9 (CH), 128.2 (CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 126.0 (CH), 125.9 (CH), 125.5 (CH), 124.6 (CH), 80.4 (C), 79.7 (C), 61.3 (C), 61.0 (C), 32.1 (CH$_2$), 31.1 (CH$_2$), 30.3 (CH$_3$), 29.7 (CH$_2$), 29.5 (CH$_2$), 28.2 (CH$_3$), 28.1 (CH$_3$), 27.9 (CH$_3$), 23.0 (CH$_2$), 21.5 (CH$_2$); HRMS (ES) Found: MH$^+$, 338.2112. C$_{22}$H$_{28}$NO$_2$ requires MH$^+$, 338.2115; LRMS m/z (ES) 338 (5%, MH$^+$), 282 (100%, MH$^+$–t-Bu+H), 238 (10, MH$^+$–Boc+H).
5,5-Dimethyl-6-phenyl-4-oxa-2-azatricyclo[8.4.0.0²,6]tetradeca-1(10),11,13-trien-3-one (120e)

Using general procedure B, carbamate 96 (100 mg, 0.36 mmol), n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and acetone (0.07 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate 120e (66 mg, 70%) as a clear oil; Rf 0.37 [petrol–EtOAc (70:30)]; FT-IR νmax ATR/cm⁻¹ 2965, 2925, 2855, 1745 (C=O), 1165; ¹H NMR (400 MHz, CDCl₃) δ = 7.58 (1H, d, J = 8.0 Hz, CH), 7.45–7.04 (8H, m, 8 × CH), 2.86–2.68 (3H, m, 3 × CH), 2.28–2.17 (1H, m, CH), 1.99–1.88 (1H, m, CH), 1.56 (3H, s, CH₃), 1.36–1.30 (1H, m, CH), 1.02 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 156.6 (C=O), 139.4 (C), 136.5 (C), 136.4 (C), 131.0 (CH), 130.6 (CH), 129.6 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 85.0 (C), 72.3 (C), 36.2 (CH₂), 35.9 (CH₂), 26.2 (CH₃), 21.1 (CH₃), 21.0 (CH₂); HRMS (ES) Found: MH⁺, 308.1648. C₂₀H₂₂NO₂ requires MH⁺, 308.1645; LRMS m/z (ES) 330 (10%, MNa⁺), 308 (100, MH⁺).

5,6-Diphenyl-4-Oxa-2-azatricyclo[8.4.0.0²,6]tetradeca-1(10),11,13-trien-3-one (120f)

Using general procedure B, carbamate 226 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and benzaldehyde (0.09 mL, 0.93 mmol) gave after flash column chromatography on silica gel eluting with petrol–EtOAc (92:7), the carbamate trans-257 (76 mg, 75 %) as as needles; m.p. 93–94 °C; Rf 0.43, 0.24 [petrol–EtOAc (70:300)]; FT-IR νmax ATR/cm⁻¹ 3065, 2925, 2850, 1750, 1390, 1040; ¹H NMR (400 MHz, CDCl₃) δ = 7.50 (1H, d, J = 8 Hz, CH), 7.43–7.26 (9H, m, 9 × CH), 7.16–7.05 (4H, m, 4 × CH), 5.62 (1H, s, OCH), 2.89–2.68 (2H, m, 2 × CH), 1.96–1.83 (3H, m, 3 × CH), 1.56–1.45 (1H, m, CH); ¹³C NMR
(101 MHz, CDCl₃) δ = 156.3 (C=O), 140.0 (C), 137.9 (C), 135.2 (C), 133.0 (C), 130.9 (CH), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.1 (CH), 126.7 (CH), 126.1 (CH), 125.8 (CH), 125.6 (CH), 88.8 (CH), 69.9 (C), 35.3 (CH₂), 33.6 (CH₂), 20.5 (CH₂); HRMS (ES) Found: MH⁺, 356.1645. C₂₄H₂₂NO₂ requires MH⁺, 356.1643; LRMS m/z (ES) 356 (100%, MH⁺).

tert-Butyl 2-(2-(Methoxycarbonyl)phenyl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate (127a)

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.07 mL, 0.91 mmol) gave, after flash column chromatography on silica gel, eluting with petrol‒EtOAc (95:5), the carbamate 127a (71 mg, 68%) as a yellow oil; Rₚ 0.43 [petrol‒EtOAc (60:40)]; FT-IR νmax ATR/cm⁻¹ 2975, 2940, 2860, 1720 (C=O), 1695 (C=O) ; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 7.92 (1H, d, J = 8.0 Hz, CH), 7.64–7.43 (3H, m, 3 × CH), 7.42–7.36 (1H, m, CH), 7.35–7.29 (1H, m, CH), 7.27–7.20 (2H, m, 2 × CH), 5.96 (0.3H, d, J = 12.0 Hz, CH), 5.81 (0.7H, d, J = 12.0 Hz, CH), 3.95 (3H, s, CH₃), 3.07–2.90 (1H, m, CH), 2.67 (1H, dd, J = 13.0, 7.0 Hz, CH), 2.16–2.03 (1H, m, CH), 1.96–1.87 (1H, m, CH), 1.70–1.59 (1H, m, CH), 1.39–1.32 (1H, m, CH), 1.28 (3H, s, t-Bu), 1.18 (6H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃, rotamers) δ = 167.6 (C=O), 167.3 (C=O), 154.7 (C=O), 154.3 (C=O), 150.6 (C), 149.1 (C), 139.7 (C), 139.2 (C), 137.9 (C), 137.2 (C), 132.4 (CH), 132.1 (CH), 130.1 (CH), 130.6 (CH), 129.7 (CH), 129.3 (CH), 128.6 (CH), 128.3 (CH), 127.9 (C), 127.5 (C), 127.1 (CH), 126.9 (CH), 126.8 (CH), 126.3 (CH), 126.0 (CH), 125.7 (CH), 125.5 (CH), 125.3 (CH), 80.1 (C), 80.1 (C), 57.2 (CH), 56.6 (CH), 52.3 (OCH₃), 52.0 (OCH₃), 31.8 (CH₂), 31.5 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 28.2 (CH₃), 27.9 (CH₃), 23.9 (CH₂), 23.8 (CH₂); HRMS (ES) Found: MH⁺, 382.1942. C₂₃H₂₈NO₄ requires MH⁺, 382.1930; LRMS m/z (ES) 382 (100%, MH⁺), 281 (60, MH⁺‒Boc+H).

Alternatively, compound 127a was prepared as follows: Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and
methyl chloroformate (0.07 mL, 0.93 mmol) gave the carbamate 127a (66 mg, 63%) as a yellow oil; data as above.

**tert-Butyl 2,3,4,5-Tetrahydro-2-(2-(phenylthio)phenyl)benzo[b]azepine-1-carboxylate (127b)**

Using general procedure B, carbamate 96 (100 mg, 0.31 mmol), n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and S-phenyl benzenethiosulfonate (0.23 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate 127b (110 mg, 85%) as an amorphous white solid; m.p. 94–96 °C; R_f 0.42 [petrol–EtOAc (60:40)]; FT-IR ν_{max} ATR/cm\(^{-1}\) 2930, 2855, 1670 (C=O), 1151; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) δ = 7.69–7.08 (13H, m, 13 × CH), 5.17 (0.5H, d, J = 12.0 Hz, CH), 4.93 (0.5H, d, J = 12.0 Hz, CH), 3.10–2.88 (1H, m, CH), 2.65 (1H, dd, J = 13.0, 8.0 Hz, CH), 2.04–1.89 (1H, m, CH), 1.83–1.62 (2H, m, 2 × CH), 1.57–1.43 (1H, m, CH), 1.30 (9H, s, t-Bu); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), rotamers) δ = 154.8 (C=O), 154.6 (C=O), 146.5 (C), 145.0 (C), 143.0 (C), 142.7 (C), 138.9 (C), 138.7 (C), 137.3 (C), 137.1 (C), 136.6 (CH), 135.4 (CH), 133.6 (CH), 132.2 (CH), 131.6 (CH), 131.4 (CH), 130.3 (CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.8 (C), 127.7 (C), 127.5 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 126.4 (CH), 126.0 (CH), 125.5 (CH), 125.4 (CH), 80.4 (C), 79.7 (C), 61.0 (CH), 59.3 (CH), 32.1 (CH\(_2\)), 31.1 (CH\(_2\)), 29.7 (CH\(_2\)), 29.5 (CH\(_2\)), 28.3 (CH\(_3\)), 28.2 (CH\(_3\)), 23.6 (CH\(_2\)), 23.0 (CH\(_2\)); HRMS (ES) Found: MH\(^+\), 432.1909. C\(_{27}\)H\(_{30}\)NO\(_2\)S requires MH\(^+\), 432.1906; LRMS m/z (ES) 432 (100%, MH\(^+\)), 331 (45, MH\(^+\)-Boc+H).

**Kinetic Resolution of tert-Butyl 2,3,4,5-Tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (96) in Presence of (+)-Sparteine (Scheme 80)**

n-BuLi (0.12 mL, 0.370 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (94 mg, 0.402 mmol) and N-Boc-2-phenylbenzazepine 96 (100 mg, 0.31 mmol)
in dry toluene (6 mL) at –50 °C. After 3 h, tributyltin chloride (0.25 mL, 0.93 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with petrol/EtOAc (99:1), gave the recovered starting material (S)-96 (57 mg, 57%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 61:39 by CSP HPLC using a Beckman system fitted with a Lux × 3u cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of n-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the major component eluted at 7.7 min; [α]D23 ‒15.0 (1.0, CHCl₃), 61:39 er.

11-Phenyl-1-azatricyclo[9.4.0.0²,7]pentadeca-2(7),3,5-triene (129)

![11-Phenyl-1-azatricyclo[9.4.0.0²,7]pentadeca-2(7),3,5-triene (129)](image)

To a solution of tert-butyl 2-(4-bromobutyl)-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepane-1-carboxylate 120b (100 mg, 0.31 mmol) in CH₂Cl₂ (1 mL) was added trifluoroacetic acid (0.23 mL, 3.90 mmol) and the mixture was allowed to stir for 1 h at room temperature. After this time, the acid was evaporated and the crude mixture was diluted with (2 mL) CH₂Cl₂. Aqueous NaOH (5 mL, 2 M) was added and the mixture was stirred vigorously for 15 min. The organic layer was separated, dried over MgSO₄ and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (95:5), to give the bicyclic product 129 (53 mg, 88%) as a brown oil; Rf 0.46 [petrol–EtOAc (60:40)]; FT-IR νmax ATR/cm⁻¹ 2990, 2875, 2750, 1150; ¹H NMR (400 MHz, CDCl₃) δ = 7.60‒6.82 (9H, m, 9 × CH), 3.55‒3.25 (2H, m, 2 × CH), 3.13‒2.85 (1H, m, CH), 2.79‒2.46 (1H, m, CH), 2.34‒2.08 (1H, m, CH), 1.91‒1.83 (1H, m, CH), 1.76‒1.68 (1H, m, CH), 1.64‒1.47 (5H, m, 5 × CH), 1.35‒1.22 (2H, m, 2 × CH); ¹³C NMR (100 MHz, CDCl₃) δ = 141.9 (C), 137.2 (C), 134.9 (C), 133.8 (CH), 128.5 (CH), 128.2 (CH), 127.0 (CH), 125.7 (CH), 121.0 (CH), 120.2 (CH), 60.4 (C), 47.8 (CH₂), 40.7 (CH₂), 30.6 (CH₂), 29.7 (CH₂), 126
26.2 (CH$_2$), 21.3 (CH$_2$), 19.8 (CH$_2$); HRMS (ES) Found: MH$^+$, 278.1906. C$_{20}$H$_{24}$N requires \(\text{MH}^+\), 278.1903; LRMS \textit{m/z} (ES) 278 (100\%, MH$^+$).

**Methyl 2-(2,3,4,5-Tetrahydro-1H-benzo[b]azepin-2-yl)benzoate (130)**

![Methyl 2-(2,3,4,5-Tetrahydro-1H-benzo[b]azepin-2-yl)benzoate (130)](image)

To a solution of tert-butyl 2-(2-(methoxycarbonyl)phenyl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate 127a (100 mg, 0.26 mmol) in CH$_2$Cl$_2$ (1 mL) was added trifluoroacetic acid (0.20 mL, 2.62 mmol) and the mixture was allowed to stir for 1 h at room temperature. After this time, the acid was evaporated, and the crude mixture was diluted with (2 mL) CH$_2$Cl$_2$. Aqueous NaOH (5 mL, 2 M) was added and the mixture was stirred vigorously for 15 min. The organic layer was separated, dried with MgSO$_4$, and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol‒EtOAc (95:5), to give amine 130 (63 mg, 86\%) as a brown oil; R$_f$ 0.15 [petrol‒EtOAc (70:30)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 3350, 2960, 2920, 1700 (C=O); $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.03$–7.78 (2H, m, 2 × CH), 7.66–7.44 (2H, m, 2 × CH), 7.43–7.34 (1H, m, CH), 7.14–7.04 (1H, m, CH), 6.99–6.69 (2H, m, 2 × CH), 4.50–4.40 (1H, m, CH), 3.86 (3H, s, CH$_3$), 2.95–2.83 (2H, m, 2 × CH), 2.22–2.02 (2H, m, 2 × CH), 1.97–1.83 (1H, m, CH), 1.59–1.51 (1H, m, CH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 168.1$ (C=O), 149.1 (C), 146.3 (C), 138.6 (C), 133.9 (C), 132.3 (CH), 130.6 (CH), 129.8 (CH), 128.2 (CH), 127.0 (CH), 126.8 (CH), 121.3 (CH), 120.3 (CH), 59.2 (CH), 52.2 (CH$_3$), 39.8 (CH$_2$), 35.7 (CH$_2$), 26.5 (CH$_2$); HRMS (ES) Found: MH$^+$, 282.1490. C$_{18}$H$_{20}$NO$_2$ requires MH$^+$, 282.1489; LRMS \textit{m/z} (ES) 282 (100\%, MH$^+$), 250 (15, MH$^+$–OCH$_3$).
(1E)-N,6-Dimethoxy-3,4-dihydro-2H-naphthalen-1-imine (131)

![Chemical Structure](image1)

To a solution of 6-methoxy-1-tetralone 100 (4.87 g, 27.7 mmol) and pyridine (2.67 mL, 33.2 mmol) in methanol (60 mL) was added O-methylhydroxylamine hydrochloride (2.83 g, 33.2 mmol) dropwise. The reaction mixture was stirred under argon for 20 h at room temperature. The solvent was removed under vacuum and the mixture was poured into water (300 mL). Aqueous HCl (100 mL, 1 M) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 × 150 mL). The organic layers were washed with water (300 mL) and dried over Na$_2$SO$_4$. The solvent was removed under vacuum to give the oxime 131 (5.19 g, 91%) as a brown oil; $^0$RF 0.41 [petrol–EtOAc (80:20)]; FT-IR $\nu_{\max}$ ATR/cm$^{-1}$ 2940, 1615, 1590, 1055; $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.95 (1H, d, $J = 9.0$ Hz, CH), 6.78 (1H, dd, $J = 9.0$, 3.0 Hz, CH), 6.66 (1H, d, $J = 3.0$ Hz, CH), 3.99 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$), 2.78–2.70 (4H, m, 4 × CH), 1.90–1.81 (2H, m, 2 × CH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 160.1 (C), 153.8 (C=N), 141.2 (C), 125.8 (CH), 123.4 (C), 112.9 (CH), 112.7 (CH), 61.8 (OCH$_3$), 55.2 (OCH$_3$), 30.1 (CH$_2$), 24.1 (CH$_2$), 21.5 (CH$_2$); HRMS (ES) Found: MH$^+$, 206.1176. C$_{12}$H$_{15}$NO$_2$, requires MH$^+$, 206.1176; LRMS m/z (ES) 206 (100%, MH$^+$), 191 (10, MH$^+$–CH$_3$), 175 (15, MH$^+$–OCH$_3$).

N,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine (115)

![Chemical Structure](image2)

To a solution N,6-dimethoxy-3,4-dihydro-2H-naphthalen-1-imine 131 (10.0 g, 48 mmol) in methanol (100 mL) was added methyl orange which change the solution colour to orange. Sodium cyanoborohydride (3.08 g, 60 mmol) was added dropwise at 15 ºC. The reaction mixture was left to stir and HCl was added portionwise until the solution colour changed to
red. The solution was stirred at room temperature for 24 h then was quenched with aqueous NaOH (50 mL, 2 M) and extracted with CH$_2$Cl$_2$ (4 × 40 mL). The organic layers were combined and washed with water (2 × 40 mL) and brine (20 mL), then dried over MgSO$_4$. The solvent was removed under reduced pressure to give hydroxylamine 115 (6.22 g, 63%) as a brown oil; R$_f$ 0.44 [petrol–EtOAc (90:10)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2940, 3400, 1610; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.26 (1H, d, $J = 8.5$ Hz, CH), 6.75 (1H, dd, $J = 8.5$, 3.0 Hz, CH), 6.65 (1H, d, $J = 3.0$ Hz, CH), 4.10 (1H, t, $J = 4.5$ Hz, CH), 3.79 (3H, s, OCH$_3$), 3.60 (3H, s, OCH$_3$), 2.85–2.68 (2H, m, 2 × CH), 2.20–2.12 (1H, m, CH), 1.84–1.71 (2H, m, 2 × CH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 158.7 (C), 139.9 (C), 130.7 (CH), 126.9 (C), 113.6 (CH), 112.1 (CH), 62.3 (CH$_3$), 57.2 (CH), 55.2 (CH$_3$), 29.7 (CH$_2$), 26.3 (CH$_2$), 18.1 (CH$_2$); HRMS (ES) Found: M$^+$–NHOCH$_3$, 161.0962. C$_{11}$H$_{13}$O requires M$^+$–NHOCH$_3$, 161.0961; LRMS m/z (ES) 161 (100%, M$^+$–NHOCH$_3$).

tert-Butyl 2,3,4,5-Tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate (97)

To a solution $N$-6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine 115 (322 mg, 1.60 mmol) in dry Et$_2$O (10 mL) at 0 ºC was added phenyllithium solution (2.50 mL, 4.80 mmol, 1.9 M in Et$_2$O) dropwise. The reaction mixture was stirred under argon for 2 h, after that a solution of Boc$_2$O (1.00 g, 4.80 mmol) in Et$_2$O (10 mL) was added dropwise. The solution was warmed to room temperature and was stirred overnight. Et$_2$O (10 mL) was added followed by water (20 mL). The organic layers were washed with water (2 × 15 mL), dried over MgSO$_4$, and the solvent was removed under reduced pressure. Purification by flash silica chromatography, eluting with petrol–EtOAc (90:10), gave the carbamate 97 (420 mg, 77%) as colourless crystals, m.p. 98–100 ºC; R$_f$ 0.26 [petrol–EtOAc (80:20)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2930, 1690 (C=O), 1600, 1245, 1150; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 7.38–7.20 (5.5H, m, CH), 7.07 (0.5H, d, $J = 8.5$ Hz, CH), 6.86 (0.5H, dd, $J = 8.5$, 3.0, CH), 6.80–6.72 (1.5H, m, CH), 5.16 (0.5H, dd, $J = 12.0$, 3.0 Hz, CH), 4.91 (0.5H, d, $J = 12.0$ Hz, CH), 3.84 (3H, s, CH$_3$), 3.03–2.88 (1H, m, CH), 2.64–2.54 (1H, m, CH), 2.01–1.89 (1H, m, CH), 1.83–1.65
(2H, m, 2 × CH), 1.56–1.47 (1H, m, CH), 1.33 (4H, s, t-Bu), 1.31 (5H, s, t-Bu); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, rotamers) δ = 158.5 (C), 158.2 (C), 155.1 (C=O), 155.0 (C=O), 138.8 (C), 138.5 (C), 132.2 (C), 132.0 (C), 131.5 (C), 131.4 (C), 130.7 (CH), 130.5 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 114.0 (CH), 113.5 (CH), 111.7 (CH), 111.4 (CH), 79.6 (C), 79.3 (C), 60.8 (CH), 59.1 (CH), 55.4 (OCH\textsubscript{3}), 55.3 (OCH\textsubscript{3}), 32.0 (CH\textsubscript{2}), 31.0 (CH\textsubscript{2}), 30.1 (CH\textsubscript{2}), 29.9 (CH\textsubscript{2}), 28.3 (CH\textsubscript{2}), 28.2 (CH\textsubscript{3}), 23.6 (CH\textsubscript{2}), 22.9 (CH\textsubscript{2}); HRMS (ES) MNa\textsuperscript{+}, 376.1885. C\textsubscript{22}H\textsubscript{27}NO\textsubscript{3}Na requires MNa\textsuperscript{+}, 376.1883; LRMS m/z (ES) 376 (5%, MNa\textsuperscript{+}), 298 (100, MH\textsuperscript{+}–t-Bu+H).

**tert-Butyl 7-methoxy-2-phenyl-2-(tributylstannyl)-4,5-dihydro-3H-1-benzazepine-1-carboxylate (135a)**

![Chemical structure of 135a](image)

Using general procedure C, carbamate \textbf{132} (100 mg, 0.28 mmol), n-BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) and tributyltin chloride (0.22 mL, 0.84 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate \textbf{134a} (118 mg, 65%) as a white solid; m.p. 86–88 °C; R\textsubscript{f} 0.53 [petrol–EtOAc (90:10)]; FT-IR ν\textsubscript{max} ATR/cm\textsuperscript{-1} 2955, 1670 (C=O), 1495, 1170; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ = 7.21 (2H, t, J = 8.0 Hz, 2 × CH), 7.12 (2H, d, J = 8.0 Hz, CH), 6.98 (1H, t, J = 8.0 Hz, CH), 6.89 (1H, d, J = 9.0 Hz, CH), 6.62 (1H, d, J = 3.0 Hz, CH), 6.55 (1H, dd, J = 9.0, 3.0 Hz, CH), 3.74 (3H, s, OCH\textsubscript{3}), 2.95–2.82 (1H, m, CH), 2.57–2.44 (2H, m, 2 × CH), 1.90–1.80 (2H, m, 2 × CH), 1.40–1.30 (16H, m, t-Bu, CH, 3 × CH\textsubscript{2}), 1.28–1.21 (6H, m, 3 × CH\textsubscript{2}), 0.86 (9H, t, J = 7.0 Hz, 3 × CH\textsubscript{3}), 0.82–0.63 (6H, m, 3 × CH\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ = 157.9 (C), 157.1 (C), 139.5 (C), 132.4 (C), 130.8 (CH), 130.1 (C), 128.8 (CH), 127.7 (CH), 123.7 (CH), 113.4 (CH), 110.8 (CH), 79.7 (C) 68.2 (C), 55.1 (CH\textsubscript{3}), 30.3 (CH\textsubscript{2}), 29.0 (CH\textsubscript{2}), 28.3 (CH\textsubscript{3}), 27.7 (CH\textsubscript{2}), 23.7 (CH\textsubscript{2}), 23.0 (CH\textsubscript{2}), 13.7 (CH\textsubscript{3}), 13.4 (CH\textsubscript{2}); HRMS (ES) Found: MNa\textsuperscript{+}, 666.2972. C\textsubscript{34}H\textsubscript{55}NO\textsubscript{3}\textsuperscript{120}SnNa requires MNa\textsuperscript{+}, 666.2945; Found: MNa\textsuperscript{+}, 664.3000. C\textsubscript{34}H\textsubscript{55}NO\textsubscript{3}\textsuperscript{118}SnNa requires MNa\textsuperscript{+}, 664.2940; LRMS m/z (ES) 666 (100%, MNa\textsuperscript{+}), 664 (80, MNa\textsuperscript{+}).
12-methoxy-5,5-dimethyl-6-phenyl-4-oxa-2-azatricyclo[8.4.0.0²,6]tetradeca-1(10),11,13-trien-3-one (134b)

Using general procedure C, carbamate 132 (100 mg, 0.28 mmol), n-BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) and acetone (0.06 mL, 0.84 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (70:30), the carbamate 134c (74 mg, 78%) as a white solid; m.p. 139–142 °C; R_f 0.26 [petrol–EtOAc (60:40)]; FT-IR ν_{max} ATR/cm⁻¹ 2935, 1750 (C=O), 1610, 1270, 1160; ^1H NMR (400 MHz, CDCl₃) δ = 7.48 (1H, d, J = 9.0 Hz, CH), 7.44–7.30 (2H, m, 2 × CH), 7.26–7.11 (3H, m, 3 × CH), 6.86 (1H, dd, J = 9.0, 3.0 Hz, CH), 6.59 (1H, d, J = 3.0 Hz, CH), 3.77 (3H, s, OCH₃), 2.86–2.74 (2H, m, 2 × CH), 2.67 (1H, dd, J = 13.0, 6.0 Hz, CH), 2.27–2.16 (1H, m, CH), 1.98–1.89 (1H, m, CH), 1.54 (3H, s, CH₃), 1.35–1.30 (1H, m, CH), 1.01 (3H, s, CH₃); ^13C NMR (100 MHz, CDCl₃) δ = 158.4 (C), 156.9 (C=O), 141.1 (C), 136.4 (C), 132.2 (CH), 129.2 (C), 128.2 (CH), 127.9 (CH), 127.4 (CH), 115.5 (CH), 112.2 (CH), 84.8 (C), 71.9 (C), 55.3 (OCH₃), 36.4 (CH₂), 36.1 (CH₂), 26.1 (CH₃), 21.2 (CH₂), 21.0 (CH₃); HRMS (ES) Found: MH⁺, 338.1757. C₂₁H₂₄NO₃ requires MH⁺, 338.1751; LRMS m/z (ES) 360 (10%, MNa⁺), 338 (100, MH⁺).

tert-Butyl 2-(2-(Ethoxycarbonyl)phenyl)-7-methoxy-2,3,4,5-tetrahydro-1-benzazepine-1-carboxylate (135)

Using general procedure C, carbamate 132 (100 mg, 0.28 mmol), n-BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) and ethyl chloroformate (0.08 mL, 0.84 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (70:30), the carbamate 134c (72 mg, 60%) as a brown oil; R_f 0.52 [petrol–EtOAc (70:30)]; FT-IR ν_{max} ATR/cm⁻¹ 2980, 1695 (C=O), 1500, 1270, 1160; ^1H NMR (400 MHz, CDCl₃, rotamers) δ = 7.91 (1H, d, J =
Kinetic Resolution of tert-Butyl 2,3,4,5-Tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate (97) in Presence of (+)-Sparteine (Scheme 93)

$n$-BuLi (0.14 mL, 0.34 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (86 mg, 0.37 mmol) and N-Boc-2-phenyl-7-methoxybenzazepine 97 (100 mg, 0.28 mmol) in dry toluene (6 mL) at −50 °C. After 3 h, tributyltin chloride (0.23 mL, 0.85 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with petrol/EtOAc (99:1), gave the recovered starting material (S)-97 (46 mg, 46%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 57:43 by CSP HPLC using a Beckman system fitted with a Lux × 3u cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of $n$-hexane/isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the major component eluted at 13.1 min; $[\alpha]_D^{22}$ −12.5 (0.75, CHCl₃), 57:43 er.
**tert-Butyl 2-Oxopiperidine-1-carboxylate (145)**

![Chemical Structure](image)

To a solution of piperidin-2-one 144 (5.00 g, 50.4 mmol) and \(N,N\)-dimethylpyridin-4-amine (6.77 g, 55.5 mmol) in dry THF (60 mL) at room temperature was added di-\(t\)-butyl dicarbonate (12.74 g, 55.5 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature under nitrogen for 3 h. The reaction mixture was concentrated under vacuum, and diluted with EtOAc (30 mL), before being washed with 0.5 M HCl (3 × 30 mL), saturated brine solution (3 × 25 mL) and saturated NaHCO\(_3\) solution (3 × 25 mL). The organic layer was dried over MgSO\(_4\), filtered and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol–EtOAc (75:25), gave the carbamate 145 (8.6 g, 86%) as a clear oil; \(R_f\) 0.51 [petrol–EtOAc (60:40)]; FT-IR \(v_{_{\text{max}}}\) ATR/cm\(^{-1}\) 2980, 2955, 2895, 1770 (C=O), 1700 (C=O), 1130; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 3.68\text{–}3.46 (2H, m, N\text{-}CH}_2\), 2.62\text{–}2.26 (2H, m, 2 \times \text{CH}), 1.86 \text{–}1.65 (4H, m, 4 \times \text{CH}), 1.44 (9H, s, \text{-}t\text{-}Bu); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 171.3\) (C=O), 152.5 (C=O), 82.6 (C), 46.2 (CH\(_2\)), 34.8 (CH\(_2\)), 27.9 (CH\(_3\)), 22.7 (CH\(_2\)), 20.4 (CH\(_2\)); HRMS (ES) Found: MH\(^+\), 200.1007. C\(_{10}\)H\(_{18}\)NO\(_3\) requires MH\(^+\), 200.1003; LRMS m/z (ES) 118 (100%, MH\(^+\)\text{--}t\text{-}Bu\text{+}H). Data in accordance with the literature.\(^{130}\)

**tert-Butyl 2-Hydroxypiperidine-1-carboxylate (146)**

![Chemical Structure](image)

To a solution of carbamate 145 (8.60 g, 43.1 mmol) in dry THF (120 mL) at \(-78\) °C was added DIBAL-H (60.4 mL, 60.4 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at \(-78\) °C under nitrogen for 1 h, before gradually warming to room temperature over a further 1 h. The reaction was carefully quenched with saturated aqueous potassium...
acetate solution (30 mL). The solids were filtered off and were washed with EtOAc (3 × 25 mL). The organic layers were combined, washed with saturated brine solution (4 × 25 mL), dried over MgSO4 and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol– EtOAc (75:25), gave the carbamate 146 (7.1 g, 83%) as a clear oil; Rf 0.44 [petrol–EtOAc (60:40)]; FT-IR νmax ATR/cm⁻¹ 3420 (OH), 2980, 2940, 2860, 1670 (C=O), 1160; 1H NMR (400 MHz, CDCl3) δ = 5.88–5.49 (1H, m, NCH), 3.88–3.71 (1H, m, NCH), 3.14–3.05 (1H, m, NCH), 1.91–1.83 (1H, m, CH), 1.79–1.65 (2H, m, 2 × CH), 1.64–1.53 (2H, m, 2 × CH), 1.51–1.41 (10H, m, t-Bu, CH); 13C NMR (100 MHz, CDCl3) δ = 155.5 (C=O), 80.1 (C), 74.7 (CH), 39.3 (CH2), 30.4 (CH2), 28.4 (CH3), 24.7 (CH2), 17.7 (CH2); HRMS (ES) Found: MNa+, 224.1261. C10H19NO3Na requires MNa+, 224.1257; LRMS m/z (ES) 128 (100%, MH+-t-Bu+H, OH). Data in accordance with the literature.130

tert-Butyl 2-(1H-Benzo[d][1,2,3]triazol-1-yl)piperidine-1-carboxylate (147)

To a solution of carbamate 146 (7.00 g, 34.8 mmol) in toluene (100 mL) was added benzotriazol (6.21 g, 52.2 mmol) and MgSO4 (1.0 g). The reaction mixture was heated to reflux for 18 h then allowed to cool to room temperature, before washing with saturated aqueous NaCO3 solution (3 × 30 mL) and saturated brine solution (3 × 30 mL). The organic layer was dried over MgSO4 and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (75:25), to give the carbamate 147a,b (10.2 g, 97%) as a mixture of isomers (ratio 1:0.6) as a white solid; m.p. 70-72 ºC; Rf 0.42, 0.60 [petrol-EtOAc (80:20)]; FT-IR νmax ATR/cm⁻¹ 2970, 2930, 2860, 1690 (C=O), 1160, 1110; 1H NMR (400 MHz, CDCl3, mixture of isomers) δ = 8.09–7.32 (4H, m, 4 × CH), 6.94–6.77 (1H, m, CH), 4.26–3.86 (1H, m, CH), 3.67–3.43 (0.4H, m, CH), 3.33–3.10 (0.4H, m, CH), 3.03–2.90 (0.6H, m, CH), 2.88–2.69 (0.4H, m, CH), 2.65–2.55 (0.6H, m, CH), 2.50–2.25 (0.6H, m, CH), 2.20–2.04 (1H, m, CH), 1.88–1.74 (2H, m, CH), 1.70–1.62 (1H, m, CH), 1.49 (2H, s, t-Bu), 1.47 (7H, s, t-Bu); 13C NMR (100 MHz, CDCl3,
mixture of isomers) δ = 155.4 (C=O), 154.3 (C=O), 145.6 (C), 144.0 (C), 132.7 (C), 131.6 (C), 127.3 (CH), 126.1 (CH) 123.9 (CH), 119.6 (CH), 118.4 (CH), 110.7 (CH), 105.6 (CH), 105.1 (CH), 81.1 (C), 80.9 (C), 66.5 (CH), 64.2 (CH), 41.4 (CH$_2$), 40.2 (CH$_2$), 29.2 (CH$_2$), 28.7 (CH$_2$), 28.3 (CH$_3$), 28.2 (CH$_3$), 24.6 (CH$_2$), 24.1 (CH$_2$), 19.4 (CH$_2$), 18.1 (CH$_2$); HRMS (ES) Found: MNa$^+$, 325.1638. C$_{16}$H$_{22}$N$_4$O$_2$Na requires MNa$^+$, 325.1640; LRMS $m/z$ (ES) 128 (100%, MH$^+$$\text{-t-Bu}$$+$$H$, C$_6$H$_4$N$_3$). Data in accordance with the literature.¹³⁰

**tert-Butyl 2-Vinylpiperidine-1-carboxylate (136)**

![tert-Butyl 2-Vinylpiperidine-1-carboxylate (136)](image)

To a solution of carbamate 147a,b (5.00 g, 16.5 mmol) in dry THF (40 mL) at 0 ºC was added vinylmagnesium bromide solution (66.2 mL, 66.2 mmol, 1 M in THF) dropwise. The reaction mixture was stirred under argon for 20 h, slowly warming to room temperature, then diluted with a saturated solution of NH$_4$Cl (10 mL) and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated brine solution (4 × 25 mL), dried over MgSO$_4$, and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol–EtOAc (97:3), gave the carbamate 136 (0.95 g, 27%) as a colourless oil; R$_f$ 0.69 [petrol–EtOAc (80:20)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2970, 2935, 2860, 1690 (C=O), 1670 (C=C), 1445; $^1$H NMR (400 MHz, CDCl$_3$) δ = 5.76 (1H, ddd, $J$ = 16.0, 10.5, 4.0 Hz, CH=CH$_2$), 5.18 (1H, dt, $J$ = 10.5, 1.5 Hz, CH=CH$_2$), 5.04 (1H, dt, $J$ = 16.0, 1.5 Hz, CH=CH$_2$), 4.84–4.76 (1H, m, NCH), 3.95 (1H, br d, $J$ = 13.0 Hz, NCH), 2.83 (1H, td, $J$ = 13.0, 3.0 Hz, NCH), 1.77–1.54 (6H, m, 6 × CH), 1.45 (9H, s, t-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 155.5 (C=O), 136.9 (=CH), 115.4 (=CH$_2$), 79.2 (C), 52.6 (NCH), 39.8 (NCH$_2$), 28.9 (CH$_2$), 28.4 (CH$_3$), 25.5 (CH$_2$), 19.4 (CH$_2$); HRMS (ES) Found: MNa$^+$, 234.1463. C$_{12}$H$_{21}$NO$_2$Na requires MNa$^+$, 234.1465; LRMS $m/z$ (ES) 156 (100%, MH$^+$$\text{-t-Bu}$$+$$H$). Data in accordance with the literature.¹³¹
**tert-Butyl (2Z)-[2-(Tributylstannyl)ethylidene]piperidine-1-carboxylate (149)**

To a solution of tert-butyl 2-ethenylpiperidine-1-carboxylate 136 (100 mg, 0.47 mmol) in dry THF (2 mL) at −50 °C under nitrogen, was added n-BuLi (0.25 mL, 0.57 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.45 mL, 1.42 mmol) was added. The mixture was allowed to warm gradually warming to room temperature overnight. MeOH (1 mL) was added and the mixture was absorbed onto silica. Purification by flash column chromatography, eluting with petrol–Et₂O (98:2), gave the carbamate 149 (164 mg, 69%) as a yellow oil; Rf 0.72 [petrol–Et₂O (60:40)]; FT-IR νmax ATR/cm⁻¹ 2960, 2920, 2850, 1695 (C=O), 1660 (C=C); ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 5.57–5.00 (1H, m, =CH), 4.30 (0.62H, d, J = 12.0 Hz, NCH), 3.45 (0.38H, br s, NCH), 2.62 (0.62H, t, J = 12.0 Hz, NCH), 2.19–1.98 (2H, m, 2 × CH), 1.88–1.74 (1.38H, m, CH), 1.71–1.63 (2H, m, 2 × CH), 1.52–1.43 (15H, m, t-Bu, 6 × CH), 1.38–1.26 (9H, m, 9 × CH), 0.94–0.85 (15H, m, 17 × CH); ¹³C NMR (100 MHz, CDCl₃, rotamers, one CH₃ overlaps) δ = 154.1 (C=O), 153.7 (C=O), 132.9 (C), 131.8 (C), 122.0 (CH), 120.9 (CH), 79.0 (C), 78.9 (C) 47.3 (CH₂), 46.1 (CH₂), 33.3 (CH₂), 32.9 (CH₂), 29.6 (CH₂), 29.1 (CH₂), 28.4 (CH₃), 27.8 (CH₂), 27.3 (CH₂), 26.8 (CH₂), 26.5 (CH₂), 26.0 (CH₂), 25.7 (CH₂), 19.1 (CH₂), 17.5 (CH₂), 13.7 (CH₃), 13.6 (CH₃), 9.8 (CH₂), 9.3 (CH₂); HRMS (ES) Found: MH⁺, 502.2716. C₂₄H₄₈NO₂¹²⁰Sn requires MH⁺, 502.2707; Found: MH⁺, 500.2733. C₂₄H₄₈NO₂¹¹₈Sn requires MH⁺, 500.2733; LRMS m/z (ES) 502 (100%, MH⁺), 500 (70, MH⁺), 444 (30, MH⁺–t-Bu+H), 442 (20, MH⁺–t-Bu+H).

**Kinetic Resolution of tert-butyl 2-vinylpiperidine-1-carboxylate (136) in Presence of (+)-Sparteine (Scheme 104)**

n-BuLi (0.15 mL, 0.38 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (101 mg, 0.42 mmol) and N-Boc 2-vinylpiperidine 136 (100 mg, 0.47 mmol) in dry toluene (6 mL) at −78 °C. After 3 h, tributyltin chloride (0.38 mL, 1.41 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with
petrol/EtOAc (97:2), gave the recovered starting material 136 (43 mg, 43%) as colourless oil; data as above; the enantiomeric ratio was not determined.

**tert-Butyl 2-(2-Phenylethynyl)piperidine-1-carboxylate (137)**

To a solution of carbamate 147a,b (4.00 g, 13.2 mmol) in dry THF (40 mL) at 0 °C was added phenylethynylmagnesium bromide (52.95 mL, 52.95 mmol, 1 M in THF) dropwise. The reaction mixture was stirred under argon for 1 h at room temperature, then heated at 66 °C for 48 h, then cooled to room temperature, diluted with a saturated solution of NH₄Cl (10 mL) and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated brine solution (4 × 25 mL), dried over MgSO₄ and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with petrol–EtOAc (95:5), gave the carbamate 137 (2.65 g, 70%) as needles, m.p. 82–84 °C (reported as oil); Rf 0.60 [petrol–EtOAc (80:20)]; FT-IR νmax ATR/cm⁻¹ 2975, 2940, 2860, 1690 (C=O), 1405, 1155; ¹H NMR (400 MHz, CDCl₃) δ = 7.47–7.41 (2H, m, 2 × CH), 7.34–7.29 (3H, m, 3 × CH), 5.31 (1H, br s, NCH), 3.98 (1H, d, J = 13.0 Hz, NCH), 3.13 (1H, br t, J = 13.0 Hz, NCH), 1.95–1.80 (2H, m, 2 × CH), 1.79–1.63 (3H, m, 3 × CH), 1.50 (9H, s, t-Bu), 1.48–1.37 (1H, m, CH); ¹³C NMR (100 MHz, CDCl₃) δ = 154.7 (C=O), 131.7 (CH), 128.2 (CH), 128.0 (CH), 123.2 (C), 87.6 (C), 84.0 (C), 79.9 (C), 43.9 (NCH), 40.5 (CH₂), 30.7 (CH₂), 28.4 (CH₃), 25.4 (CH₂), 20.1 (CH₂); HRMS (ES) Found: MNa⁺, 308.1627. C₁₈H₂₃NO₂Na requires MNa⁺, 308.1621; LRMS m/z (ES) 230 (100%, MH⁺–t-Bu+H), 186 (10, MH⁺–Boc+H). Data in accordance with the literature.
**tert-Butyl 2-[(E)-2-(Tributylstannyl)-2-phenylethenyl]-5,6-dihydro-4H-pyridine-1-carboxylate (151a)**

To a solution of carbamate 137 (100 mg, 0.35 mmol) in dry THF (2 mL) at –78 °C under nitrogen, was added n-BuLi (0.18 mL, 0.42 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.28 mL, 1.05 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (97:3), to give the carbamate 151a (149 mg, 74%) as a yellow oil; R₂ 0.65 [petrol–EtOAc (80:20)]; FT-IR νmax ATR/cm⁻¹ 2955, 2930, 2870, 1690 (C=O), 1635 (C=C), 1160; ¹H NMR (400 MHz, CDCl₃) δ = 7.35–7.10 (5H, m, 5 × CH), 6.77 (1H, br s, =CH), 5.15 (1H, td, J = 4.0, 1.5 Hz, =CH), 3.65–3.61 (2H, m, 2 × CH), 2.38–2.09 (2H, m, 2 × CH), 1.88–1.79 (2H, m, 2 × CH), 1.49–1.38 (15H, m, t-Bu, 6 × CH), 1.32–1.24 (6H, m, 6 × CH), 0.96–0.89 (6H, m, 6 × CH), 0.86 (9H, t, J = 7 Hz, 3 × CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 153.8 (C=O), 147.0 (C), 143.2 (C), 142.6 (CH), 140.5 (C), 128.0 (CH), 126.7 (CH), 125.4 (CH), 112.2 (CH), 80.7 (C), 43.9 (CH₂), 29.1 (CH₂), 28.5 (CH₃), 27.4 (CH₂), 23.8 (CH₂), 23.4 (CH₂), 13.6 (CH₃), 11.9 (CH₂); HRMS (ES) Found: MNa⁺, 598.2700. C₃₀H₄₈NO₂¹²⁰SnNa requires MNa⁺, 598.2683; Found: MNa⁺, 596.2708. C₃₀H₄₉NO₂¹¹⁸SnNa requires MNa⁺, 596.2708; LRMS m/z (ES) 598 (45%, MNa⁺), 596 (30, MNa⁺), 356 (100).

**tert-Butyl 2-[(1Z)-2-phenylprop-1-en-1-yl]-5,6-dihydro-4H-pyridine-1-carboxylate (151b)**

To a solution of carbamate 137 (100 mg, 0.35 mmol) in dry THF (2 mL) at –78 °C under nitrogen, was added n-BuLi (0.175 mL, 0.42 mmol, 2.4 M in hexanes). After stirring for 10 minutes, iodomethane (0.065 mL, 1.05 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was
evaporated and the crude mixture was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (97:3), to give the carbamate 151b (85 mg, 82%) as a clear oil; Rf 0.53 [petrol–Et2O (60:40)]; FT-IR v_{max} ATR/cm^{−1} 2980, 2925, 2860, 1700 (C=O), 1600 (C=C), 1160; ^1H NMR (400 MHz, CDCl₃, mixture of isomer E:Z, approximately 1:9) δ = 7.47–7.44 (0.3H, m, CH), 7.36–7.27 (3.8H, m, CH), 7.22–7.16 (0.9H, m, CH), 6.25 (0.1H, br s, =CH), 5.92 (0.9H, br s, =CH), 5.15 (0.1H, td, J = 4.0, 1.0 Hz, =CH), 4.74 (0.9H, br t, J = 4.0 Hz, =CH), 3.65–3.62 (0.2H, m, NCH), 3.46–3.40 (1.8H, m, NCH), 2.20 (0.3H, s, CH₃), 2.10 (2.7H, s, CH₃), 1.94–1.89 (1.8H, m, CH), 1.87–1.84 (0.2H, m, CH), 1.73–1.66 (2H, m, 2 × CH), 1.48 (8.1H, s, t-Bu), 1.38 (0.9H, s, t-Bu); ^13C NMR (100 MHz, CDCl₃, the major isomer reported) δ = 153.7 (C=O), 142.2 (C), 136.0 (C), 134.3 (C), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.3 (CH), 115.4 (CH), 80.1 (C), 43.6 (CH₂), 28.4 (CH₃), 25.4 (CH₃), 23.2 (CH₂), 23.1 (CH₂); HRMS (ES) Found: MH⁺, 322.1780. C_{19}H_{25}NO₂Na requires MNa⁺, 322.1778; LRMS m/z (ES) 322 (5%, MH⁺), 244 (100, MH⁺–t-Bu+H).

**tert-Butyl 2-[(1E)-3-Hydroxy-3-methyl-2-phenylbut-1-en-1-yl]-5,6-dihydro-4H-pyridine-1-carboxylate (151c)**

To a solution of carbamate 137 (100 mg, 0.35 mmol) in dry THF (2 mL) at −78 °C under nitrogen, was added n-BuLi (0.18 mL, 0.42 mmol, 2.4 M in hexanes). After stirring for 10 minutes, acetone (0.06 mL, 1.05 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate 151c (97 mg, 81%) as a brown oil; Rf 0.33 [petrol–EtOAc (60:40)]; FT-IR v_{max} ATR/cm^{−1} 3385, 2980, 2920, 2850, 1690 (C=O), 1640 (C=C),1155; ^1H NMR (400 MHz, CDCl₃, mixture of isomer E:Z, 9:1) δ = 7.39–7.37 (0.4H, m, CH), 7.33–7.29 (2H, m, 2 × CH), 7.26–7.21 (0.9H, m, CH), 7.19–7.15 (1.7H, m, CH), 6.80 (0.1H, br s, =CH), 6.37 (0.9H, d, J = 1.5 Hz, =CH), 4.77 (0.9H, br t, J = 4.0 Hz, =CH), 4.73–4.67 (0.1H, m, =CH), 3.15–3.12 (0.2H, m, CH), 3.12–3.07 (1.8H, m, CH), 1.90–1.85 (2H, m, 2 × CH), 1.60–1.55 (2H, m, 2 × CH), 1.51 (8.1H, s, t-Bu), 1.46 (0.9H, s, t-
Bu), 1.41 (0.6H, s, CH₃), 1.39 (5.4H, s, CH₃);¹³C NMR (100 MHz, CDCl₃) δ = 156.2 (C=O), 146.0 (C), 139.6 (C), 135.7 (C), 129.5 (CH), 127.7 (CH), 126.5 (CH), 124.1 (CH), 116.4 (CH), 80.2 (C), 73.1 (C), 43.5 (CH₂), 28.5 (CH₃), 25.6 (CH₂), 23.0 (CH₂); HRMS (ES) Found: MH⁺, 344.4600. C₂₁H₃₀NO₃ requires MH⁺, 344.2142; LRMS m/z (ES) 344 (30%, MH⁺), 243 (20, MH⁺‒Boc+H), 210 (100).

tert-Butyl 2-[(Z)-2-Phenylethenyl]-5,6-dihydro-4H-pyridine-1-carboxylate (151d)

To a solution of carbamate 137 (100 mg, 0.35 mmol), n-BuLi (0.175 mL, 0.42 mmol, 2.4 M in hexanes) at −78 °C, after 10 min MeOH (1mL) was added. The reaction mixture was allowed to warm to room temp. and then was stirred at room temperature under nitrogen for 16 h. Purification by flash silica chromatography, eluting with petrol–EtOAc (97:3), gave the carbamate 151d (91 mg, 91%) as yellow oil; Rf 0.55 [petrol – Et₂O (60:40)]; FT-IR νmax ATR/cm⁻¹ 2960, 2920, 2865, 1695 (C=O), 1610 (C=C), 1160; ¹H NMR (400 MHz, CDCl₃, mixture of isomer E:Z, nearly 1:12) δ = 7.43–7.39 (2H, m, CH), 7.30–7.24 (2.08H, m, CH), 7.20–7.15 (0.92H, m, CH), 6.63 (0.08H, d, J = 16 Hz, =CH), 6.57 (0.08H, d, J = 16 Hz, =CH), 6.29 (0.92H, d, J = 12.0 Hz, =CH), 6.06 (0.92H, dd, J = 12.0, 1.0 Hz, =CH), 5.48 (0.08H, br t, J = 4.0 Hz, =CH), 5.16 (0.92H, td, J = 4.0, 1.0 Hz , =CH), 3.64–3.61 (0.16H, m, NCH), 3.59–3.55 (1.84H, m, NCH), 2.30–2.25 (0.16H, m, CH), 2.08–2.03 (1.84H, m, CH), 1.83–1.77 (2H, m, 2 × CH), 1.42 (9H, s, t-Bu);¹³C NMR (100 MHz, CDCl₃, the major isomer reported) δ = 153.6 (C=O), 137.5 (C), 135.6 (C), 131.7 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 115.2 (CH), 80.7 (C), 43.7 (CH₂), 28.2 (CH₃), 23.2 (CH₂), 23.1 (CH₂); HRMS (ES) Found: MH⁺, 286.1802. C₁₈H₂₄NO₂ requires MH⁺, 286.1802; LRMS m/z (ES) 286 (5%, MH⁺), 230 (100, MH⁺‒t-Bu+H).

Alternatively, compound 151d was prepared as follows:

To a solution of tert-butyl 2-[(E)-2-(tributylstannyl)-2-phenylethenyl]-5,6-dihydro-4H-pyridine-1-carboxylate 151a (100 mg, 0.17 mmol) in THF (2 mL), n-BuLi (0.086 mL, 0.21 mmol, 2.4 M in hexanes) at −78 °C was added. After 10 min MeOH (1 mL) was added. The reaction mixture was stirred at room temperature under nitrogen for 16 h. The reaction
mixture was purified by flash silica chromatography as above to give the carbamate 151d (62 mg, 60%) as a mixture of isomers E:Z, nearly 1:12, as yellow oil, data as above.

tert-Butyl 2-[2-(Tributylstannyl)-2-phenylethenylidene]piperidine-1-carboxylate (152)

![Chemical structure](image)

To a solution of carbamate 137 (100 mg, 0.35 mmol) in dry THF (2 mL) at −78 ºC under nitrogen was added n-BuLi (0.18 mL, 0.42 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.28 mL, 1.05 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel, and eluting with petrol‒EtOAc‒Et₃N (97:2:1), to give the carbamate 152 (110 mg, 55%) as an unstable yellow oil; Rₐ 0.63 [petrol‒EtOAc (80:20)]; FT-IR νmax ATR/cm⁻¹ 2960, 2920, 1695 (C=O), 1645 (C=C), 1150; ¹H NMR (400 MHz, CDCl₃) δ = 7.31–7.25 (4H, m, 4 × CH), 7.21–7.13 (1H, m, CH), 4.08 (1H, br d, J = 12.0 Hz, CH), 3.08 (1H, br t, J = 12.0 Hz, CH), 2.43–2.22 (2H, m, 2 × CH), 1.94–1.86 (1H, m, CH), 1.72–1.67 (1H, m, CH), 1.65–1.59 (2H, m, 2 × CH), 1.38–1.31 (6H, m, 3 × CH₂), 1.24 (9H, m, t-Bu), 1.15–0.99 (6H, m, 3 × CH₂), 0.94–0.79 (15H, m, 3 × CH₃, 3 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ = 200.6 (C), 154.2 (C=O), 139.0 (C), 128.5 (CH), 128.2 (CH), 126.1 (CH), 103.7 (C), 103.2 (C), 79.7 (C), 46.2 (CH₂), 30.6 (CH₂), 29.0 (CH₂), 28.5 (CH₃), 27.3 (CH₂), 25.7 (CH₂), 25.5 (CH₂), 13.8 (CH₃), 11.2 (CH₂); HRMS (ES) Found: MH⁺, 598.4300. C₃₀H₄₉NO₂¹²⁰SnNa requires MNa⁺, 598.2810; Found: MH⁺, 596.4310. C₃₀H₄₉NO₂¹¹⁸SnNa requires MNa⁺, 596.4310; LRMS m/z (ES) 598 (100%, MNa⁺), 596 (75, MNa⁺).
Kinetic Resolution of tert-Butyl 2-(2-Phenylethynyl)piperidine-1-carboxylate (137) in Presence of (+)-Sparteine (Scheme 115)

$n$-BuLi (0.11 mL, 0.28 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (73 mg, 0.32 mmol) and $N$-Boc 2-(2-Phenylethynyl)piperidine 137 (100 mg, 0.35 mmol) in dry toluene (6 mL) at –78 °C. After 3 h, tributyltin chloride (0.28 mL, 1.05 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with petrol/EtOAc (97:3), gave the recovered starting material (S)-137 (35 mg, 35%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 80:20 by CSP HPLC using a Beckman system fitted with a phenomenex Lux Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of $n$-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the major component eluted at 16.0 min; $\left[\alpha\right]_{D}^{23}$ –4.8 (3.75, CHCl$_3$), 80:20 er.

tert-Butyl 2-[(Z)-2-phenylethenyl]piperidine-1-carboxylate (138)

To a solution of 137 (1.00 g, 3.50 mmol) in dry MeOH (15 mL) was added 1 drop of quinoline followed by Lindlar’s catalyst (500 mg) at room temp. The reaction flask was evacuated, purged with hydrogen five times, and then stirred under a hydrogen atmosphere for 16 h. The reaction mixture was filtered over Celite and washed with MeOH/CH$_2$Cl$_2$ (50 mL). The solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (97:3), to give the carbamate 138 (730 mg, 73%) as a colourless oil; R$_f$ 0.5 [petrol–Et$_2$O (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2970, 2935, 2860, 1695 (C=O), 1615 (C=C), 1400; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.37–7.27 (4H, m, $4 \times$ CH), 7.26–7.21 (1H, m, CH), 6.50 (1H, d, $J = 12.0$ Hz, =CH), 5.99 (1H, dd, $J = 12.0, 10.0$ Hz, =CH), 5.54–5.13 (1H, m, CH), 3.99 (1H, br d, $J = 12.0$ Hz, CH), 2.99 (1H, td, $J = 12.0, 2.5$ Hz, CH), 1.84–1.74 (2H, $2 \times$ CH), 1.70–1.63 (2H, $2 \times$ CH), 1.51–1.44 (2H,
m, 2 × CH), 1.25 (9H, m, t-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 155.2 (C=O), 136.8 (C), 129.5 (CH), 129.2 (CH), 128.6 (CH), 128.2 (CH), 126.9 (CH), 79.3 (C), 48.6 (CH), 39.3 (CH$_2$), 30.4 (CH$_2$), 28.1 (CH$_3$), 25.4 (CH$_2$), 19.7 (CH$_2$); HRMS (ES) Found: MH$^+$, 288.1963. 

C$_{18}$H$_{26}$NO$_2$ requires MH$^+$, 288.1958; LRMS m/z (ES) 288 (5%, MH$^+$), 232 (65, MH$^+$–t-Bu+H), 171 (50, MH$^+$–Boc+H), 128 (100).

tert-Butyl (2Z)-2-[2-Phenyl-2-(tributylstannyl)ethylidene]piperidine-1-carboxylate (158)

To a solution of carbamate 138 (80 mg, 0.28 mmol) in dry THF (2 mL) at $-78{^\circ}$C under nitrogen was added $n$-BuLi (0.14 mL, 0.33 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.23 mL, 0.83 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the crude was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the carbamate 158 (116 mg, 58%) as a clear oil; $R_f$ 0.85 [petrol–EtOAc (80:20)]; FT-IR $\nu_{\text{max}}$ ATR/cm$^{-1}$ 2960, 2925, 1690 (C=O), 1640 (C=C), 1160; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 7.21–7.15 (2H, m, 2 × CH), 7.06–6.92 (3H, m, 3 × CH), 5.88–5.72 (1H, m, =CH), 4.38 (0.75H, d, $J$ = 12.0 Hz, CH), 3.83–3.61 (1H, m, CH), 2.69–2.60 (0.75H, m, CH), 2.35–2.16 (1.25H, m, CH), 2.13–2.03 (0.75H, m, CH), 2.00–1.78 (1H, m, CH), 1.60–1.49 (3.5H, m, CH), 1.43–1.33 (6H, m, 3 × CH$_2$), 1.31–1.07 (15H, m, t-Bu, 3 × CH$_2$), 0.89–0.78 (15H, m, 3 × CH$_2$, 3 × CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 153.9 (C), 144.7 (C), 132.3 (C), 128.2 (CH), 125.4 (CH), 123.1 (CH), 122.6 (CH), 79.4 (C), 46.3 (CH$_2$), 34.2 (CH), 33.5 (CH$_2$), 28.9 (CH$_2$), 27.8 (CH$_3$), 27.4 (CH$_2$), 27.1 (CH$_2$), 25.7 (CH$_2$), 13.6 (CH$_3$), 9.7 (CH$_2$); HRMS (ES) Found: MH$^+$, 578.4412. C$_{30}$H$_{52}$NO$_2^{120}$Sn requires MH$^+$, 578.2912; Found: MH$^+$, 576.4400. C$_{30}$H$_{52}$NO$_2^{118}$Sn requires MH$^+$, 576.2910; LRMS m/z (ES) 578 (100%, MH$^+$), 576 (80, MH$^+$).
Kinetic Resolution of tert-Butyl 2-[(Z)-2-phenylethenyl]piperidine-1-carboxylate (138) in Presence of (+)-Sparteine (Scheme 120)

n-BuLi (0.11 mL, 0.28 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (89 mg, 0.38 mmol) and N-Boc-2-[(Z)-2-phenylethenyl]piperidine 138 (100 mg, 0.35 mmol) in dry toluene (6 mL) at –78 °C. After 3 h, tributyltin chloride (0.28 mL, 1.04 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and then MeOH (1.0 mL) was added. Purification by flash column chromatography on silica gel, eluting with petrol/EtOAc (97:3), gave the recovered starting material (S)-138 (45 mg, 45%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 79:21 by CSP HPLC using a Beckman system fitted with a phenomenex Lux Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of n-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL/min, ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the major component eluted at 12.5 min; \([α]_D^{23} –46.6 \text{ (0.75, CHCl}_3\), 79:21 er. 
Appendices

Appendix 6.1: X-ray crystal structures

Appendix 6.1a: X-ray crystal structure determination data of compound *trans-73g*

![Structure of trans-73g](image_url)

### Table 1 Crystal data and structure refinement for oic287v_0m.

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<th>Value</th>
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<tbody>
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</tr>
<tr>
<td>Empirical formula</td>
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<tr>
<td>Formula weight</td>
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<td>Temperature/K</td>
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<tr>
<td>Crystal system</td>
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<tr>
<td>Space group</td>
<td>P2_1/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>7.1861(4) Å</td>
</tr>
<tr>
<td>α</td>
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</tr>
<tr>
<td>b</td>
<td>12.9276(7) Å</td>
</tr>
<tr>
<td>β</td>
<td>94.0032(2)°</td>
</tr>
<tr>
<td>c</td>
<td>17.0022(9) Å</td>
</tr>
<tr>
<td>γ</td>
<td>90°</td>
</tr>
<tr>
<td>Volume</td>
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</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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</tr>
<tr>
<td>F(000)</td>
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<tr>
<td>Crystal size</td>
<td>0.232 × 0.227 × 0.05 mm³</td>
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<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
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Appendix 6.1b: X-ray crystal structure determination data of compound 95

Table 1 Crystal data and structure refinement for oic297v_2_0m.

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<td>Formula weight</td>
<td>201.26</td>
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<tr>
<td>Temperature/K</td>
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<tr>
<td>Crystal system</td>
<td>triclinic</td>
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<td>Space group</td>
<td>P1</td>
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<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>α = 92.980(2)°</td>
</tr>
<tr>
<td></td>
<td>b = 7.7414(3) Å</td>
</tr>
<tr>
<td></td>
<td>β = 99.128(3)°</td>
</tr>
<tr>
<td></td>
<td>c = 11.8446(5) Å</td>
</tr>
<tr>
<td></td>
<td>γ = 93.940(2)°</td>
</tr>
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</table>
Volume: 1575.63(15) Å³

Z: 2

Density (calculated): 1.256 g/cm³

Absorption coefficient: 0.622 mm⁻¹

F(000): 216.0

Crystal size: 0.15 × 0.1 × 0.05 mm³

Wavelength: 1.54178 Å

Theta range for data collection: 7.574 to 133.35

Index ranges: -7 ≤ h ≤ 7, -9 ≤ k ≤ 9, -14 ≤ l ≤ 14

Reflections collected: 13872

Independent reflections: 3613 [R(int) = 0.0553, R(sigma) = 0.0489]

Data/restraints/parameters: 3613/3/272

Goodness-of-fit on F²: 1.086

Final R indexes [I>2σ(I)]: R₁ = 0.0378, wR₂ = 0.0707

Final R indexes [all data]: R₁ = 0.0470, wR₂ = 0.0741

Largest diff. peak and hole: 0.16/-0.19 e Å⁻³

**Appendix 6.1c**: X-ray crystal structure determination data of compound 96

![Compound 96](image)

**Table 1** Crystal data and structure refinement for OIC296v_0m.

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<th>Identification code</th>
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<tr>
<td>Empirical formula</td>
<td>C₂₁H₂₅NO₂</td>
</tr>
</tbody>
</table>

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Appendix 6.1d: X-ray crystal structure determination data of compound \textit{trans-120f}

![Image of compound trans-120f]
Table 1 Crystal data and structure refinement for oic298k_0m.

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<tr>
<td>Empirical formula</td>
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<td>Formula weight</td>
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<td>Crystal system</td>
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<td>Space group</td>
<td>P-1</td>
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<td></td>
<td>α = 104.496(5)º, β = 103.712(5)º, γ = 101.491(5)º</td>
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<tr>
<td>Volume</td>
<td>879.2(3) Å³</td>
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<td>Z</td>
<td>2</td>
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<tr>
<td>Density (calculated)</td>
<td>1.343 g/cm³</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
<td>376.0</td>
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<td>Crystal size</td>
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<td>Wavelength</td>
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<td>Theta range for data collection</td>
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<tr>
<td>Index ranges</td>
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<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
<td>3970 [R_{int} = 0.0713, R_{sigma} = 0.0680]</td>
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<tr>
<td>Data/restraints/parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indexes [I&gt;2sigma (I)]</td>
<td>R_1 = 0.0497, wR_2 = 0.0994</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R_1 = 0.0926, wR_2 = 0.1158</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.29/-0.26 e Å⁻³</td>
</tr>
</tbody>
</table>
Appendix 6.2: Variable temperature $^1$H NMR spectra

Appendix 6.2a: Variable temperature $^1$H NMR spectra for N-Boc-2-phenylazepane 71

NMR in DMSO-d$_6$

A sample of N-Boc-2-phenylazepane 71 (28 mg, 0.10 mmol) in DMSO-d$_6$ (0.7 mL) was placed in an NMR tube and the NMR spectrometer was heated gradually from 20 to 100 °C. Heating allowed coalescence of the signals for most protons, most prominently those around 3.8 ppm and 5.1 ppm, which both occurred at about 75–80 °C as shown below.

Calculations:

The NMR spectrum is a function of the difference in their resonance frequencies, $\Delta \nu = \nu_A - \nu_B$ of the rate of exchange, $k$. The linewidths at $\nu_A$ and $\nu_B$ are affected by the difference of temperature as shown in the figure below.

A rotation rate $k$ at different temperatures can be calculated from spectral data using several approximate formulas then line shape analysis was performed using the following equations:

Pre-coalescence

\[ k = [\Delta \nu_o^2 - \Delta \nu_e^2]^{1/2} \pi / \sqrt{2} \]

Coalescence:

\[ k = \pi \Delta \nu_o / \sqrt{2} \]

Post-coalescence:

\[ k = \pi \Delta \nu_e^2 / 2[\Delta \nu^{1/2}_i -(\Delta \nu_A)^{1/2}_o] \]
Where:

$\Delta \nu_o$ is the distance between the peaks at the lowest temperature

$\Delta \nu_e$ is the distance between the peaks at pre-coalescence.

$(\Delta \nu)^{0}_{1/2}$ is the peak width at half height post coalescence.

$(\Delta \nu)^{e}_{1/2}$ is the peak width at half height for the baseline (sharpest) peak

These equations gave the following data, selecting the signals coalescing about 5 ppm.

<table>
<thead>
<tr>
<th>T/K</th>
<th>1/T</th>
<th>$\Delta \nu_o$</th>
<th>$\Delta \nu_e$</th>
<th>$k$</th>
<th>ln($k/T$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>313</td>
<td>0.003195</td>
<td>99.58</td>
<td>100.6149</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>323</td>
<td>0.003096</td>
<td>99.58</td>
<td>98.6525</td>
<td>30.1618</td>
<td>-2.371076</td>
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<tr>
<td>333</td>
<td>0.003003</td>
<td>99.58</td>
<td>92.9989</td>
<td>79.0650</td>
<td>-1.437872</td>
</tr>
<tr>
<td>343</td>
<td>0.002915</td>
<td>99.58</td>
<td>78.9393</td>
<td>134.7905</td>
<td>-0.934009</td>
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<tr>
<td>353</td>
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<td></td>
<td>221.7861</td>
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<tr>
<td>363</td>
<td>0.002755</td>
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<td>46.7697$^a$</td>
<td>609.3444</td>
<td>0.5179807</td>
</tr>
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<td>373</td>
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<td>99.58</td>
<td>30.5727$^a$</td>
<td>1662.974</td>
<td>1.4947846</td>
</tr>
</tbody>
</table>

The Eyring plot is based on $1/T$ versus ln($k/T$). The presence for considerable error in these data is possible, due to variation in peak deconvolution and temperature. The activation
parameters reached should be treated with caution, particularly as they give longer half-lives than experimental data suggests.

From the Eyring plot:

\[ \Delta H^\ddagger = 73.2 \text{ kJ/mol and } \Delta S^\ddagger = 8.8 \text{ J/K mol} \]

Similar values are obtained by using the peaks coalescing about 3.9 ppm.

These values provide:

\[ \Delta G^\ddagger = 70.8 \text{ kJ/mol at } -5 \degree \text{C, that equates to } k = 8.7 \times 10^{-2} \text{ s}^{-1}, \ t_{1/2} = 8 \text{ s} \]

\[ \Delta G^\ddagger = 71.5 \text{ kJ/mol at } -78 \degree \text{C, that equates to } k = 2.9 \times 10^{-7} \text{ s}^{-1}, \ t_{1/2} = 28 \text{ d} \]

These values are consistent with the slow rotation and lithiation at \(-78 \degree \text{C, as shown by the ReactIR plots (figure 15, 17, chapter 2)}\)

Furthermore, for comparison the coalescence studies were also carried out in toluene
NMR in toluene-d8

A sample of \( N\)-Boc-2-phenylazepane \( \textbf{71} \) (28 mg, 0.10 mmol) in toluene-d8 (0.7 mL) was placed in an NMR tube and the NMR spectrometer was heated gradually from 30 to 80 °C. Heating allowed coalescence of the signals, most prominently those around 2.6 ppm, which occurred between 50 and 60 °C as shown below. Coalescence was also observed for other signals, \textit{e.g.} around 5 ppm, at about 80 °C.

Using the signals at 2.53 and 2.63 ppm

<table>
<thead>
<tr>
<th>( T/K )</th>
<th>( 1/T )</th>
<th>( \Delta v_0 )</th>
<th>( \Delta v_e )</th>
<th>( k )</th>
<th>( \ln(k/T) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 323 )</td>
<td>0.003096</td>
<td>47.138</td>
<td>39.8051</td>
<td>56.09229</td>
<td>-1.75065</td>
</tr>
<tr>
<td>( 333 )</td>
<td>0.003003</td>
<td>47.138</td>
<td>51.9397</td>
<td>123.1366</td>
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</tr>
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<td>( 343 )</td>
<td>0.002915</td>
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<td>( 353 )</td>
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<td>30.45</td>
<td>509.1147</td>
<td>0.366205</td>
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</table>
From the Eyring plot:

\[ \Delta H^\ddagger = 68.1 \text{ kJ/mol} \text{ and } \Delta S^\ddagger = -1.2 \text{ J/K·mol} \]

These values provide:

\[ \Delta G^\ddagger = 67.8 \text{ kJ/mol at } -5 \text{ °C}, \text{ that equates to } k = 3.4 \times 10^{-1} \text{ s}^{-1}, \text{ } t_{1/2} = 2 \text{ s} \]

\[ \Delta G^\ddagger = 67.9 \text{ kJ/mol at } -78 \text{ °C}, \text{ that equates to } k = 2.7 \times 10^{-6} \text{ s}^{-1}, \text{ } t_{1/2} = 72 \text{ h} \]

These values indicate a small solvent effect with a slightly faster rate of rotation of the Boc group in toluene compared with in DMSO, although there is some margin of error in the data.

**Appendix 6.2b:** Variable temperature \(^1\)H NMR spectra for \(N\)-Boc-2-phenylbenzazepine 96

**NMR in DMSO-d6**

A sample of \(N\)-Boc-2- phenylbenzazepine 96 (28 mg, 0.10 mmol) in DMSO-d6 (0.7 mL) was placed in an NMR tube and the NMR spectrometer was heated gradually from 25 to 100 °C. Heating allowed coalescence of the signals for benzylic protons, most prominently those around 4.8 ppm and 5.2 ppm, which occurred at about 60–70 °C as shown below.
Using the signals at 4.8 and 5.2 ppm

<table>
<thead>
<tr>
<th>T/K</th>
<th>1/T</th>
<th>Δν₀</th>
<th>Δνₑ</th>
<th>k</th>
<th>ln(k/T)</th>
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<td>0.003356</td>
<td>88.65</td>
<td>88.65</td>
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\[
\ln\left(\frac{k}{T}\right) = -6.707742x + 19.874 \\
R^2 = 0.987
\]
From the Eyring plot:

$$\Delta H^\ddagger = 55.77 \text{ kJ/mol and } \Delta S^\ddagger = -32.31 \text{ J/K} \cdot \text{mol}$$

These values provide:

$$\Delta G^\ddagger = 62.98 \text{ kJ/mol at } -50 \, ^\circ\text{C}, \text{ that equates to } k = 8.2 \times 10^{-3} \text{ s}^{-1}, \, t_{1/2} = 1.4 \text{ min}$$

$$\Delta G^\ddagger = 62.07 \text{ kJ/mol at } -78 \, ^\circ\text{C}, \text{ that equates to } k = 1.0 \times 10^{-4} \text{ s}^{-1}, \, t_{1/2} = 120 \text{ min}$$

These values are consistent with the quick rotation and lithiation at -50 °C, as shown by the ReactIR plots (figure 26, chapter 3).

**Appendix 6.3: HPLC traces**

![HPLC traces](image)

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(Cellulose-2)

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(Racemic-96)

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(S)-96
rac-97

(Cellulose-2)

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**rac-138**

(Cellulose-1)

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**Boc**

(Cellulose-1)

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Chapter 6

References


(16) Luisi, R.; Capriati, V. Lithium Compounds in Organic Synthesis; From Fundamentals


(109) Jones, C. Level 4 Research Project Thesis, The University of Sheffield, **2017**.


