# Synthesis of Substituted Azepanes and Piperidines Using Organolithium Chemistry

**Submitted by**


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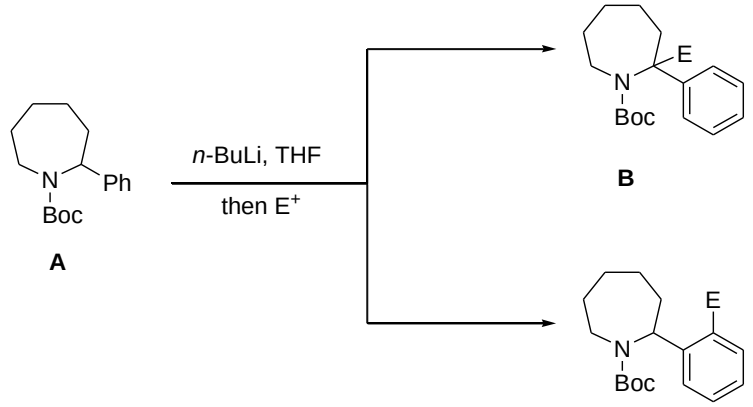
# Abstract


*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.

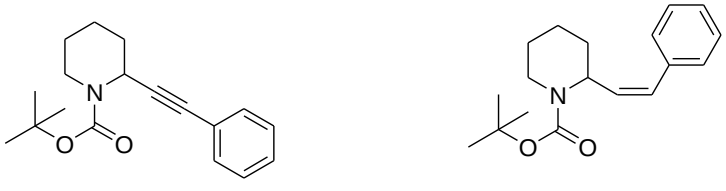
Chapter 2 details the optimization of the time required for the lithiation of *N*-Boc-2-phenylazepane and trapping of the lithiated intermediate. A variety of novel *α*-substituted and unusual *ortho*-substituted products were obtained in good to excellent yields.




**A** **B** **C**

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.




**D** **E**

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بسم الله الرحمن الرحيم

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

﴿وَيَسْأَلُونَكَ عَنِ الرُّوحِ ۖ قُلِ الرُّوحُ مِنْ أَمْرِ رَبِّي وَمَا أُوتِيتُم مِّنَ الْعِلْمِ إِلَّا قَلِيلًا﴾

(الحمد لله حتى يبلغ الحمد منتهاه)

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| aq | aqueous |
| Ar | aryl |
| Bt | benzotriazole |
| Bn | benzyl |
| Boc | *t*-butoxycarbonyl |
| $Boc_2O$ | 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 | dimethylpropylidineurea |
| 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 |

| | |
|---|---|
| er | enantiomeric ratio |
| Et | Ethyl |
| $Et_2O$ | Diethyl ether |
| g | grams |
| $\Delta G^{\ddagger}$ | Gibbs energy of activation |
| h | hours |
| $\Delta H^{\ddagger}$ | enthalpy of activation |
| HFIP | *bis*-1,1,1,3,3,3-hexafluoroisopropoxide |
| HMPA | *N*,*N*,*N*',*N*',*N''*,*N''*-hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| HPLC | high-performance liquid chromatography |
| Hz | hertz |
| i.d. | internal diameter |
| IR | Infra-red |
| $^{i}$Pr or *i*-Pr | Isopropyl |
| inv. | inversion |
| KR | kinetic resolution |
| *k* | reaction rate constant |
| K | Kelvin |
| KJ | kilojoule(s) |
| L | litre |
| L* | chiral ligand |
| LDA | lithium diisopropylamide |
| LRMS | low resolution mass spectrometry |
| lit. | literature |
| M | molar |
| m | multiplet |
| μL | microlitre |
| Me | methyl |
| mg | milligram |
| MHz | megahertz |
| Mes | mesityl |
| min | minutes |

| | |
|---|---|
| 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 |
| $R_f$ | retention factor |
| RSM | recovered starting material |
| $R_t$ | 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 |
| $\Delta S^{\ddagger}$ | entropy of activation |

| | |
|---|---|
| *s*-Bu | secondary butyl |
| T | temperature |
| t | time |
| *t*-Bu | tertiary butyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THQ | 1,2,3,4-tetrahydroquinoline |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N*',*N*'-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl |
| UV | ultraviolet |

# *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).

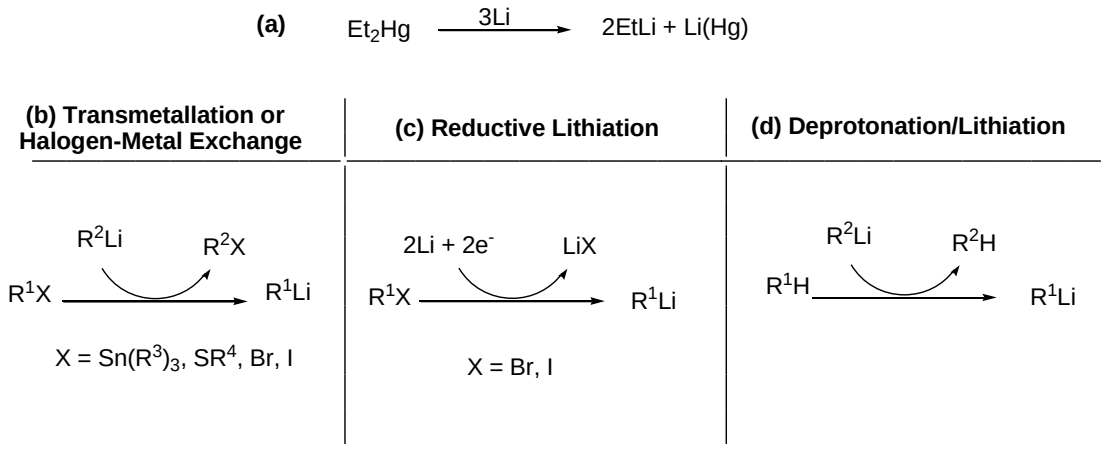



**Figure 1**

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 p$K_a$ > 35.[3]

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 (≤ 5 ºC) temperatures.[1]

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.[5]

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).[6,7] A common use for commercially available organolithium compounds (like *n*-BuLi, *sec*-BuLi, *t*-BuLi, MeLi, PhLi) is as very strong bases.[5]

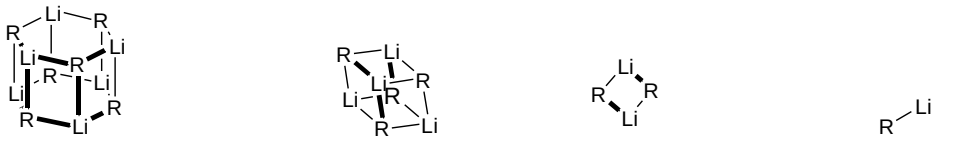



**Figure 2**

X-ray crystallographic studies and $^7$Li solid state NMR spectroscopic studies of organo-lithiums 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 $(Me_2PhSi)_2CHLi$, are dimers (Table 1).[1,7] This difference in

aggregation state is due to steric hindrance. Benzyllithium exists as dimers due to a bulky benzylic group while primary organolithiums such as *n*-butyllithium exist as hexamers.[1]

| Hexameric | Tetrameric | Dimeric | Monomeric |
|---|---|---|---|
| EtLi | *s*-BuLi | $PhCH_2Li$ | - |
| *n*-BuLi | i-PrLi | | |
| | *t*-BuLi | | |

**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 > (–)-sparteine > DMPU > DME > TMEDA > THF > $Et_2O$

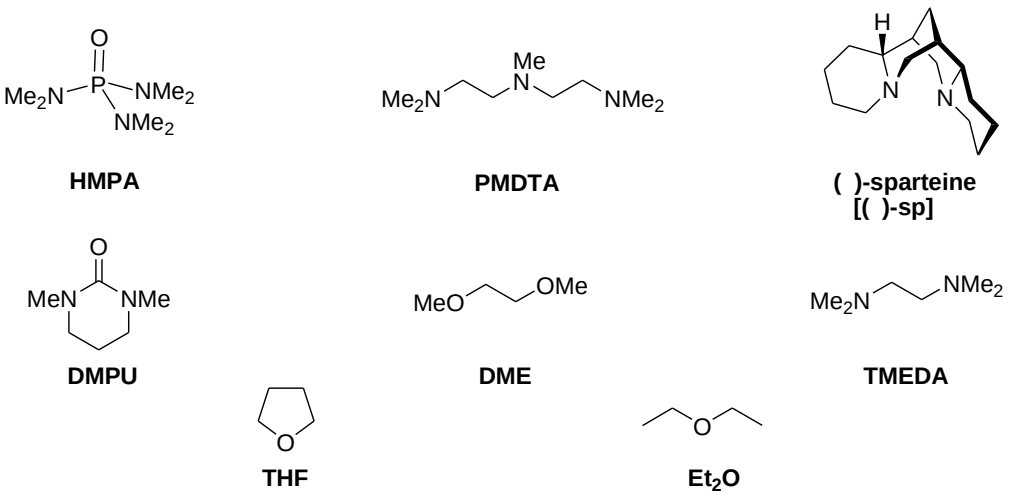



**Figure 3**

In general, it is often considered that lower aggregation states result in more reactive organolithium reagents.[12] Therefore, coordinating ligands and solvents, such as ethers or amines, can improve reactivity as they can deaggregate the organolithium. For instance, *s*-BuLi in a hydrocarbon solvent exists as a tetramer, whereas in the presence of THF, the aggregation state shifts to a dimer.[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.[13] Collum had shown that TMEDA can reduce the organolithium aggregation of *n*-BuLi in THF from a tetramer to a dimer.[13]

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

### 1.1.3 *α*-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 C–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 C–Li bond by a nearby empty orbital or electron-withdrawing group.[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.[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 *α*-lithiations make use of allylic or benzylic stabilisation as well as the effect of the heteroatom.[1] The removal of a proton from a carbon bearing a nitrogen atom gives an *α*-amino organolithium as an important intermediate, which reacts with electrophiles to produce substituted amines. *α*-Amino organolithium intermediates are classified into different types according to their stability as follows: unstabilised, dipole-stabilised, mesomerically stabilised, and dipole- and mesomerically stabilised.[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.[1,15] Tin-lithium exchange reactions and deprotonation of quaternary ammonium complexes have allowed the formation of non-stabilised $\alpha$-amino-organolithiums but a degree of dipole stabilisation gives some extra stability to the organolithium species in the latter case (Figure 4b).[16]

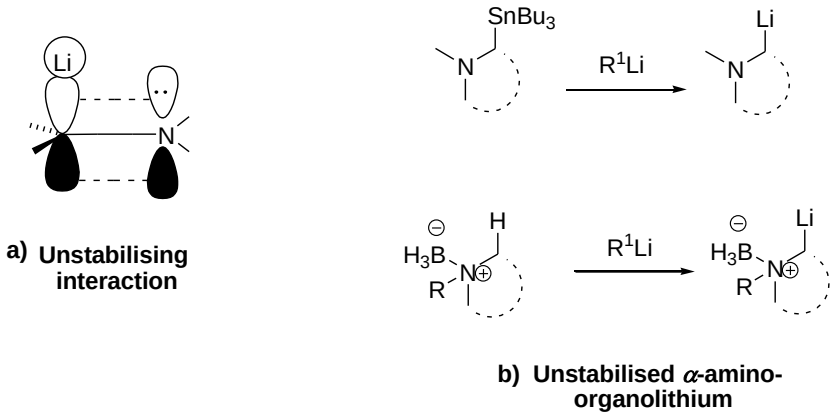



**Figure 4**

The chemistry of these compounds has limited progress not only because they have suffered from several failures,[17–19] but also there has been difficulty to find a clear reason for the success or failure of these reactions (Figure 5).

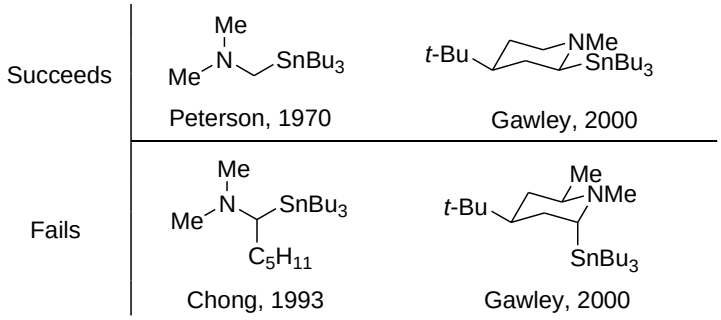
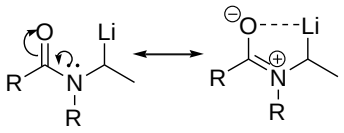



**Figure 5**

**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

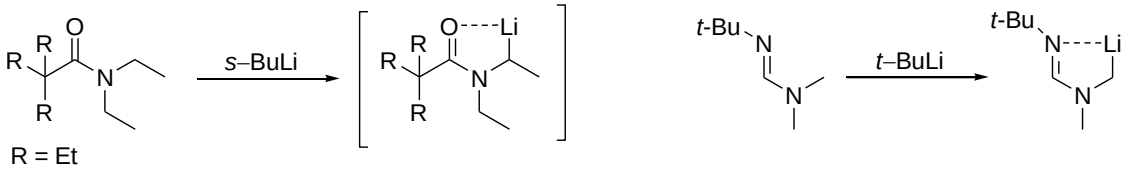
delocalisation. This conjugation provides a new, electron-rich oxygen atom which can itself stabilise the organolithium by coordination (Figure 6).[1] The delocalization of the nitrogen's lone pair into the amide carbonyl (or the dipoles of similar functional groups) is stabilised by the $N^{(\delta+)}$–$C{=}O^{(\delta-)}$ dipole and this forms an important group of compounds which have been termed “dipole-stabilised carbanions”.[1]




Dipole-stabilised
amino-organolithium

**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.




**1** **2** **3** **4**

**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.[3] There are two types of bonding that can be generated from these organolithium compounds; $\eta^1$ or $\eta^3$. Figure 7b illustrates the dynamic equilibrium between $\eta^1$ and $\eta^3$ bonding of *α*-lithio *N*,*N*-dimethylbenzyl amine in solution.[20] The position of the equilibrium is affected by the temperature: lower temperatures $\eta^1$ bonding is predominant and vice versa.

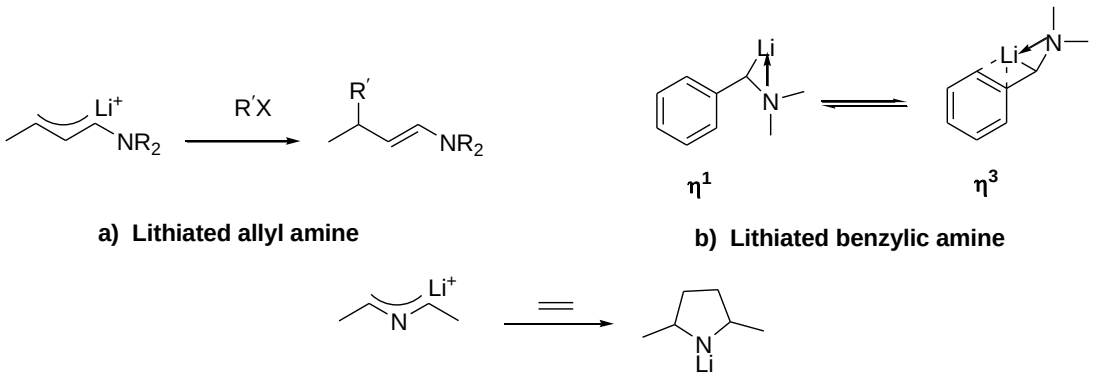
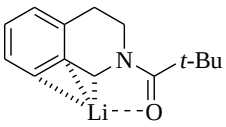



**Figure 7**

**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]




**Dipole- and mesomerically stabilised**
**α-amino-organolithium**

**Figure 8**

## 1.2 Directed Lithiation Using Organolithium Reagents

The generation of *α*-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]

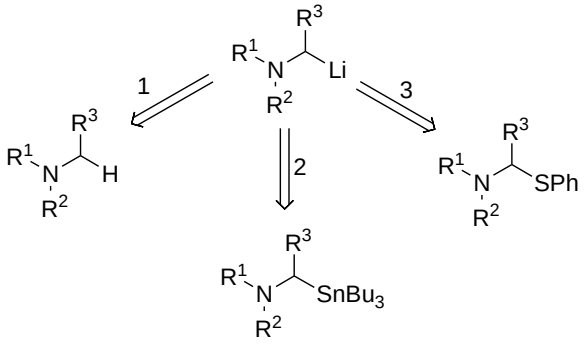
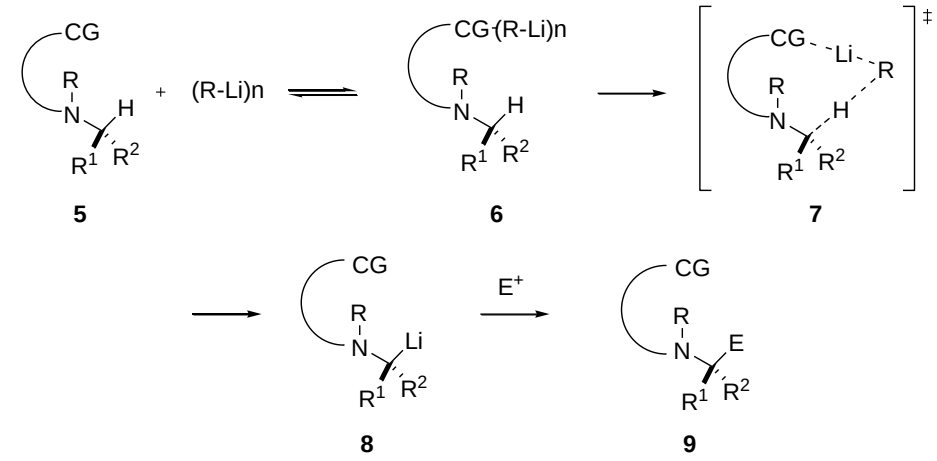



**Figure 9**

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 *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).

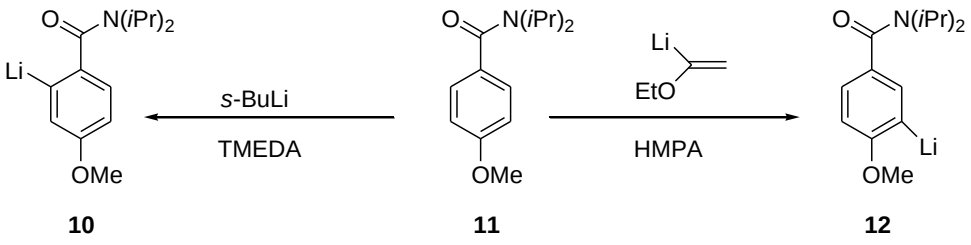
As illustrated in Scheme 2, the general CIPE can be described as a lithiation-substitution sequence from **5** to **9**. Co-ordination of **5** with an organolithium reagent provides the complex **6**. This then holds the organolithium reagent in a suitable conformation for deprotonation to give the 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]




CG = co-ordinating functional group, $E^+$ = electrophile

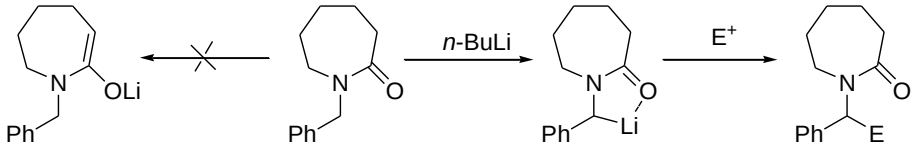
**Scheme 2**

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).[21] However, lithiation of **11** by *α*-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 *α*-ethoxyvinyl lithium-HMPA. Formation of **12** is then attributed to a favourable inductive effect of the methoxy group.[21]




**Scheme 3**

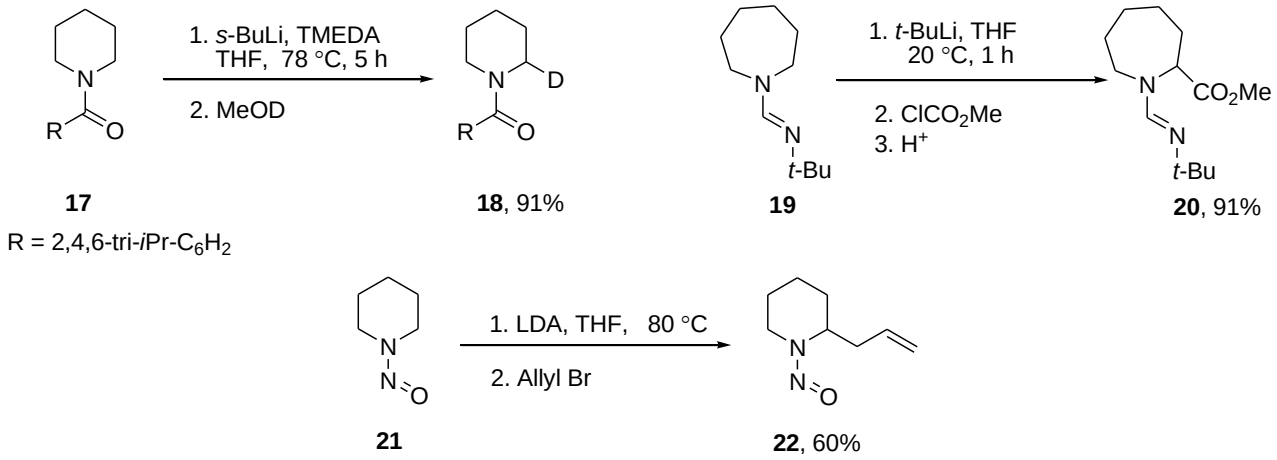
A further example (Scheme 4) of the importance of the CIPE for regioselectivity was reported by Beak and Meyers, who showed that a kinetic deprotonation of the benzyl protons to give the stable intermediate **15** was more favoured over the thermodynamic deprotonation of *α*-methylene protons to form the amide enolate product **13**.[22]




**Scheme 4**

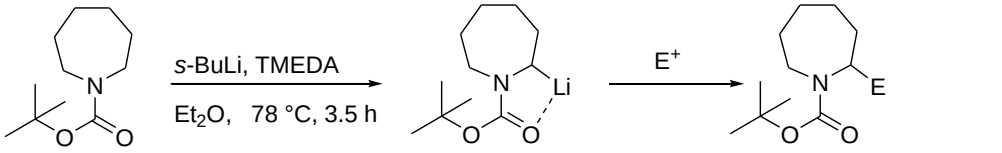
A fundamental requirement for CIPE directing groups is that they are easy to add and remove. Also, they must have some Lewis basicity to allow complexation to the organometallic reagent. As a result they must have a low reactivity towards nucleophilic attack to allow deprotonation to occur.[30]

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,[24] formamidine,[31] and nitroso[32] groups (Scheme 5). All of these groups allow complexation of the organo-lithium reagent and have a low reactivity towards nucleophilic attack to allow $\alpha$-deprotonation to occur.




**Scheme 5**

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.[33] 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 $Boc_2O$ and removed by mild acid treatment, which has made it the most prevalent directing group for the *α*-lithiation of amines.




**23** **24**

**25a**, 61% $E^+$ = TMSCl
**25b**, 45% $E^+$ = $Bu_3SnCl$

**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.[16]

The polar mechanism is a bimolecular electrophilic substitution process, which could proceed *via* retention ($S_E2ret$) or inversion ($S_E2inv$) 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).[1,34]

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 ($S_E2ret$ or $S_E2inv$). 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). [34]

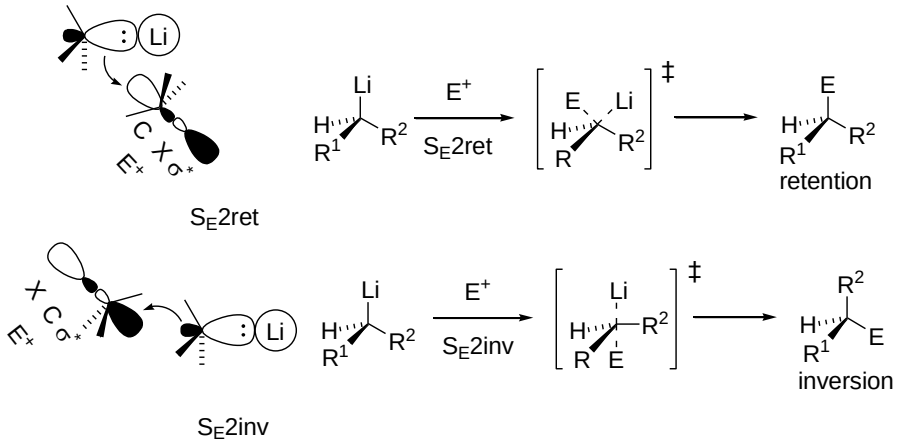



**Figure 10**

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).[35] It is possible to explain this mechanism and its competition with the polar mechanism ($S_E2ret$ and $S_E2inv$) 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.

**Single-electron transfer pathway SET**

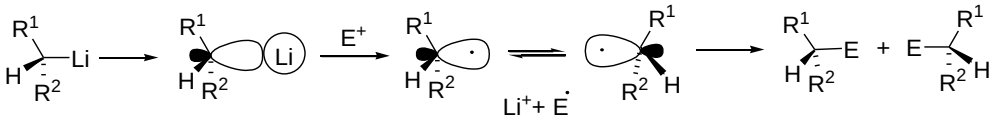



**Figure 11**

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).[1]

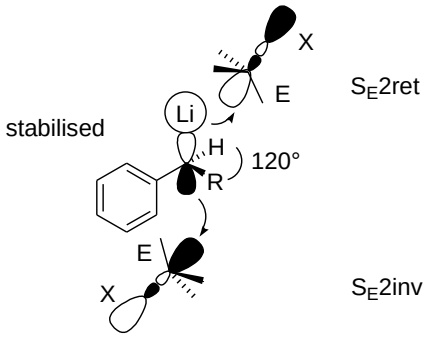
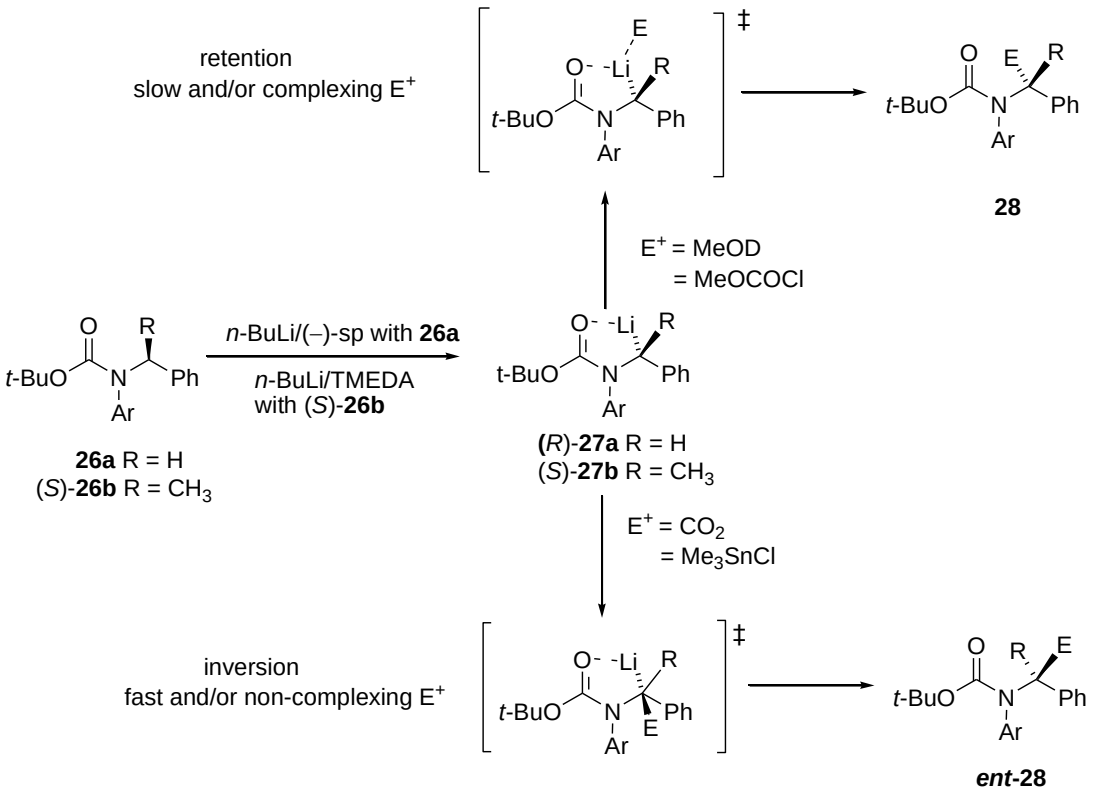


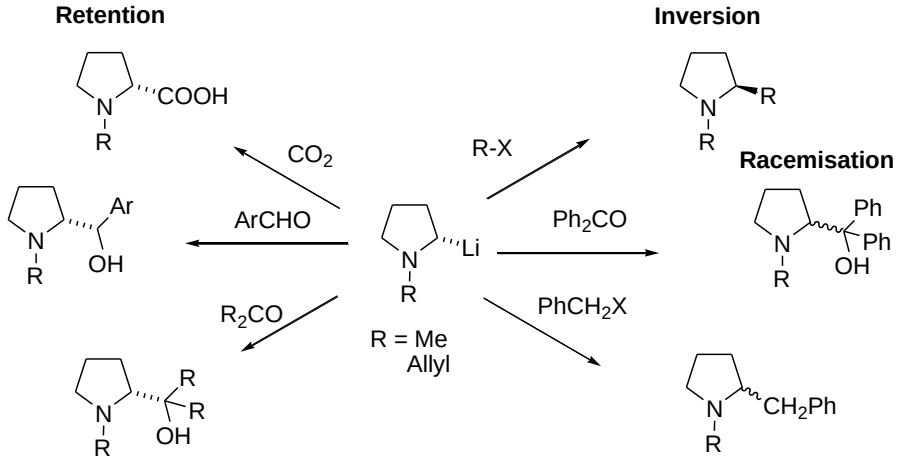

**Figure 12**

In 1994, Hoppe and Carstens showed that the steric course of electrophilic aliphatic substitutions on $\alpha$-amino-organolithiums could be classified according to the type of electrophile.[36] 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).[37]




**Scheme 7**

Gawley and co-workers have shown how the behaviour of different non-stabilised $\alpha$-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**

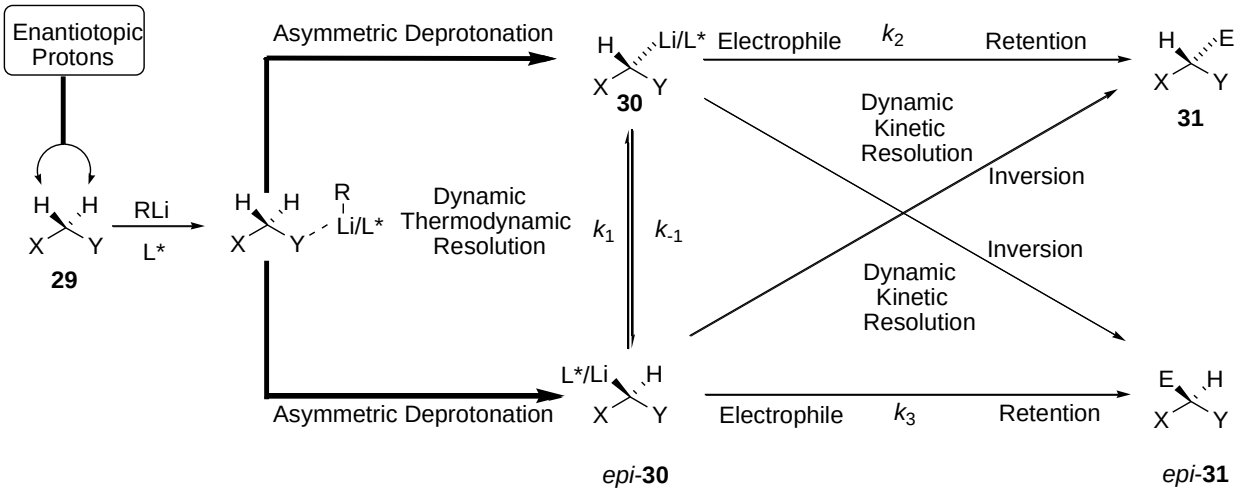
## 1.4 Asymmetric Induction Using Organolithium Reagents

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).




**Scheme 9**

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**.

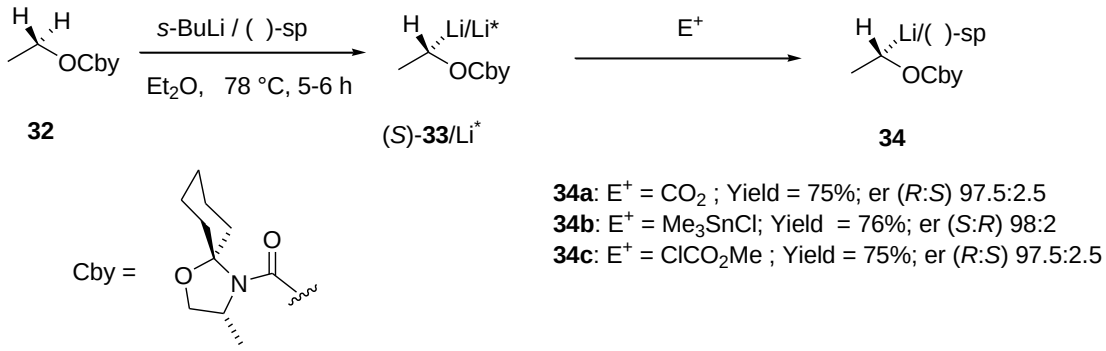
**. Dynamic Kinetic Resolution (DKR):** The diastereomeric intermediates **30** and *epi*-**30** are in equilibrium and stereoselectivity is dependent on the difference in the transition state energies of electrophilic substitution for each of the diastereomeric intermediates.

### 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]

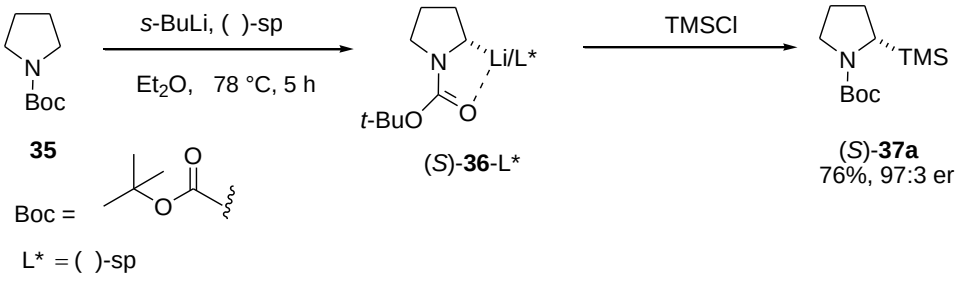
In 1990, Hoppe and co-workers were the first to achieve one of the best methods for

asymmetric deprotonation by using *sec*-BuLi with (–)-sparteine.[40] They found that the deprotonation of the achiral primary alkyl carbamate **32** with *s*-BuLi/(–)-sparteine in $Et_2O$ 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**

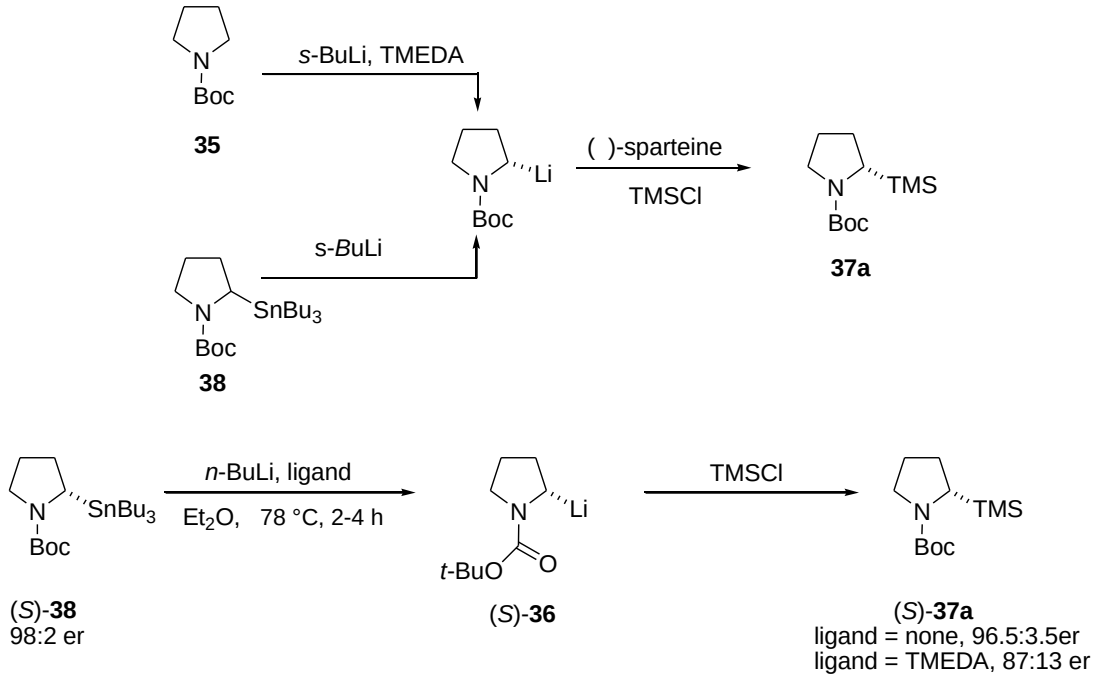
Building on work by Hoppe, in 1991 Kerrick and Beak reported methodology for the asymmetric deprotonation of *N*-Boc pyrrolidine **35** with *s*-BuLi and (–)-sparteine in $Et_2O$ at –78 ºC.[41] In the asymmetric deprotonation, the *s*-BuLi/(–)-sparteine complex selectively abstracts one of the *pro-S* 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**

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.[42] Firstly, as it was shown from scheme 12 that the racemic organolithium intermediate **36** was formed

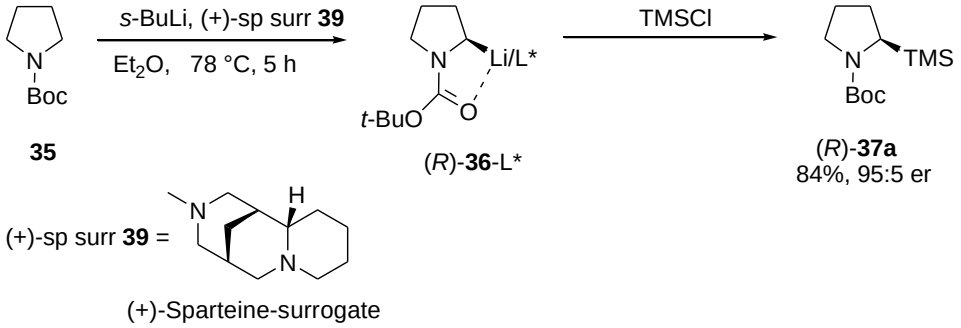
both by deprotonation of **35** with *s*-BuLi and by tin–lithium exchange of the racemic stannane **38** with *s*-BuLi. Trapping this intermediate by TMSCl, followed by (–)-sparteine, the product **37a** (E = TMSCl) in the two cases was formed as a racemate (very poor er) (Scheme 12). These results showed 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.




**Scheme 12**

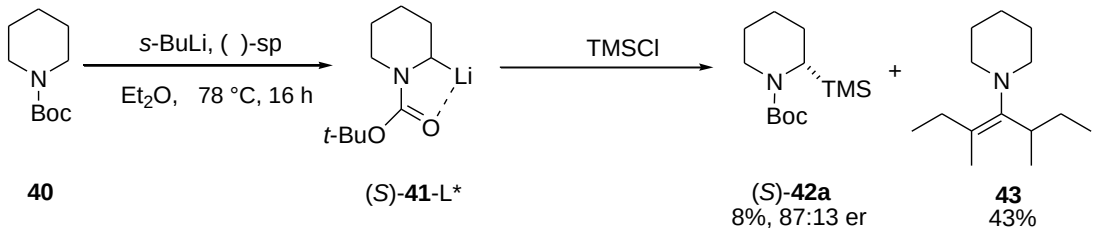
(+)-Sparteine surrogate **39** is another important diamine chiral ligand that allows access to the other enantiomeric form of the product after lithiation-substitution.[43] This ligand is less hindered than (–)-sparteine so can show different enantioselectivity.

O'Brien and co-workers developed the (+)-sparteine surrogate **39** and demonstrated its use in asymmetric deprotonation.[44] 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.



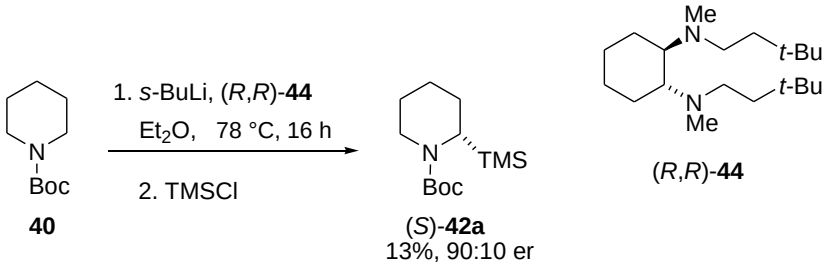

**Scheme 13**

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**.[45] 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.[45]



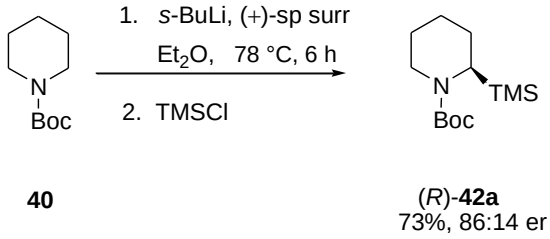

**Scheme 14**

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**.[46] 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).



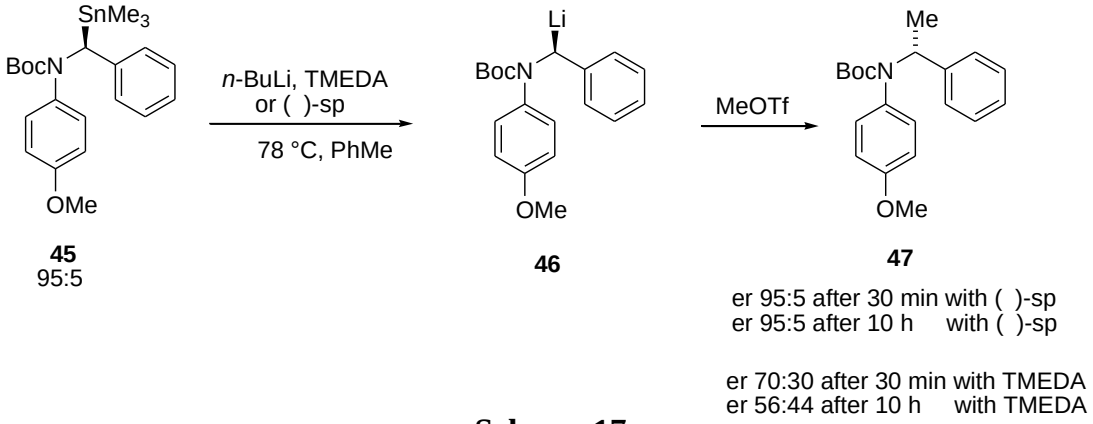

**Scheme 15**

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).



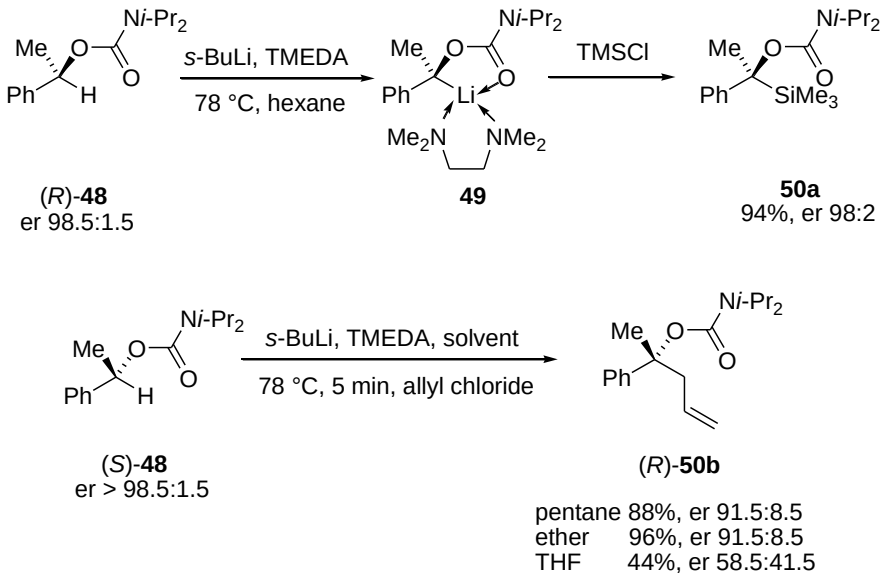

**Scheme 16**

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]




**Scheme 17**

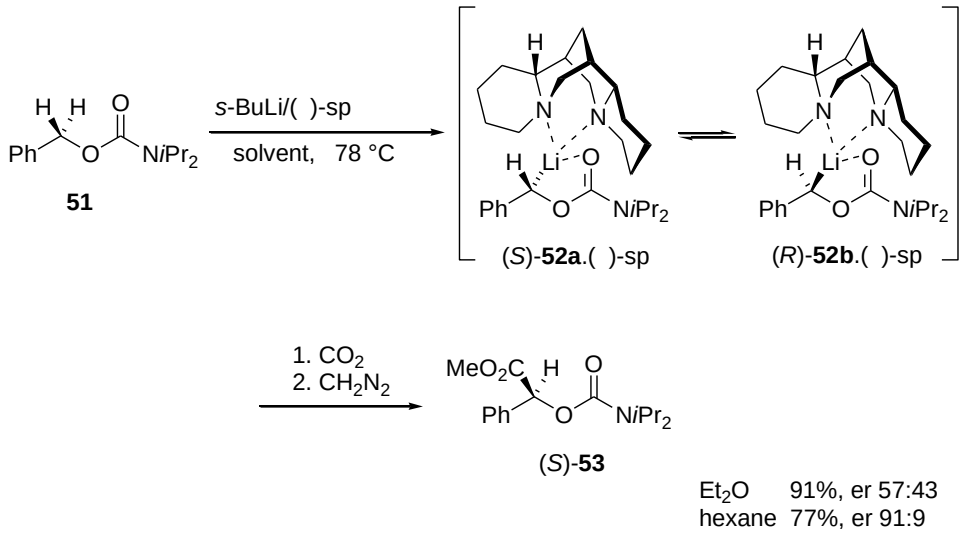
Hoppe has reported different conditions of deprotonation for (*R*) and (*S*)-**48**. Good stereoselectivity was achieved by deprotonation of (*R*)-**48** with *s*-BuLi/TMEDA at –78 °C in hexane or pentane, and then trapping with TMSCl to give **50a** with 94% yield and 98:2 er.[49] In contrast, significant 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 er of 91.5:8.5. However, if the lithiation was carried out in THF both a lower yield and er were obtained.[36]




**Scheme 18**

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 °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.[50] It was thought that there was a competition between the coordinating solvent $Et_2O$ 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**

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]

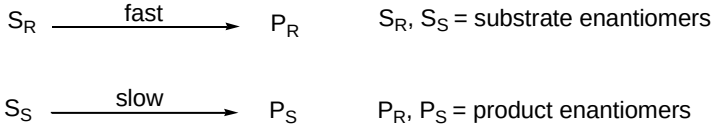
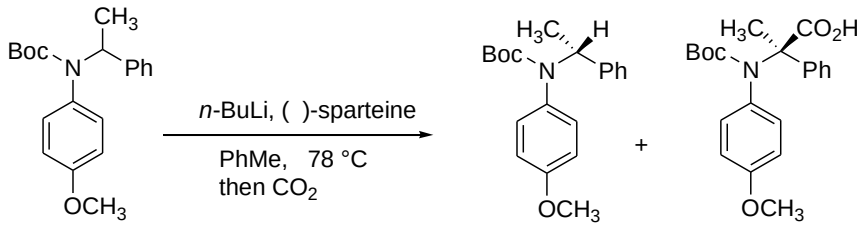



**Figure 13**

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.[51] Trapping with an electrophile can give the product in high 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[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 *rac*-**54** with *n*-BuLi/(–)-sparteine (Scheme 20).[37] Lithiation of *rac*-**54** with 0.5 equivalents of *n*-BuLi/(–)-sparteine and trapping with $CO_2$ gave 55% yield of the recovered starting material (*R*)-**54** with 75:25 er and 22% yield of (*R*)-**55** with 87:13 er. However, increasing the number of equivalents of the chiral base to 0.8 provided (*R*)-**54** (12% yield, er 81:19) and (*R*)-**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.




*rac*-**54** (*R*)-**54** (*R*)-**55**

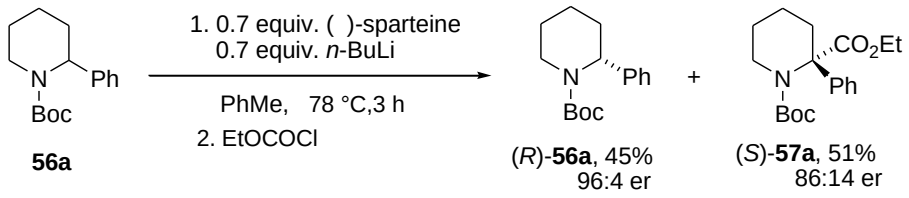
**Scheme 20**

| Equiv.of *n*-BuLi /(–)-sparteine | Yield (%) of RSM 54 | er of RSM 54 | Yield (%) of product 55 | er of product 55 |
|---|---|---|---|---|
| **0.5** | 55 | 75:25 | 22 | 87:13 |
| **0.8** | 12 | 81:19 | 66 | 57:43 |

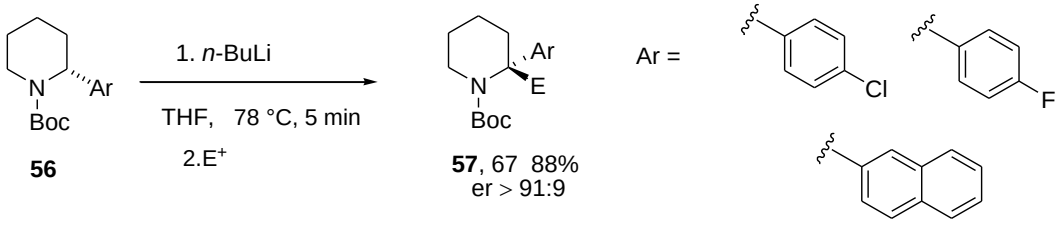
**Table 2**

More recently, the Coldham group showed that by using 0.7 equivalents of the chiral base *n*-BuLi/(–)-sparteine, a kinetic resolution of *N*-Boc-2-arylpiperidines can be promoted at –78 ºC.[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**




$E^+$ = EtOCOCl, MeI, allyl bromide

**Scheme 22**

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.

| Entry | Equiv.of *n*-BuLi /(–)-sparteine | Yield (%) and er of RSM 56a | Yield (%) and er of product 57a |
|---|---|---|---|
| **1** | 0.55 | 50%, (77:23) | 42%, (92:8) |
| **2** | 0.7 | 45%, (96:4) | 51%, (86:14) |
| **3** | 0.8 | 31%, (92:8) | 56%, (77:23) |
| **4** | 1.0 | 13%, (98:2) | 74%, (57:43) |

**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.

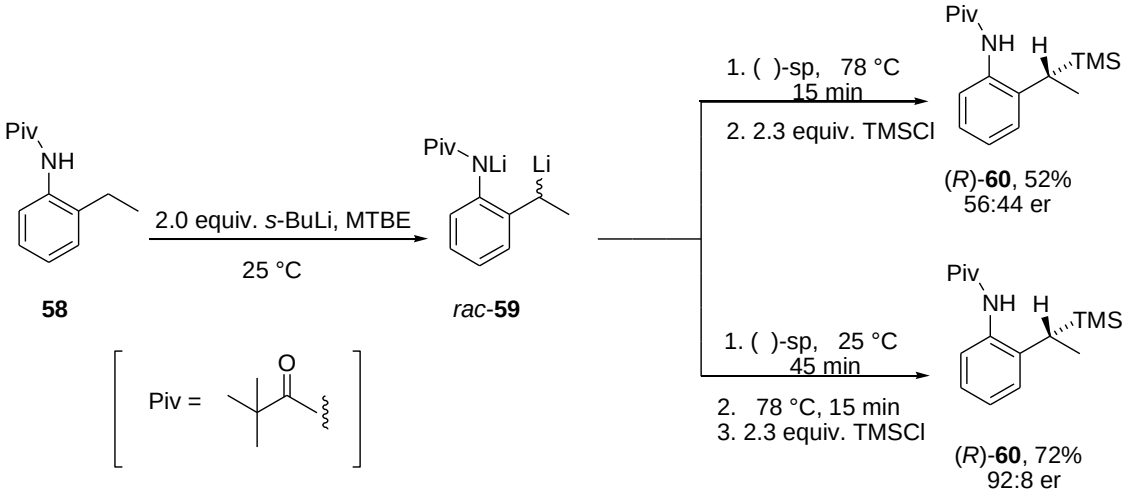
### 1.4.3 Dynamic Thermodynamic Resolution (DTR)

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.[58]

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 **58**.[59]

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

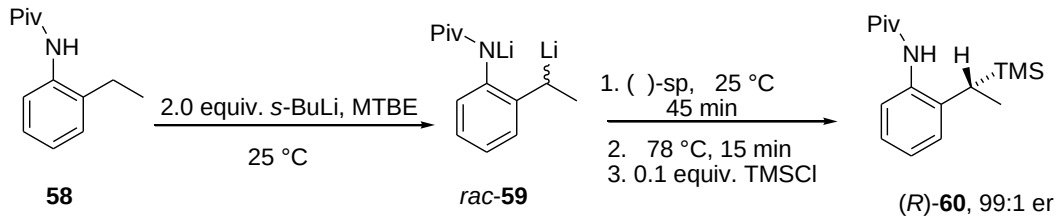
However, if (–)-sparteine was added at –25 ºC and the solution was left to stir at this temperature for 45 minutes before being cooled to –78 ºC (warm-cool protocol) and trapping *rac*-**59** with TMSCl, (*R*)-**60** was isolated in a dramatically improved 92:8 er and yield of 72% (Scheme 23).




**Scheme 23**

The need for a warm-cool cycle to accomplish high enantioselectivity demonstrated that the diastereomeric lithiated intermediates were interconverting at –25 ºC and not at –78 ºC. The organolithium must have complexed to (–)-sp, then equilibrated to a 92:8 diastereomeric ratio at −25 °C. Cooling to –78 ºC 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.

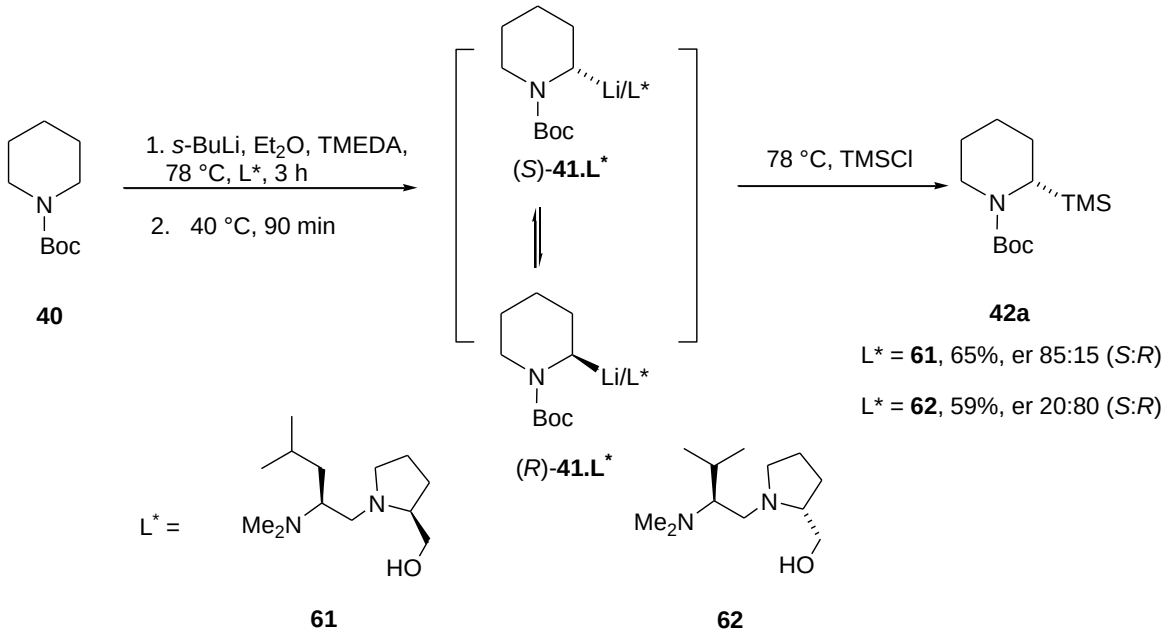
Beak also showed from this methodology that the enantiomeric ratio of the product could be improved by changing the number of electrophile equivalents. The addition of just 0.1 equiv. of TMSCl gave product (*R*)-**60** in 99:1 er but the yield was restricted to 10% (Scheme 24). This improvement in enantioselectivity 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.




**58** *rac*-**59** (*R*)-**60**, 99:1 er

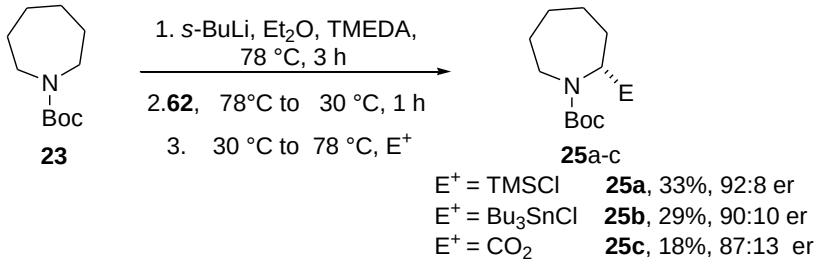
**Scheme 24**

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).




**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).[60]




**Scheme 26**

### 1.4.4 Dynamic Kinetic Resolution (DKR)

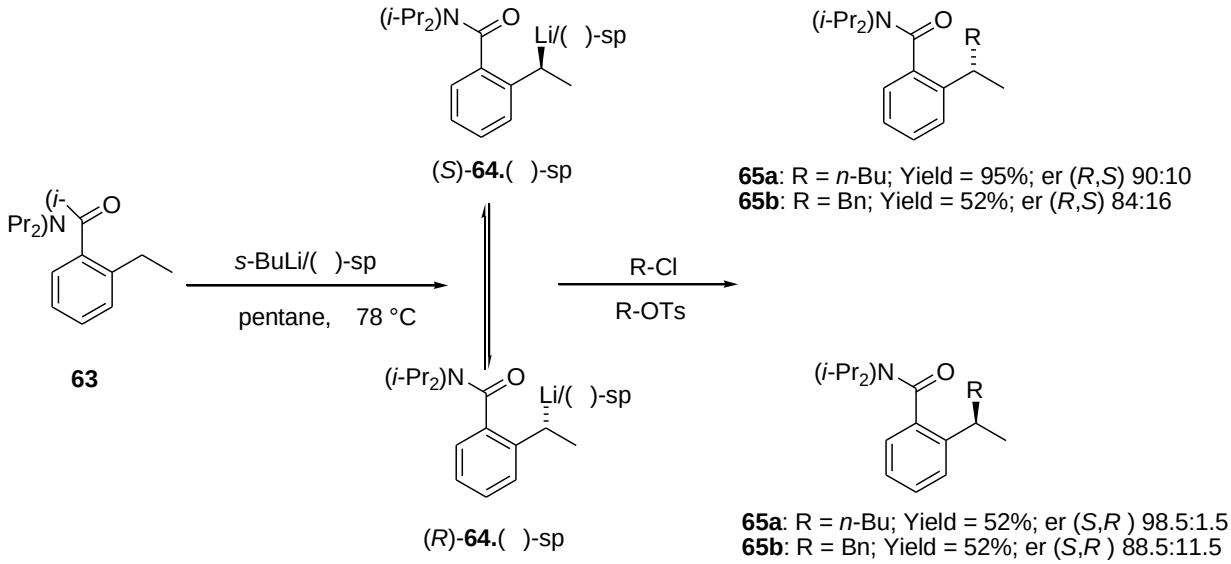
In the presence of a chiral ligand, when the rate of interconversion between the two diastereomeric complexes is fast on the timescale of the reaction of the organolithium with the electrophile, the product ratio is reflected in the different rates of reaction that the complexes have with the electrophile.

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.[51]

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.[39] 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).[39]

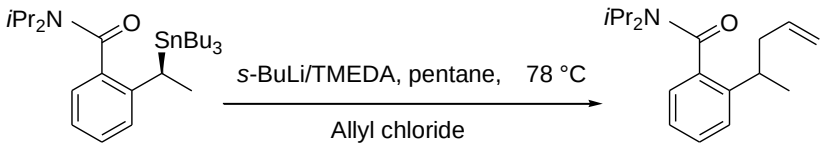
A good example of a DKR to achieve high levels of enantioselectivity was reported by Beak in 1994.[61] The lithiation of *N*,*N*-diisopropyl *o*-ethylbenzamide **63** with *sec*-BuLi/(–)-sparteine generated the rapidly interconverting diastereomeric organolithium intermediates (*S*)-**64**·(–)-sp and (*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**

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 ºC 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]

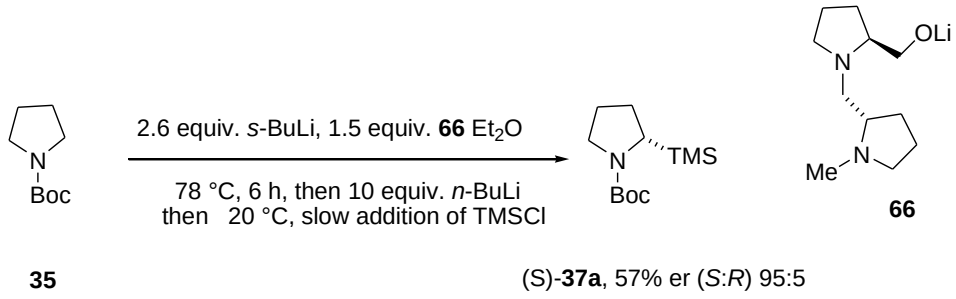



**65c**
er (*S*:*R*) 93.5: 6.5

**65d**
er (*S*:*R*) 50.5: 49.5

**Scheme 28**

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 $Et_2O$ at –78ºC 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.

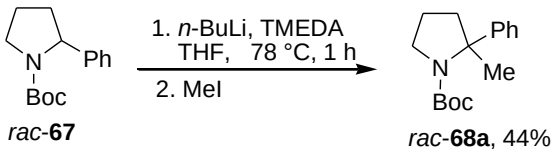



**Scheme 29**

## 1.5 Synthesis of 2,2-disubstituted saturated nitrogen heterocycles

Building on the work by Beak, that unsubstituted Boc-protected azaheterocycles 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]

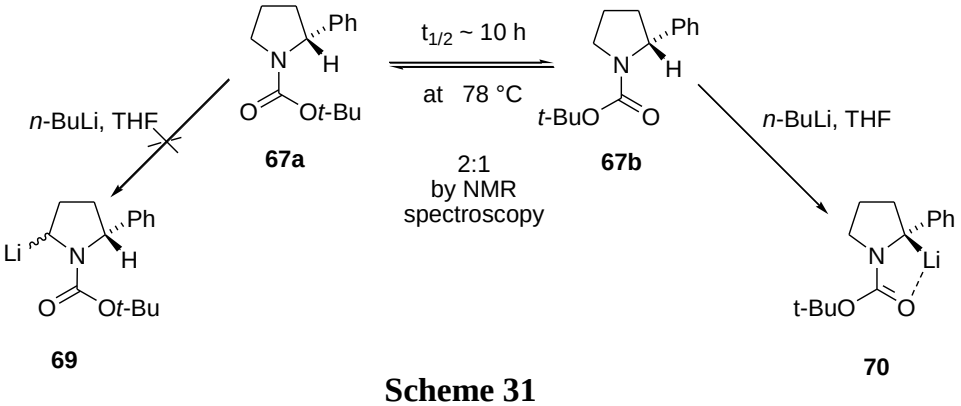
In 2005, Xiao and co-workers reported the synthesis of 2,2-disubstituted pyrrolidines in which one substituent was an aryl group.[66] This synthesis occurred readily through the increased acidity of the benzylic proton on the 2-arylpyrrolidine. Treatment of *N*-Boc-2-phenylpyrrolidine *rac*-**67** with *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).




**Scheme 30**

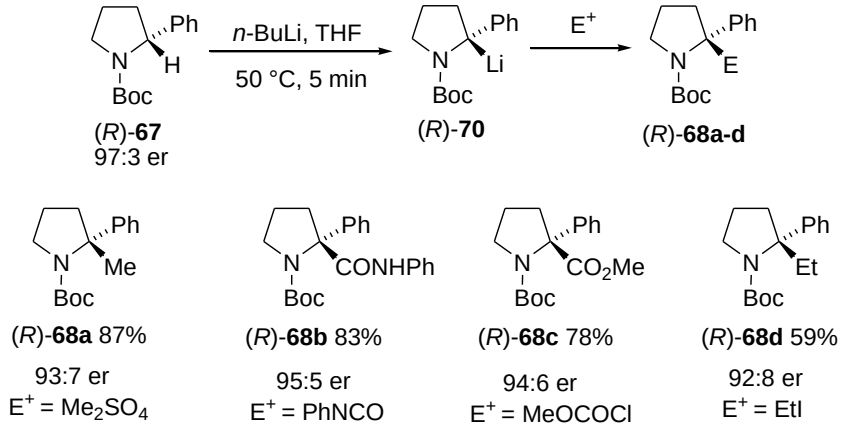
The 2,5-disubstituted pyrrolidine was not obtained under these conditions and this confirmed that lithiation using *n*-BuLi as a base proceeded solely towards the benzylic position. More recently, Coldham's group in collaboration with O'Brien's group investigated the synthesis of *N*-Boc-2-substituted 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**

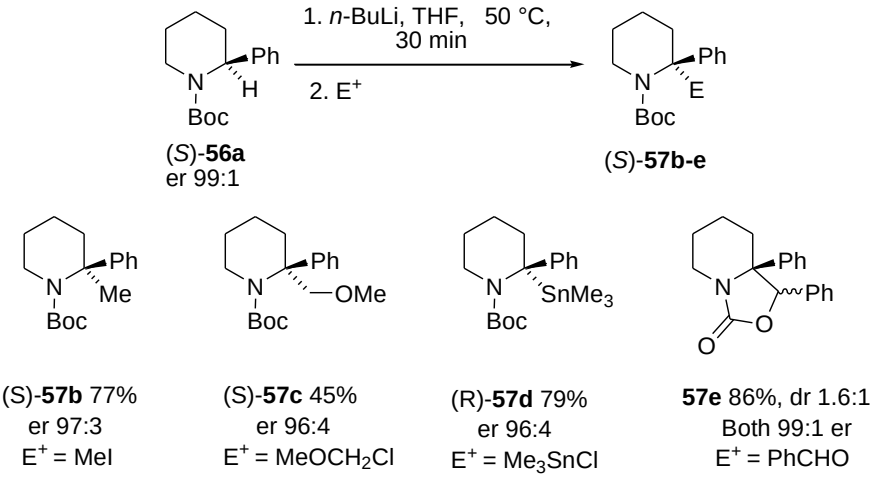
Variable temperature $^{1}$H NMR spectroscopy of **67** in *d*8-THF showed that the half-life ($t_{1/2}$) for rotation of the Boc group was ~10 h at –78 ºC, but < 1 sec at 0 °C. Therefore, when the reactions were carried out at –78 ºC low yields of the 2,2-disubstituted products were obtained. However, good yields were obtained at 0 ºC. 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).[65]




**Scheme 32**

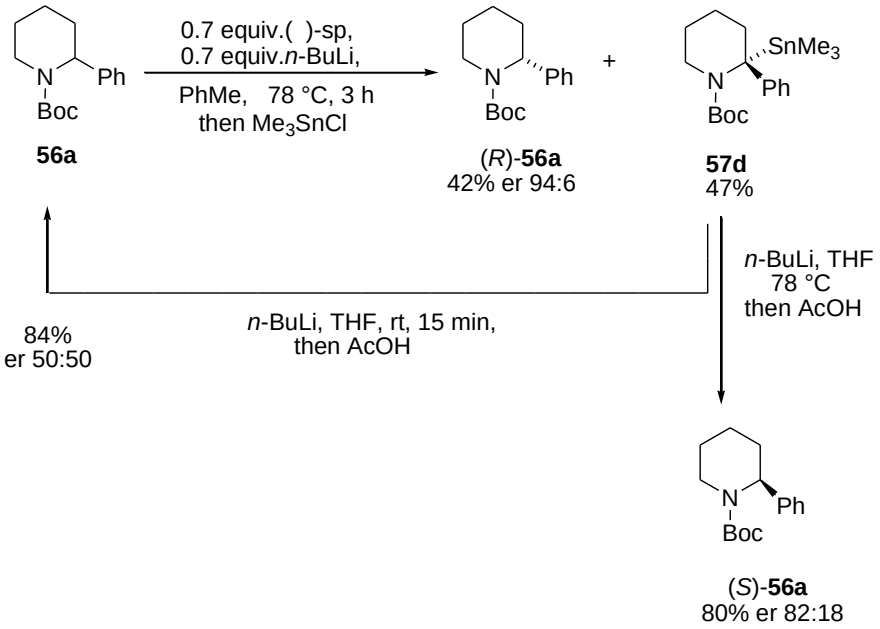
Coldham and co-workers found that lithiated (*S*)-*N*-Boc-2-phenylpiperidine **56a** showed excellent configurationally stability even at –50 °C.[65] Lithiation of (*S*)-2-phenylpiperidine **56a** at –50 °C, followed by trapping with a range of electrophiles after 30 min provided disubstituted products 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 °C ($t_{1/2}$ ~ 4 sec). Similar results were later reported by Gawley and co-workers.[70]



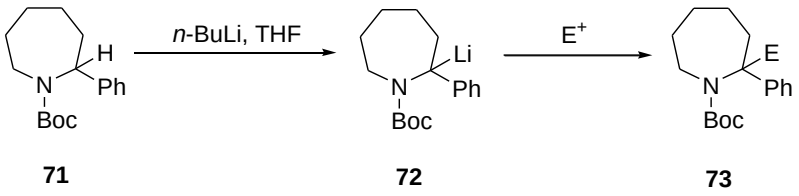

**Scheme 33**

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-arylpiperidines (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-arylpiperidines could be deprotonated with *n*-BuLi in THF at –78 ºC 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 ºC. 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).




**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 35**

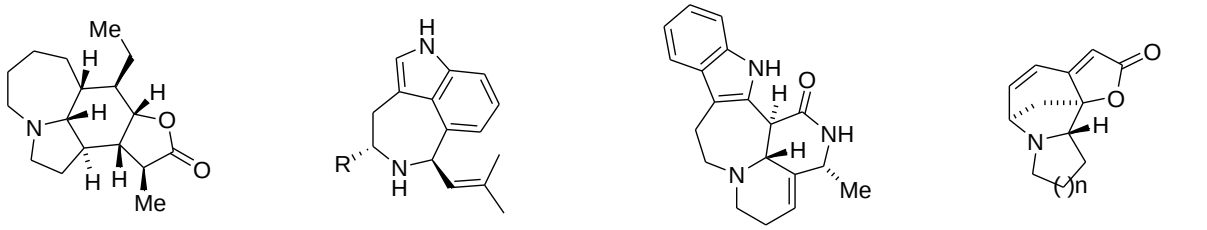
# *Chapter 2*

# 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.[71]

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),[72] ergot (e.g. aurantioclavine and clavicipitic acid),[73] kopsia (e.g. arboflorine),[74] and securinega (e.g. securinine) alkaloids.[75]




**Stenine** | **Aurantioclavine; R=H** **Clavicipitic acid R=$CO_2H$** | **Arboflorine** | **Norsecurinine; n = 1** **Securinine; n = 2**

**Figure 14**

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 azapenes

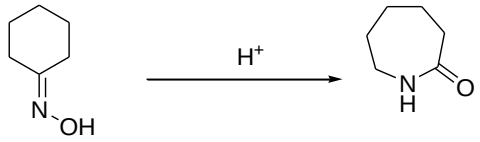
Natural and synthetic compounds containing a chiral azepane ring can display a range of potential or proven biological activities including gastroprokinetic action and protein kinase C inhibitory effects.[76] Despite extensive efforts, only a few methods exist to provide access to saturated substituted 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.[77]

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.[78]

### 2.2.1 The Beckmann Rearrangement

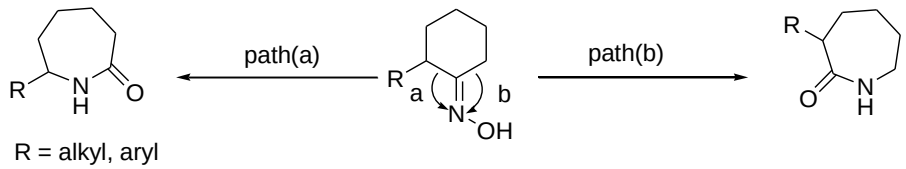
In 1886, Beckmann reported a rearrangement to prepare caprolactams from oximes by carrying out an acid mediated isomerisation (Scheme 36).[79]




**Scheme 36**

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.[80] 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.[81]

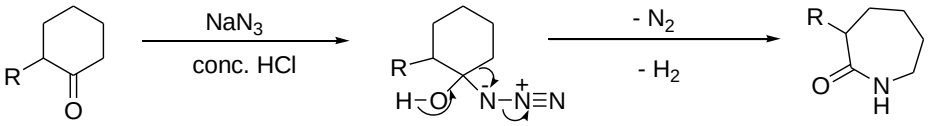
This method was unfavoured in the case of unsymmetrical oximes where two pathways are possible, as this often forms a mixture of products (Scheme 37).[79] The two pathways can occur, and the path taken will depend on the direction of OH group but path (a) is largely preferred because it is *trans* to the leaving group.




**Scheme 37**

### 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).[79]

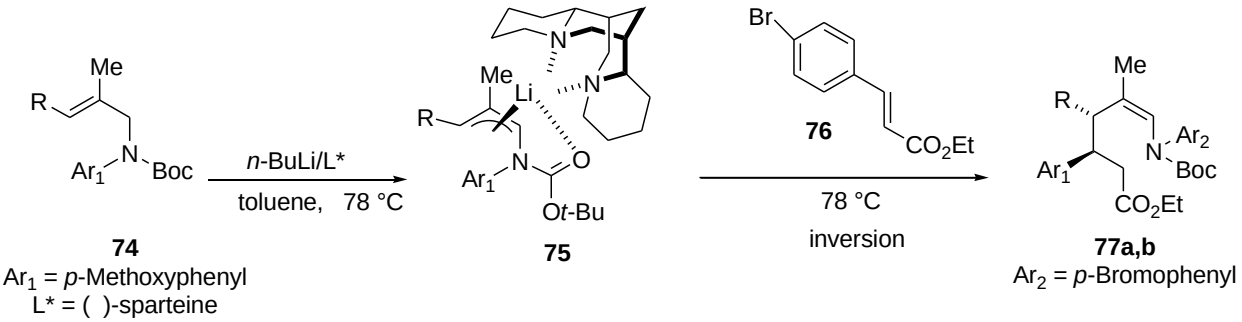



**Scheme 38**

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.[78] The highly diastereo- and enantioenriched enecarbamates **77a** and **77b** were obtained by treatment of *N*-Boc-allylamines **74** with *n*-BuLi at –78 ºC followed by addition of an $\alpha,\beta$-unsaturated ester (Scheme 39, Table 4).




**74**
$Ar_1$ = *p*-Methoxyphenyl
L* = ( )-sparteine

**75**

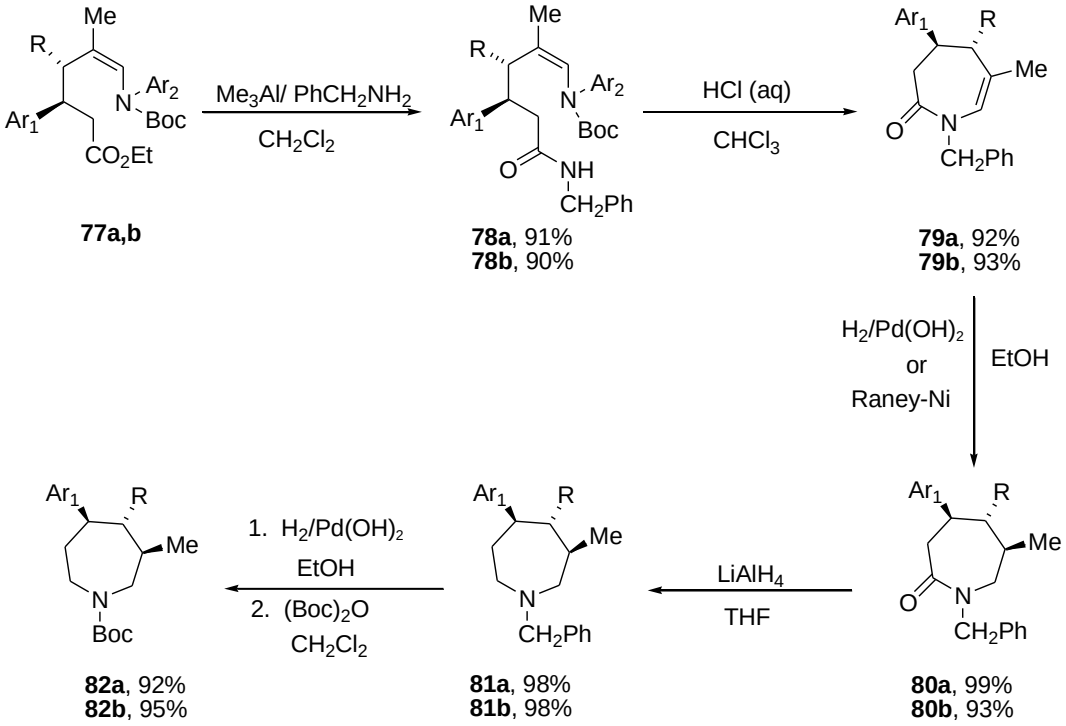
**77a,b**
$Ar_2$ = *p*-Bromophenyl

**Scheme 39**

| Entry | R | Yield (%) | dr | er |
|---|---|---|---|---|
| **77a** | $CH_3$ | 92 | 95:5 | > 95:5 |
| **77b** | Ph | 86 | 93:7 | > 97:3 |

**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).



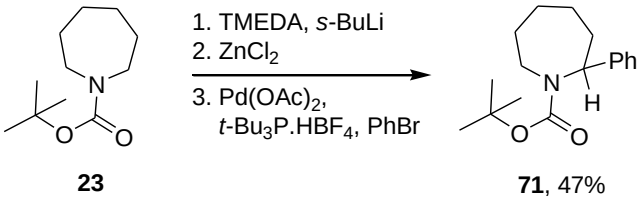

**Scheme 40**

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.[82] 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).[63]

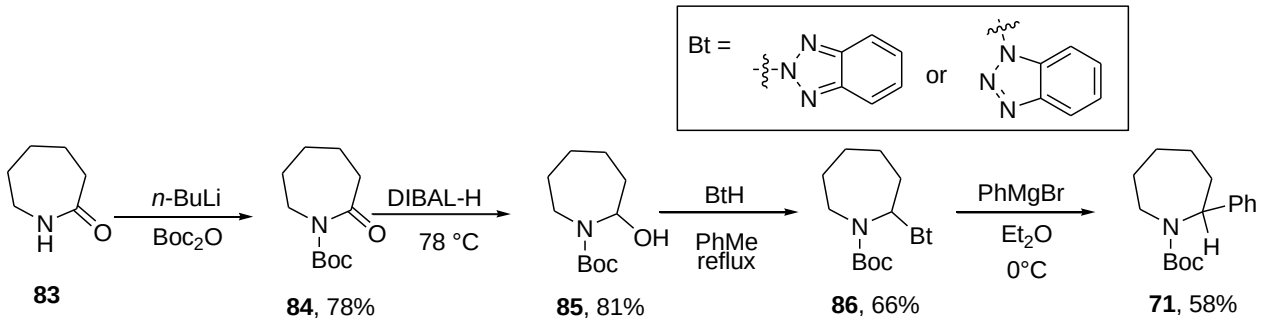



**23** **71**, 47%

**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.

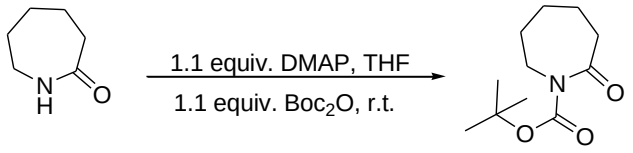
An alternative method to synthesise *N*-Boc-2-phenylazepane **71** was reported by Gawley and co-workers in 2005.[83] Gawley's protocol involved four steps to give the desired product with an overall yield of 58%. Beginning from ε-caprolactam **83**, Boc protection, followed by reduction with diisobutylaluminium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




**83** **84**, 78% **85**, 81% **86**, 66% **71**, 58%

**Scheme 42**

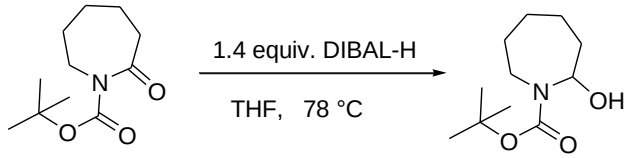
ε-Caprolactam **83** was found to be a cheap and readily available starting material, allowing work to begin on a relatively large scale. However, for the Boc protection, large quantities of butyllithium were required. It was found that by using 4-dimethylaminopyridine (DMAP), alongside $Boc_2O$ the 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 $Boc_2O$ deprotonated the amide. Both mechanisms would only require substoichiometric amounts of DMAP, but conditions in the literature used it stoichiometrically.[84]




**83** **84**, 85%

**Scheme 43**

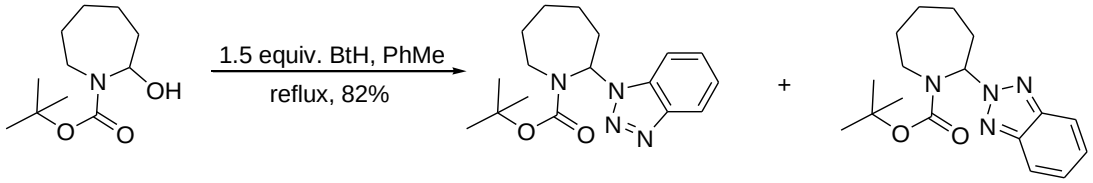
The second step used DIBAL-H to partially reduce the amide moiety. Adding DIBAL-H (1.4 equiv.) dropwise to a solution of lactam **84** at –78 ºC and stirring for 1 hour gave the desired product **85** in 86% yield, which was a slight increase when compared to the literature (Scheme 44). Two rotamers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




**84** **85**, 86%

**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.[83] 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).

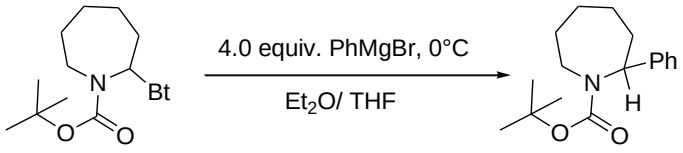



**85** **86a** **86b**

**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 $Et_2O$ to a compound **86** in $Et_2O$ and a small amount of THF to enhance the solubility. The isolated yield of 54% was slightly lower than that reported by Gawley

(Scheme 46).[83] 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.



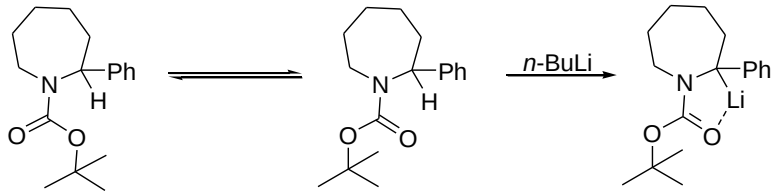

**86** **71**, 54%

**Scheme 46**

### 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 7**1b** (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.

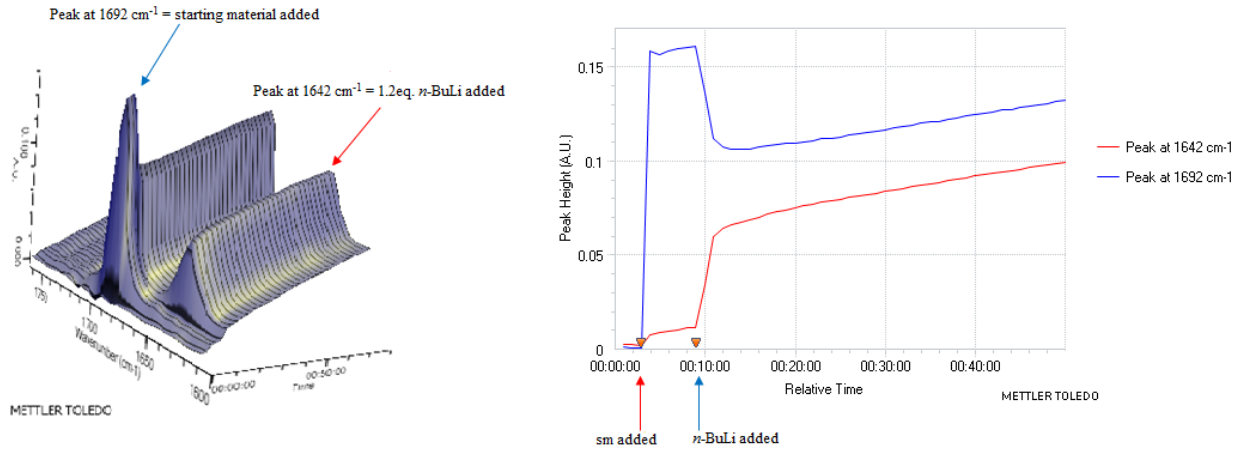



**71a** **71b** **72**

**Scheme 47**

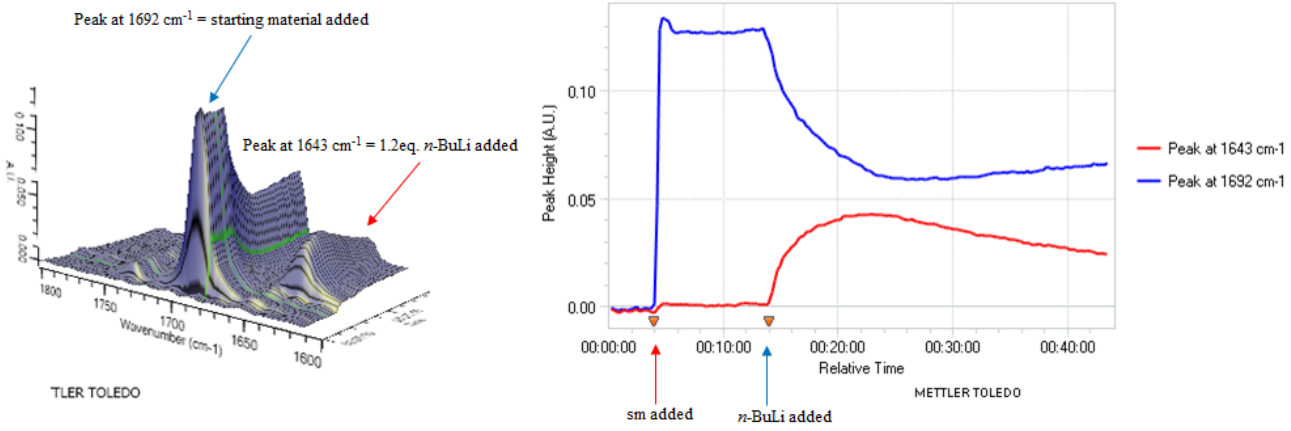
Lithiations were run at different temperatures and specific stretching frequencies were followed over time as the reaction proceeded, to determine the optimum temperature and time for the electrophilic quenches. Lithiation was only partially complete at –78 ºC (Figure 15) or at –30 ºC (Figure 16). This proved that at low temperatures *N*-Boc rotamers **71a** and **71b**

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**.




**(a)** **(b)**

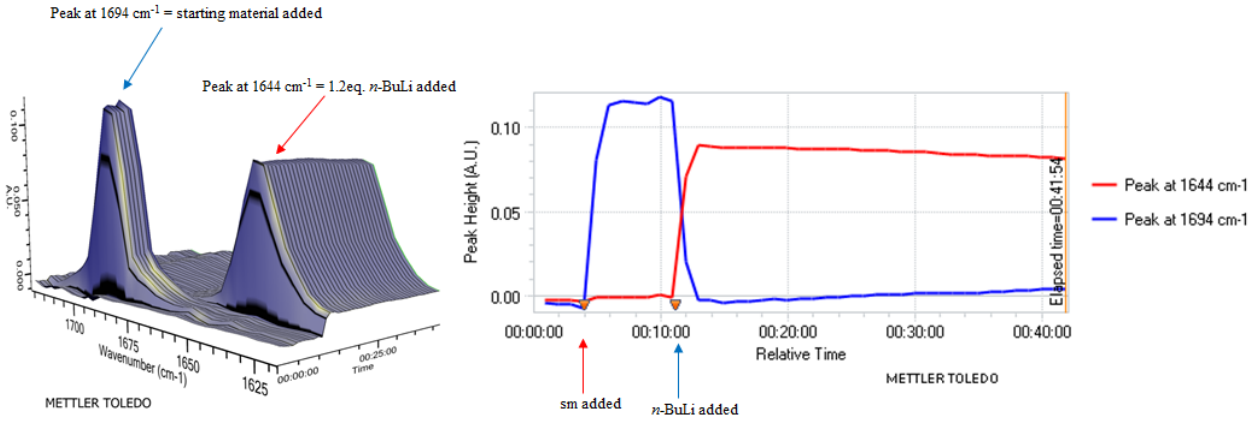
**Figure 15**: 3D and 2D plots of lithiation of **71** at –78 ºC by *in situ* IR spectroscopy. **(a)** 3D plot showing changes in the absorption spectrum with time. **(b)** 2D plot showing the time evolution of the C=O peak for **71** (blue) and for the lithiated intermediate **72** (red). The first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




**(a)** **(b)**

**Figure 16:** 3D and 2D plots of lithiation of **71** at –30 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 **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 ºC (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 ºC and –30 ºC than at –5 ºC. Therefore, at –5 ºC, *rac*-**71** ($\nu_{C=O}$ = 1694 $cm^{-1}$) was fully converted into the lithiated intermediate **72** ($\nu_{C=O}$ = 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 ºC, full lithiation was achieved in just 4 minutes.

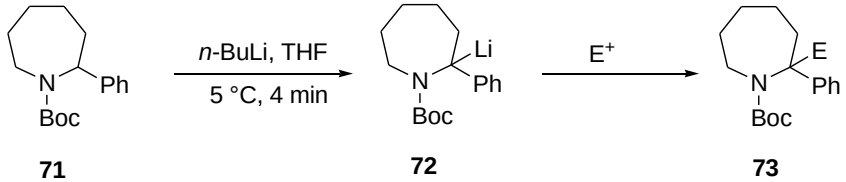



**(a)** **(b)**

**Figure 17:** 3D and 2D plots of lithiation of **71** at –5 ºC; 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

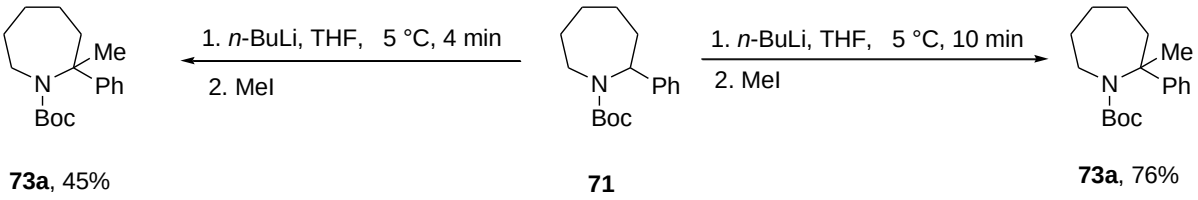
By applying the results obtained using *in situ* IR spectroscopy, *N*-Boc-2-phenylazepane **71** was deprotonated by adding 1.2 equiv. *n*-BuLi at –5 ºC and leaving the reaction mixture for 4 min. Then, the corresponding organolithium was quenched with different electrophiles (Scheme 48).




**71** **72** **73**

**Scheme 48**

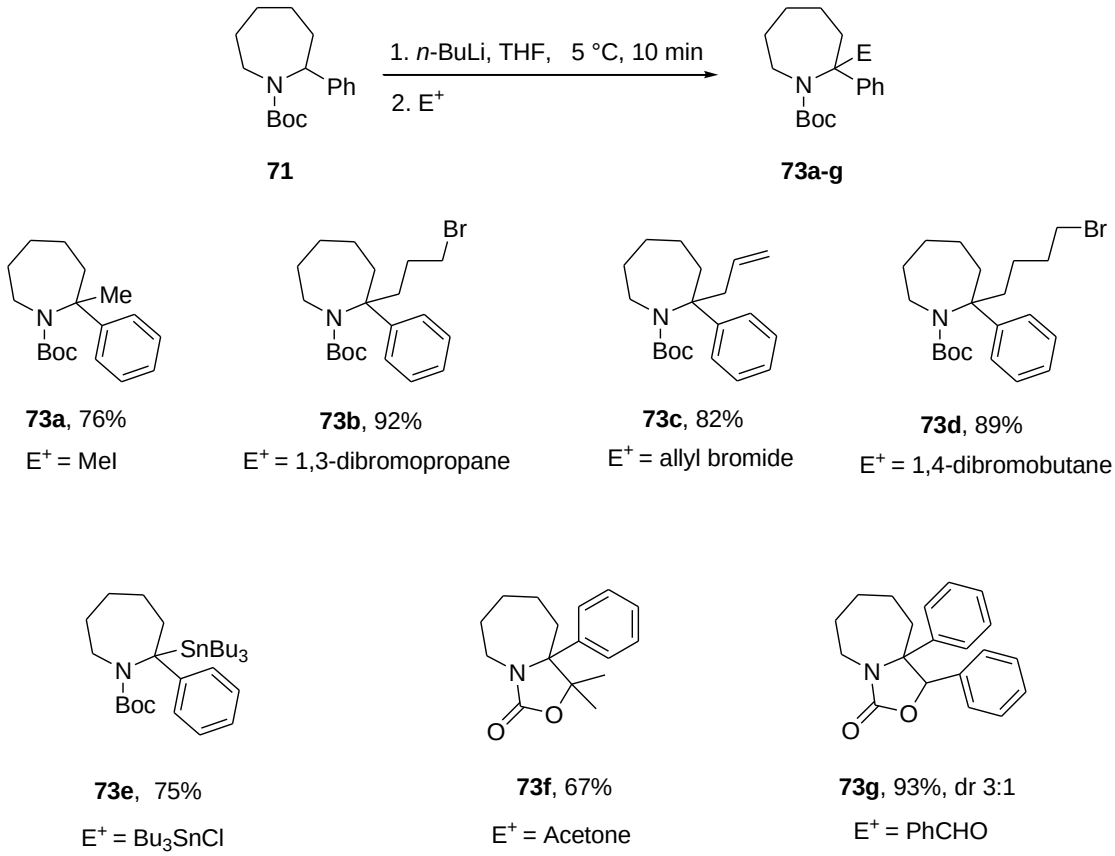
The first electrophile to be used was methyl iodide, which was known to be a reactive electrophile, and therefore should have worked well. The mixture was stirred for 4 minutes before the organolithium intermediate **72** was trapped with the electrophile, but the yield of the product was only moderate (**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.




**73a**, 45% **71** **73a**, 76%

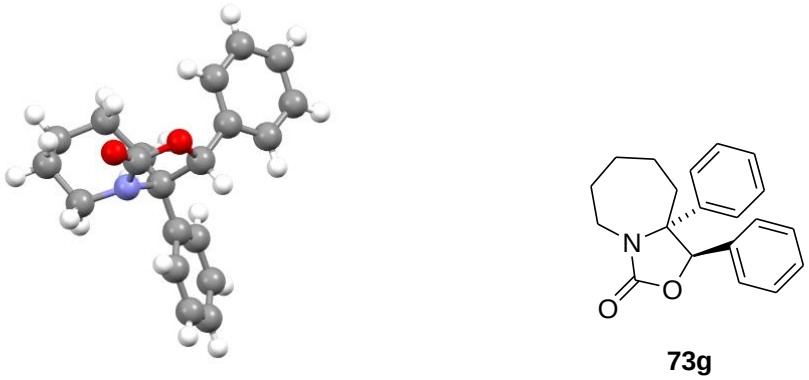
**Scheme 49**

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).




**Scheme 50**

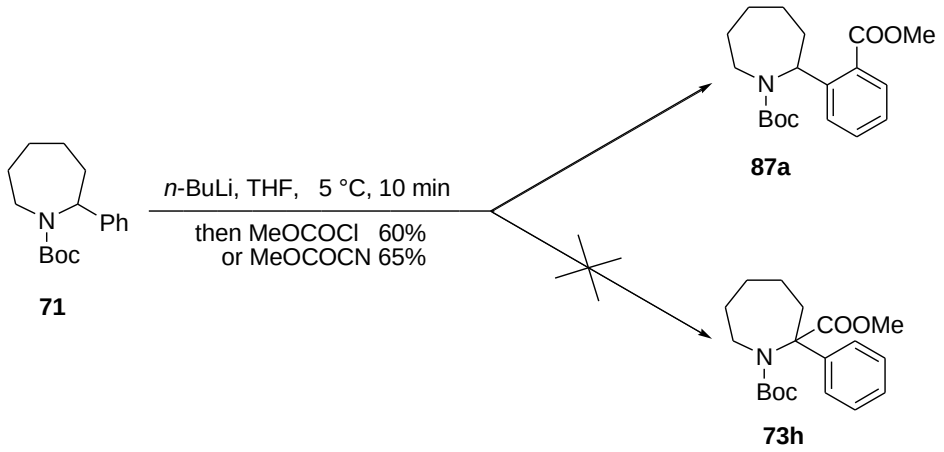
Using carbonyl electrophiles such as acetone and benzaldehyde did not proceed as expected to form alcohol products. Instead, the cyclic carbamates **73f** and **73g** were formed, where the intermediate alkoxide had cyclized on to the Boc group. In the latter case, a separable mixture of diastereomers (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).



**73g**

**Figure 18**

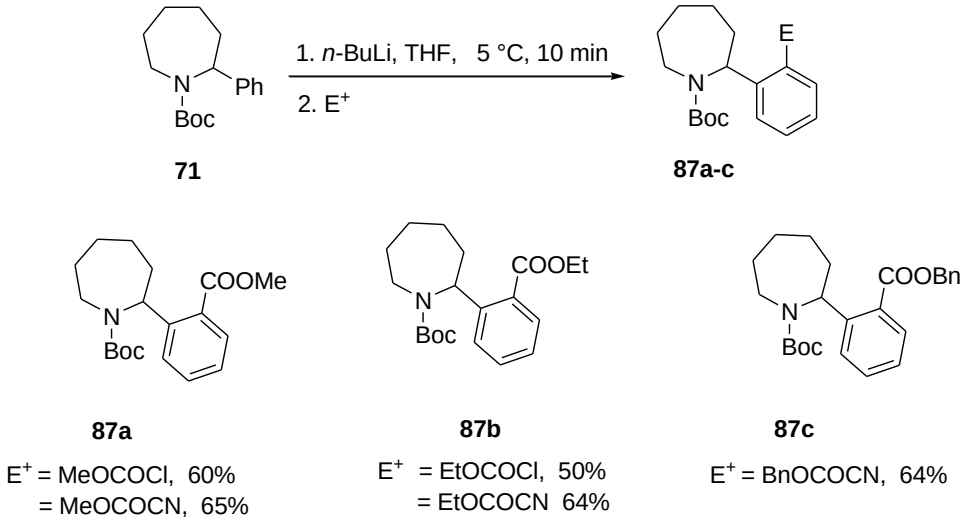
From these results we can see that electrophiles react with the organolithium intermediate **72** leading to the formation of $\alpha$-substituted products. However, an unusual interesting result was obtained where the regioselectivity for this reaction could be changed when we changed the electrophile. 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%.




**Scheme 51**

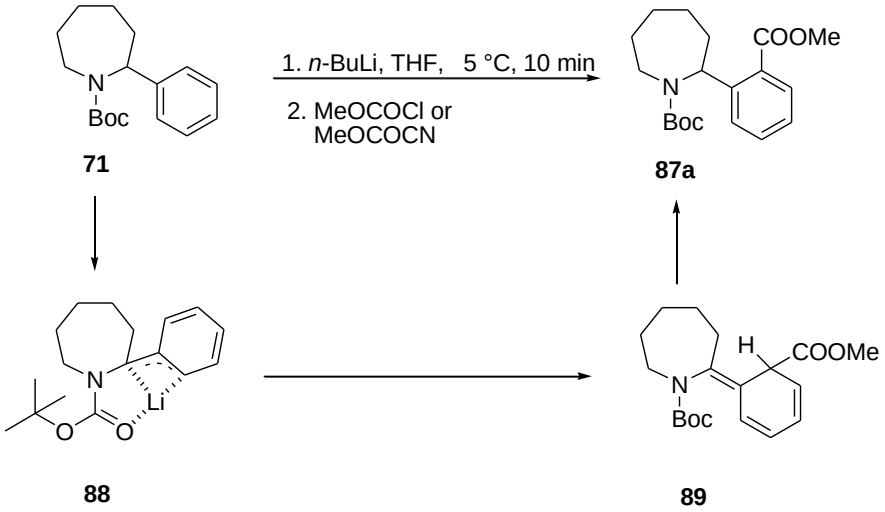
These results were confirmed by the presence of the peak for the benzylic proton in the $^1$H NMR spectrum at 5.62 ppm, together with a reduction in the number of aromatic protons that would be typical for a 1,2-disubstituted benzene ring. In this case, the binding of electrophiles could have change 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).



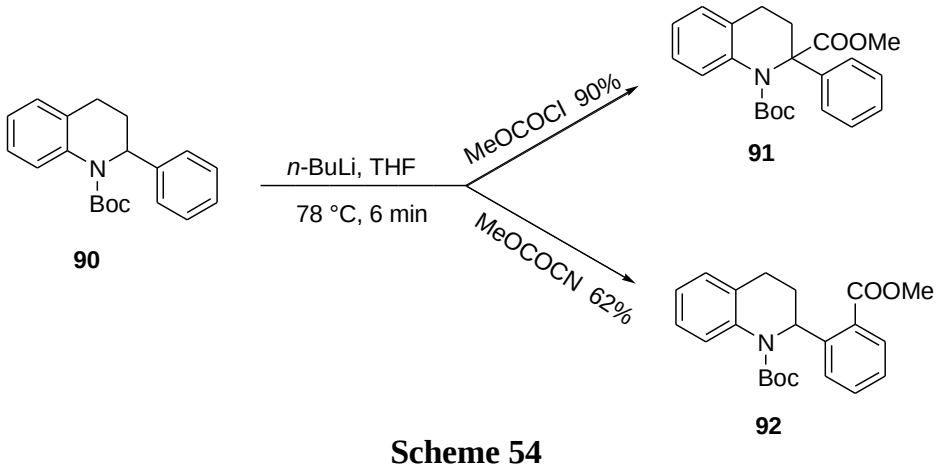

**Scheme 52**

It was difficult to explain the difference in regioselectivity in these cases. It was expected that the *ortho* protons were slightly less acidic than the $\alpha$-protons. However, there was a possibility that the activation energy of *ortho* deprotonation was less than $\alpha$-deprotonation, leading to the *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 *ortho* products could arise from the $\alpha$-lithiated intermediate **72** but with substitution at the *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 *alpha*, *ipso* and *ortho* carbons to give an $\eta^3$ intermediate **88**, which after trapping with methyl chloro- or cyanoformate could provide the *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).[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 *ortho* position.




**Scheme 53**

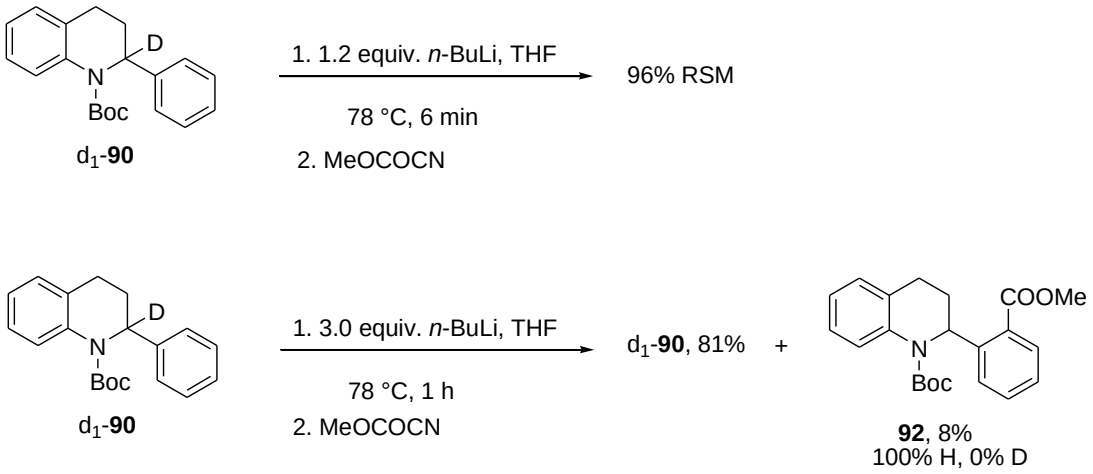
A similar *ortho*-substituted product **92** was formed from the deprotonation of *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **90** with *n*-BuLi and trapping by methyl cyanoformate. This work was discovered by another member of the Coldham group.[86] Interestingly, methyl chloroformate gave the *α*- substituted product **91**, not the *ortho*-substituted product (Scheme 54).




**Scheme 54**

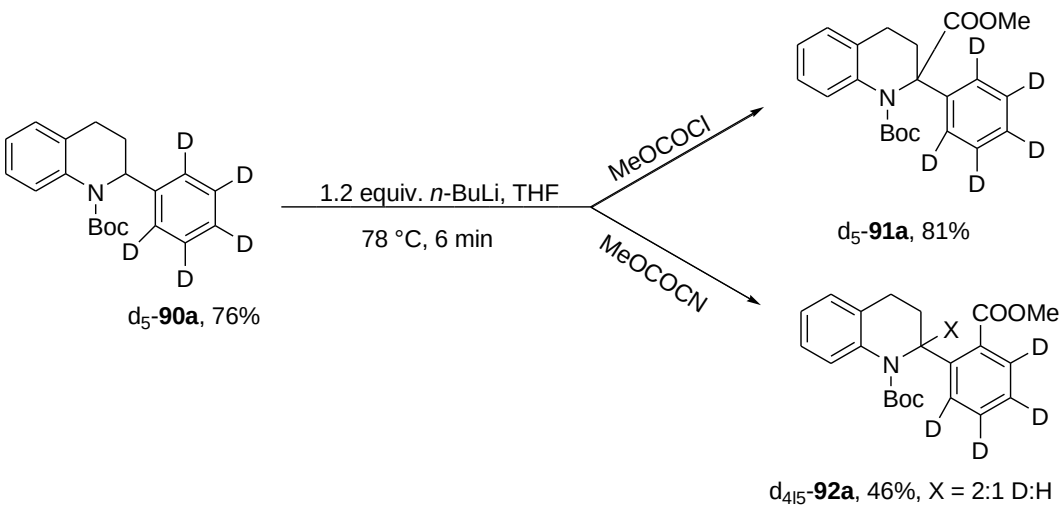
The *α*-substituted product was the expected product in these types of reaction. In order to see whether the reaction was taking place *via* an *ortho*-lithiation pathway, THQ **90** was deprotonated with *n*-BuLi at –78 °C in THF for 6 minutes then addition of $D_2O$ gave the deuterated THQ $d_1$-**90** in good yield with around 95% deuterium incorporation.[86]

By following the same strategy of deprotonation, THQ $d_1$-**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 $d_1$-**90** occurred and only the starting material was recovered (Scheme 55).[86] 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.




**Scheme 55**

Another experiment carried out by Carter used the pentadeuterated derivatives $d_5$-**90a**.[86] Compound $d_5$-**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 $d_5$-**91a**. The reaction was repeated, but methyl cyanoformate was used instead to give product $d_{4/5}$-**92a** (Scheme 56).[86]




$d_5$-**90a**, 76%

$d_5$-**91a**, 81%

$d_{4|5}$-**92a**, 46%, X = 2:1 D:H

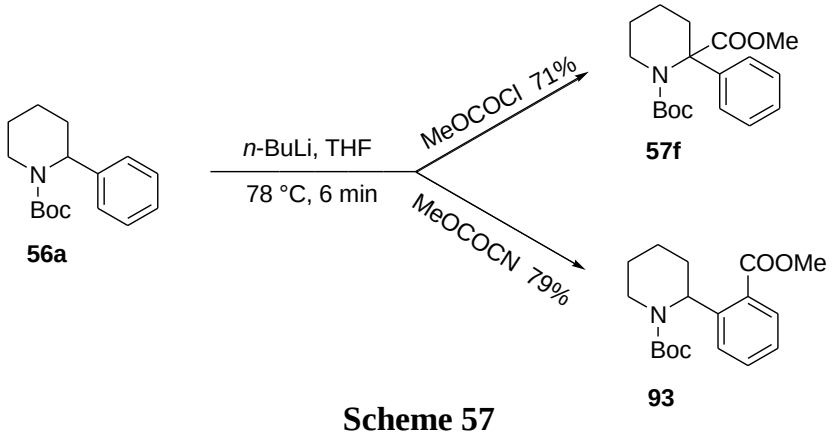
**Scheme 56**

According to Scheme 56, $d_5$-**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 $\alpha$-position occurred in a non-concerted manner. Finally, it could be concluded that with THQs, the use of chloroformate gave $\alpha$-substituted products, but with cyanoformate the *ortho*-substituted product was preferred with only $\alpha$-lithiation taking place in both cases. This result was supported by DFT calculations, which was focussed on the lithiated intermediate.[86] 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 $\alpha$-carbon, whereas when methyl cyanoformate was added, the lithium was closer to the *ortho*-position of the aromatic ring with more of an $\eta^3$ 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 $\eta^3$ 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 $\alpha$-substituted product **57a** (Scheme 21, Chapter 1).[57] 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**.




**Scheme 57**

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 $\eta^3$ 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 $^1$H 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 $^1$H 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 $\Delta G^{\ddagger}$ = 64.5 kJ mol$^{-1}$ at 46 ºC and $\Delta G^{\ddagger}$ = 50.0 kJ mol$^{-1}$ at –28 ºC respectively (Figure 19).[65]

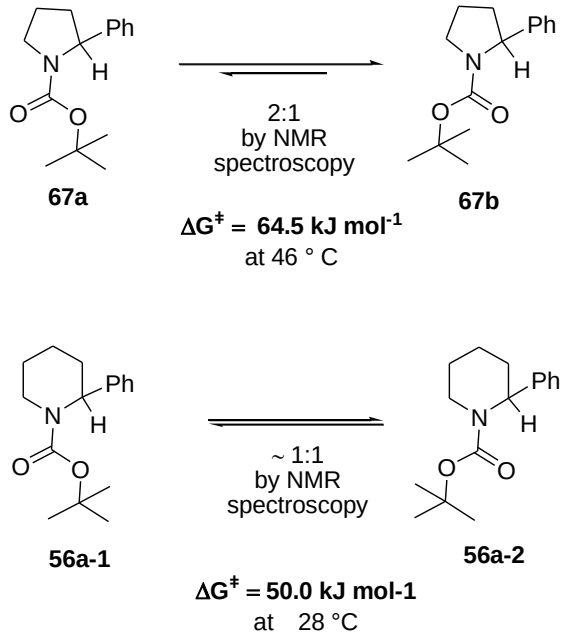



**Figure 19**

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 (δ = ~5.00). The region δ = 5.50–2.00 ppm is shown in Figure 20 with the ratio of rotamers being approximately 1:1.

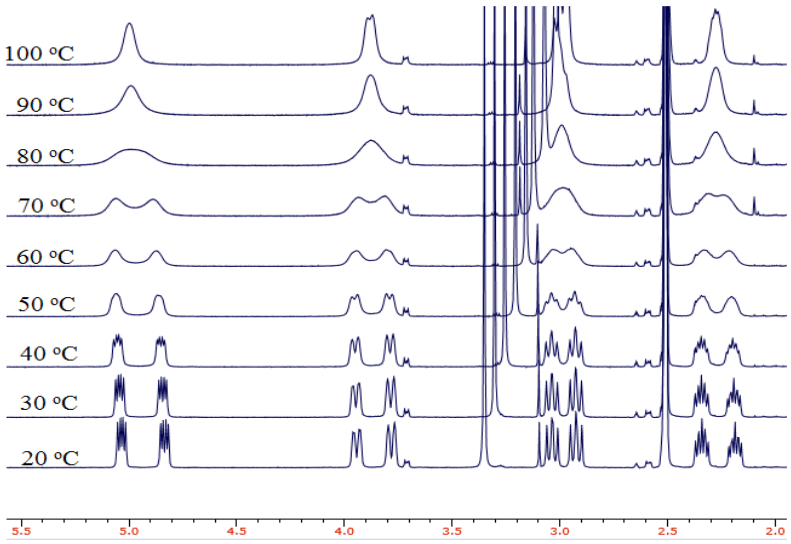



**Figure 20**

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 ºC. 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 J $K^{-1}$ $mol^{-1}$ and $\Delta H^{\ddagger}$ = 73.2 kJ $mol^{-1}$, giving a barrier of rotation where $\Delta G^{\ddagger}$ = 70.8 kJ $mol^{-1}$ at –5 ºC. These activation parameters gave a rotation rate of 8.7 x $10^{-2}$ $s^{-1}$ and a rotational half-life of $t_{1/2}$ = 8 sec at –5 °C. The half-life for rotation of the Boc group was estimated at –78 °C to be $t_{1/2}$ = 28 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-$d_8$ 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 J $K^{-1}$ $mol^{-1}$ and $\Delta H^{\ddagger}$ = 68.1 kJ $mol^{-1}$, gave a rotational barrier of $\Delta G^{\ddagger}$ = 67.8 kJ $mol^{-1}$ at –5 °C and 67.9 kJ/mol at –78 ºC. The corresponding rate constants were worked out to be 3.4 x $10^{-1}$ $s^{-1}$, leading to $t_{1/2}$ = 2 sec at –5 ºC and 2.7 x $10^{-6}$ $s^{-1}$, $t_{1/2}$ = 72 h at –78 ºC. 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-$d_8$ 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.

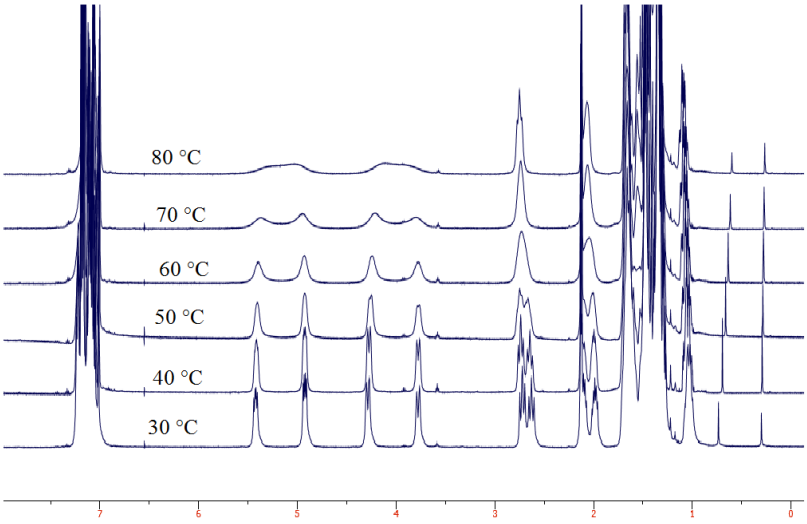
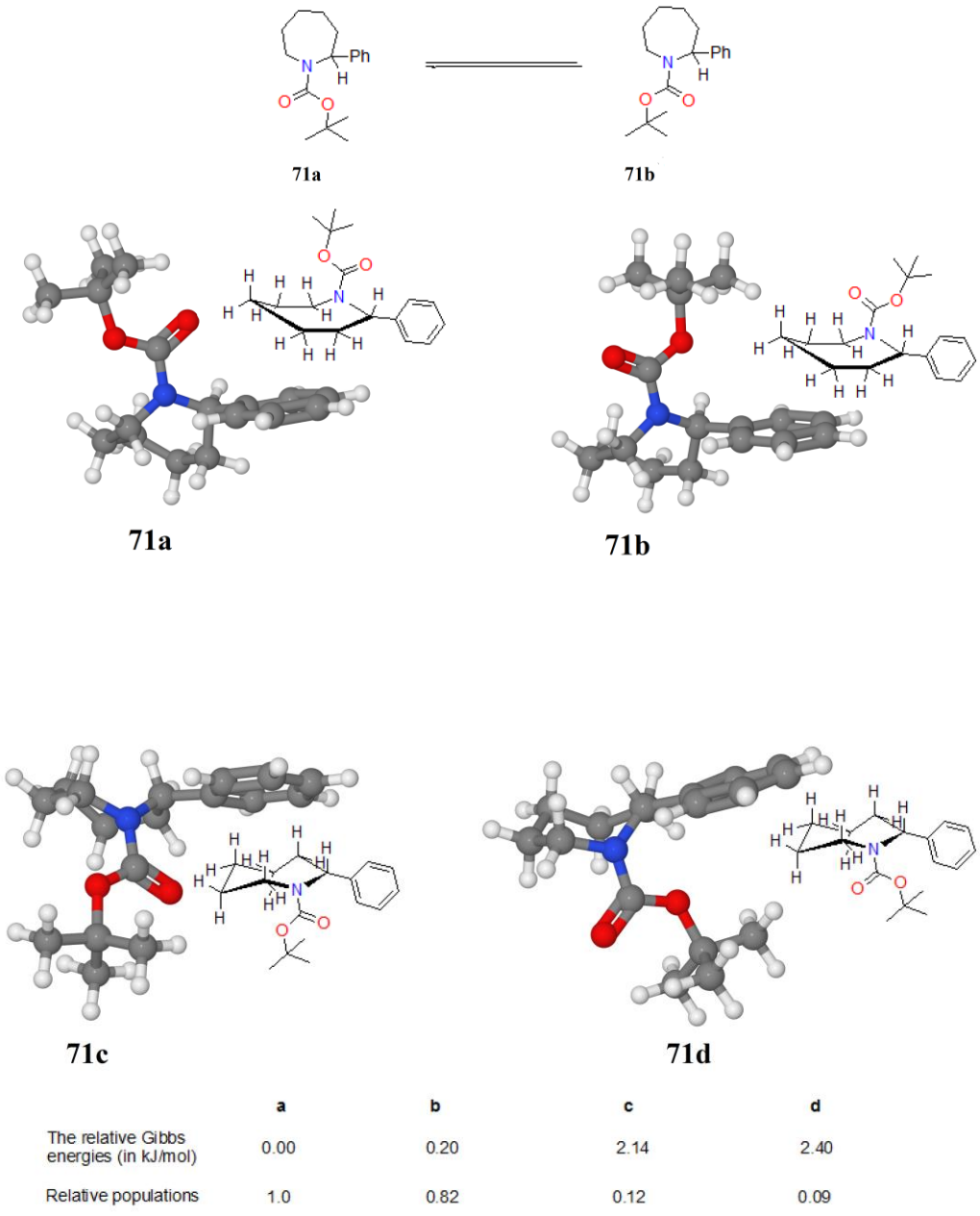



**Figure 21**

### 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.




| | a | b | c | d |
|---|---|---|---|---|
| The relative Gibbs energies (in kJ/mol) | 0.00 | 0.20 | 2.14 | 2.40 |
| Relative populations | 1.0 | 0.82 | 0.12 | 0.09 |

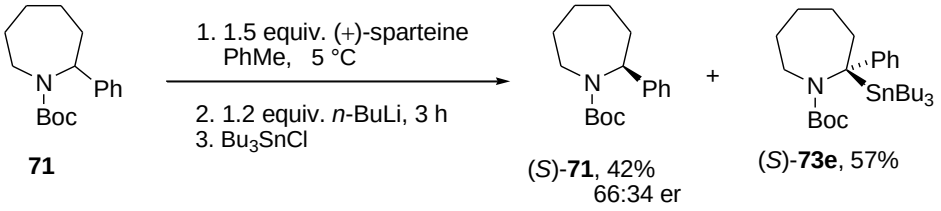
**Figure 22: DFT structures of Transition states after studying clockwise and anticlockwise rotation of the Boc group, with the lowest Gibbs energy barrier**

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 ºC, 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.

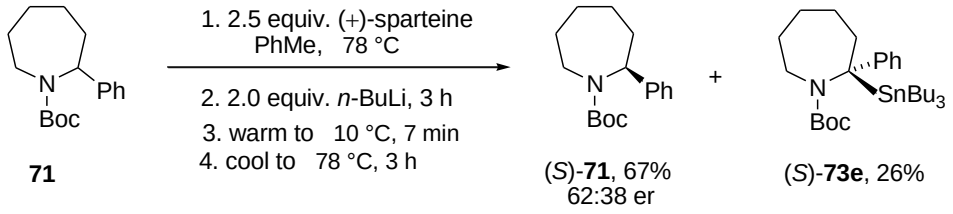
| Entry | Equiv.of *n*-BuLi | Equiv.of (+)-sp | $E^+$ | Yield (%) and er of RSM 71 | Yield (%) of product | time | Temp. | Addition of *n*-BuLi |
|---|---|---|---|---|---|---|---|---|
| **1** | 1.5 | 1.8 | $Br(CH_2)_4Br$ | 92%, (50:50) | 0% | 2 h | –5 ºC | premix |
| **2** | 1.2 | 1.5 | $Br(CH_2)_4Br$ | 82%, (55:45) | 10% | 40 min | –5 ºC | premix |
| **3** | 1.2 | 1.5 | $Bu_3SnCl$ | 63%, (55:45) | 16% | 40 min | –5 ºC | premix |
| **4** | 1.2 | 1.5 | $Bu_3SnCl$ | 70%, (55:45) | 10%, | 2 h | –5 ºC | *n*-BuLi last |
| **5** | 1.2 | 1.5 | $Bu_3SnCl$ | 42%, (66:34) | 57% | 3 h | –5 ºC | *n*-BuLi last |
| **6** | 1.3 | 1.5 | $Bu_3SnCl$ | 70%, (58:42) | 21% | 3 h | –5 ºC | premix |
| **7** | 1.5 | 1.8 | $Bu_3SnCl$ | 34%, (55:45) | 59 % | 3 h | –5 ºC | *n*-BuLi last |
| **8** | 2.0 | 2.5 | $Bu_3SnCl$ | 80%, (56:44) | 12 % | 3 h | –78 ºC | *n*-BuLi last |

**Table 5**

Leaving the reaction for less than 3 h (entries 1-4) led to poor ers 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 ºC, however the starting material was recovered with poor er.

Changing the solvent to $Et_2O$ 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.

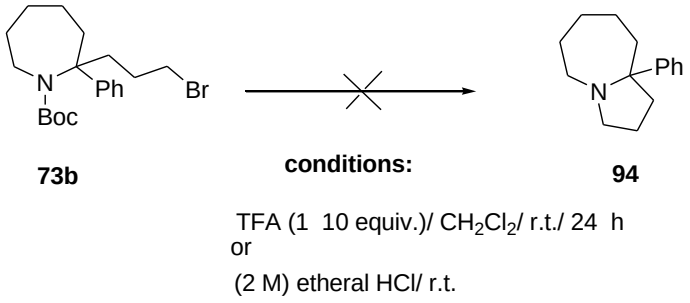
The DTR methodology was also used to check if it was possible to resolve the enantiomers using a warm-cool procedure but unfortunately this gave poor er as well (Scheme 59).




**Scheme 59**

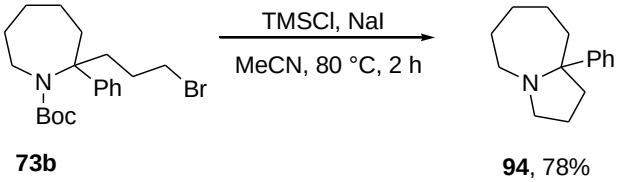
### 2.3.6 Removal of the Boc group

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 $CH_2Cl_2$ at room temperature) to compound **73b** did not give the desired product. $^1$H 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 e failed to give the desired product (Scheme 60).



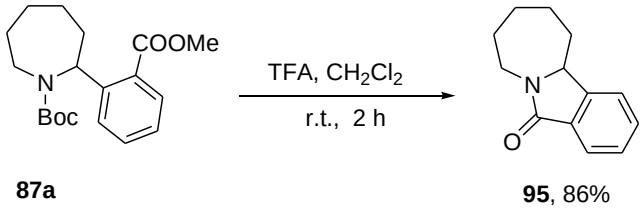

**Scheme 60**

Interestingly, deprotection of **73b** was successful by using a different method previously used by Gawley.[89] Compound **73b** was reacted with TMSI, which was generated *in-situ* from TMSCl and NaI. This promoted *in-situ* cyclization to give the desired bicyclic product **94** (Scheme 61).




**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 $CH_2Cl_2$ 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 on to the carbonyl of the ester group.




**Scheme 62**

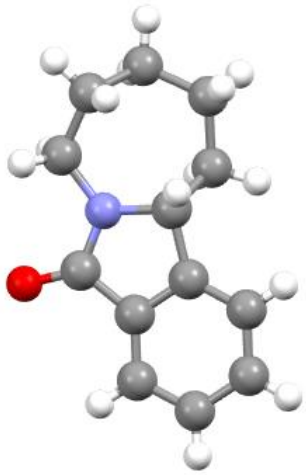


**Figure 23**

## 2.4 Conclusions and future work

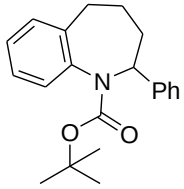
In conclusion, *N*-Boc-2-phenylazepane was synthesised in an overall yield of 54% in four steps starting from cheap and commercially available compounds. Different studies were used to determine the energy barrier of rotation for the Boc group such as VT-NMR and DFT calculations. The lithiation of *N*-Boc-2-phenylazepane **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 °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 *α*-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*

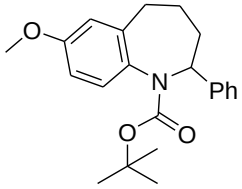
# Synthesis and Lithiation–Substitution of *N*-Boc-2-phenylbenzazepine and *N*-Boc-2-phenyl-7-methoxybenzazepine

## 3.1 Importance of benzazepine derivatives

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




**96**

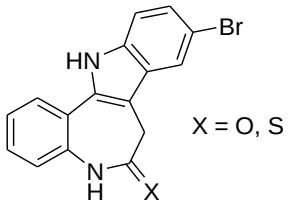



**97**

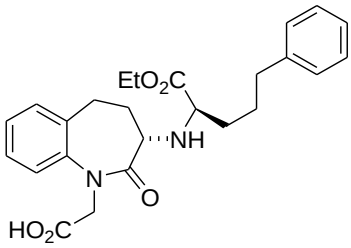
**Scheme 63**

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

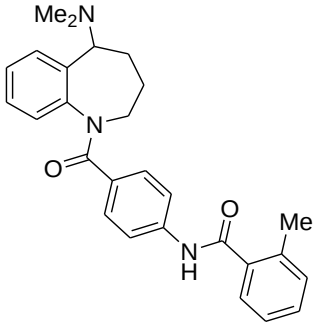
This chapter describes research on the synthesis of substituted benzazepines and focuses on the electrophilic quench of organolithium intermediates.




**Kenpaullone and its thiolactam derivative**




**Lotensin (Benzazepril)**




**Mozavaptan**

**Figure 24**

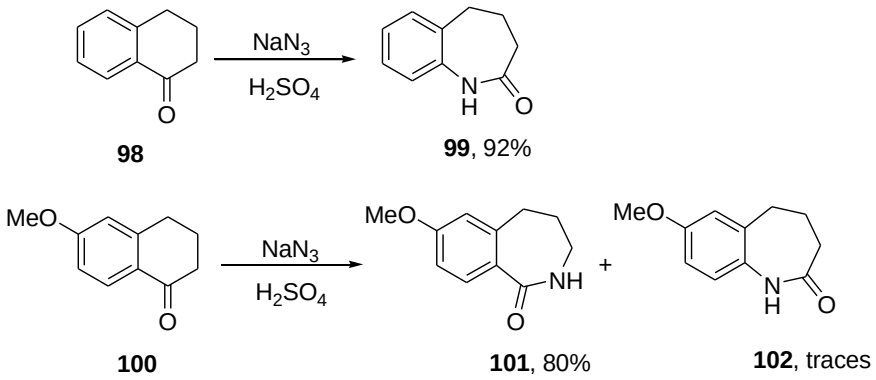
## 3.2 Previous methods used to prepare substituted benzazepines

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.[96] Different routes were used such as rearrangement of tetralones by the reaction of 1,2-dihydroquinoline with dibromocarbene followed by dehydrobromination,[97,98] reaction with ethyl azidoformate[99] and free-radical ring expansion of six-membered heterocycles[100] to give benzazepines.

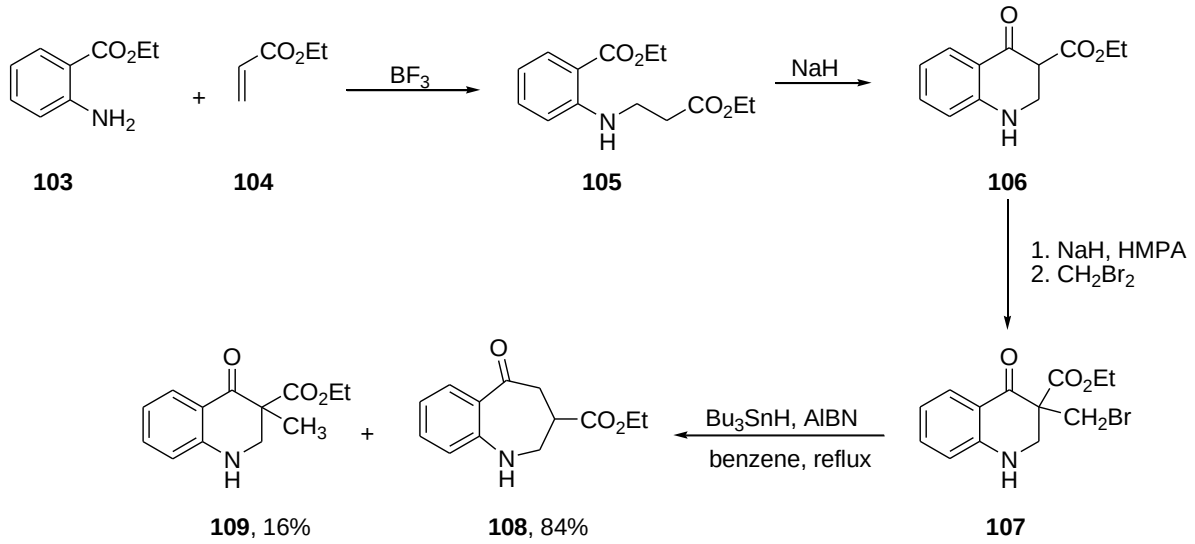
Scheme 64 illustrates the synthesis of 1-benzazepin-2-one **99** by treatment of 1-tetralone **98** with sodium azide in concentrated sulphuric acid.[101,102] However, the same reaction when applied to 6-methoxy-1-tetralone **100** produced 2-benzazepin-1-one derivative **101** as the major product and only traces of 1-benzazepin-2-one derivative **102**.[101] An electronic effect influences whether the product is the benzamide or the acetanilide.




**Scheme 64**

Ring expansion of an aza-six-membered ring by a free radical mechanism gave benzazepine **108** firstly by Dieckmann condensation of the Michael adduct of ethyl anthranilate **103** with ethyl acrylate **104** to give β-keto ester **106** (Scheme 65). β-Keto ester **106** was alkylated with dibromomethane and sodium hydride under reflux in THF to give **107**. This was finally

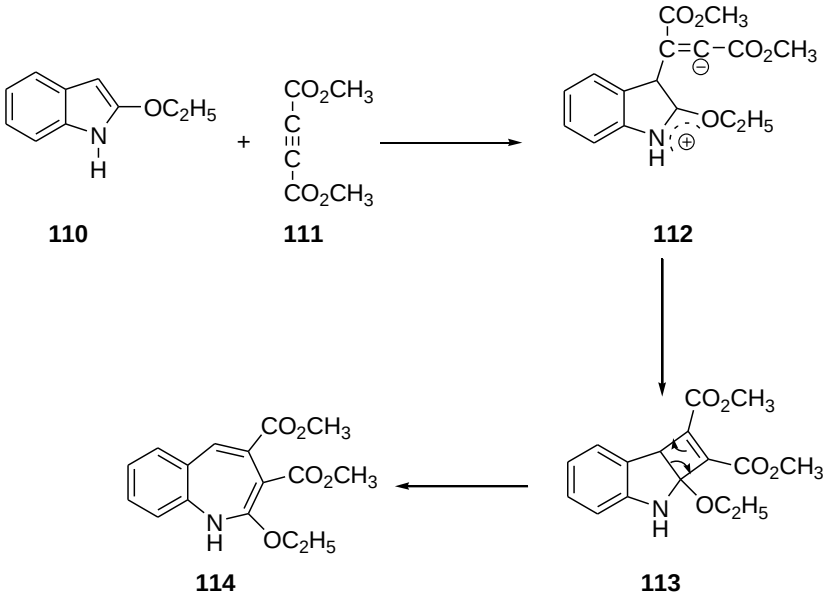
treated with tri-*n*-butyltin hydride in the presence of AIBN catalyst to obtain 84% yield of benzazepine **108** as the major product.[100]




**Scheme 65**

### 3.2.2 Electrocyclic ring opening

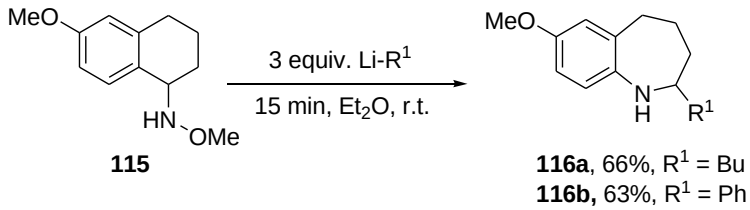
The reaction of indoles with dimethyl acetylene dicarboxylate[103] or ethyl cyanoacetate[104] has been used as a source to synthesise 1H-benzazepine derivatives *via* electrocyclic ring-opining. The cycloaddition of 2-alkoxy-indole **110** to acetylene **111** gave benzazepine derivative **114** *via*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




**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.[105] The treatment of 1-methoxyaminotetraline **115** with *n*-BuLi or PhLi in $Et_2O$ gave the 2-butyl- or 2-phenylbenzazepines **116a** and **116b** in 66% and 63% yields respectively (Scheme 67).

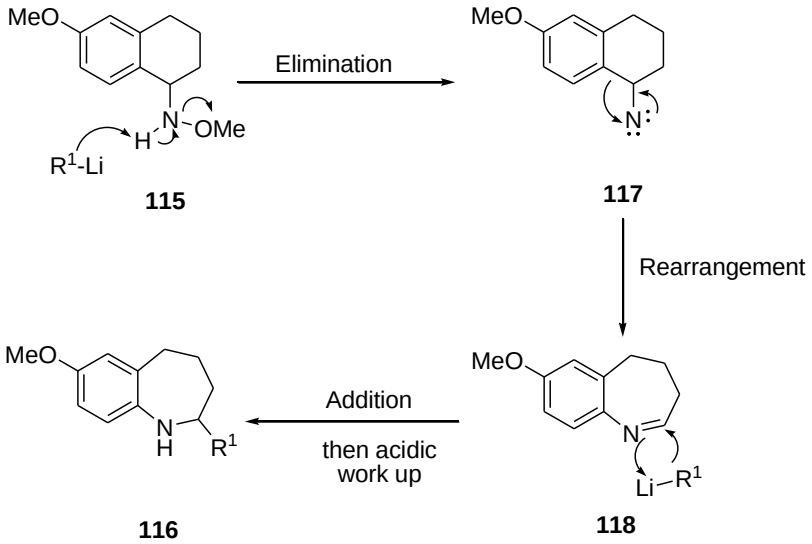



**115**

**116a**, 66%, $R^1$ = Bu
**116b,** 63%, $R^1$ = Ph

**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 **115** is firstly deprotonated by organolithium followed by elimination of methoxide to generate the nitrene intermediate **117**. This intermediate undergoes a rearrangement to form imine **118**. Finally, the addition of the organolithium to the imine **118** gives benzazepine derivative**s 116** (Scheme 68).



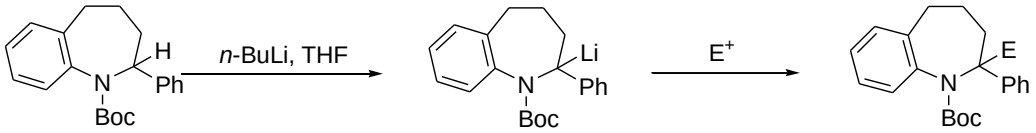

**115** **117** **118** **116**

**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.

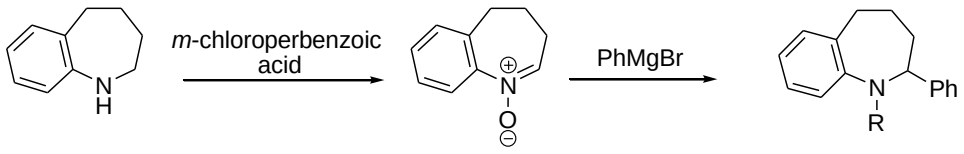



**96** **119** **120**

**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 $HN_3$ 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**.



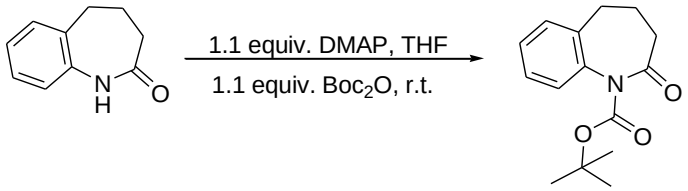

**121** **122** **123**

**123a**, R = H
**123b**, R = OH

**Scheme 70**

It was interesting to begin thinking about following the same synthetic route used for the synthesis of *N*-Boc-2-phenylazepane **71** due to the easy availability of starting materials and simple reaction conditions (Gawley methodology).[83] As mentioned before, this methodology involved four steps to give the desired product.

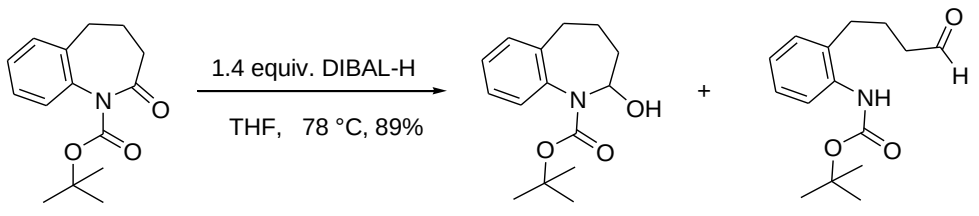
The first step was Boc protection of benzazepin-2-one **99** which was available commercially at a low price. A high yield of 93% of protected product **124** was obtained by reaction of benzazepin-2-one **99** with $Boc_2O$ in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 71). Attempting to do the reaction in the absence of DMAP did not give the product.




**99** **124**, 93%

**Scheme 71**

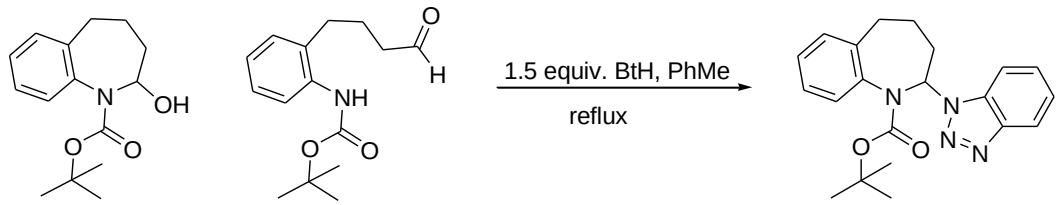
The second step was treatment of **124** with by DIBAL-H to reduce the lactam's amide moiety. Adding DIBAL-H (1.4 equiv.) dropwise to a solution of lactam **124** at –78 ºC gave a mixture of **125a** and **125b** in 89% yield (Scheme 72). The reduction therefore led to the formation of two different 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.




**124** **125a** **125b**

**Scheme 72**

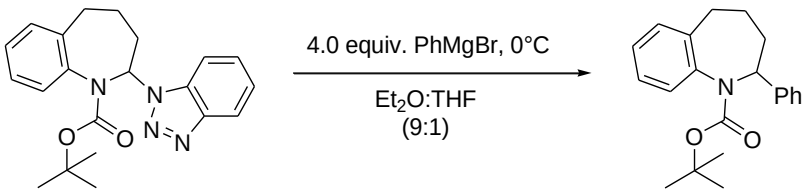
Next, a substitution reaction using benzotriazole was performed by heating a 1.0:0.7 mixture of **125a** and **125b** under reflux in toluene, resulting in an 84% yield of the desired product **126** (Scheme 73).




**125a** **125b** **126**, 84%

**Scheme 73**

To form the desired target *N*-Boc-2-phenylbenzazepine, phenylmagnesium bromide as a solution in $Et_2O$ was added to compound **126** in a mixture of $Et_2O$/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 $Et_2O$:THF was used to enhance the solubility of **126** which was less soluble in neat diethyl ether. The $^1$H 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.




**126** **96**, 70%

**Scheme 74**

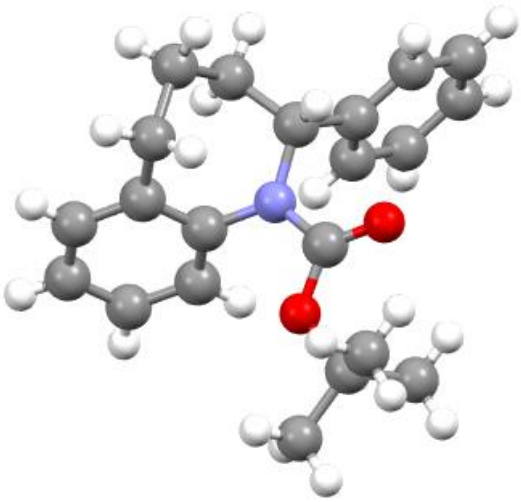
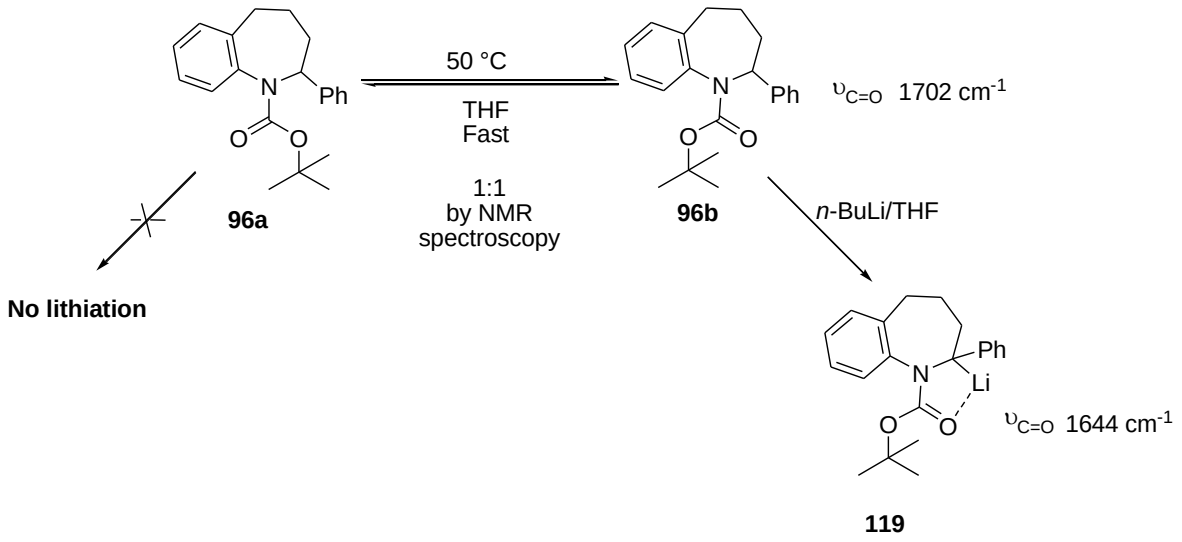


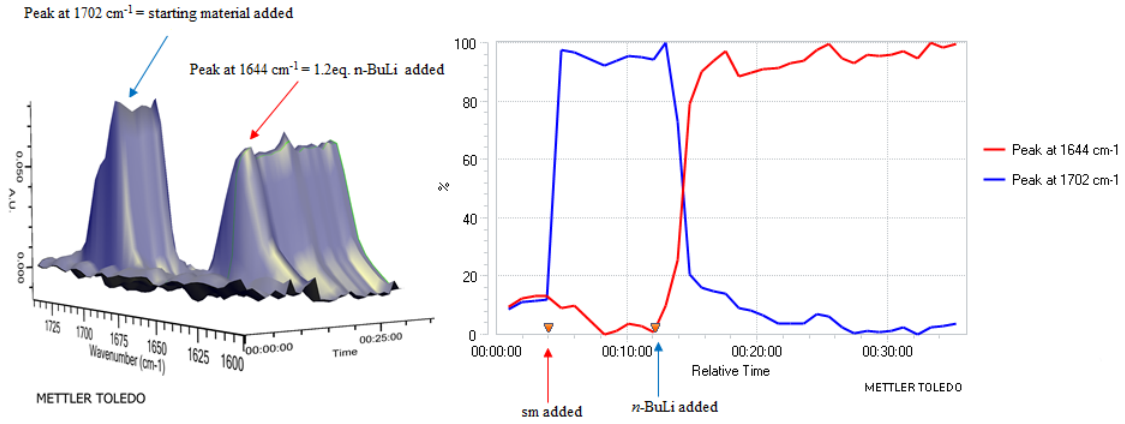
**Figure 25**

### 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 ºC 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**

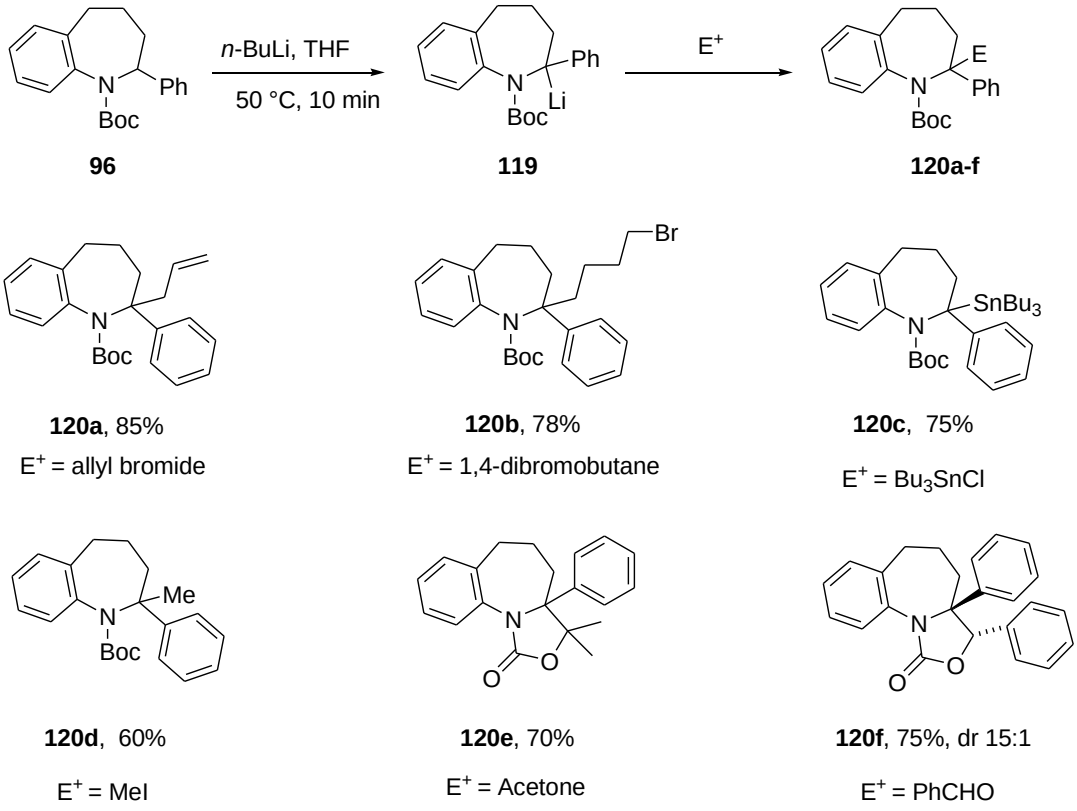



**(a)** **(b)**

**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

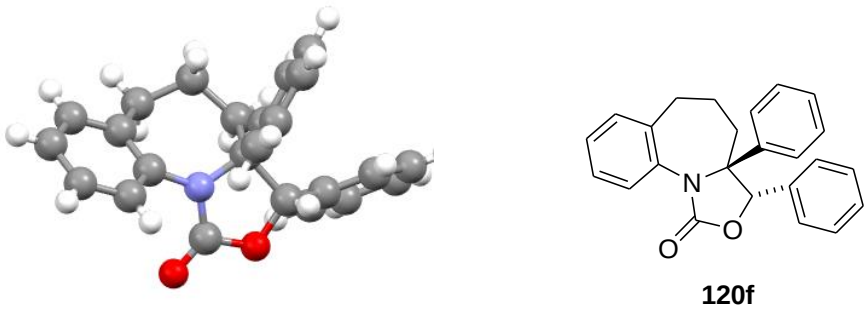
Based on the *in-situ* ReactIR results above, *N*-Boc-2-phenylbenzazepine **96** was deprotonated by adding 1.2 equiv. of *n*-BuLi at –50 ºC and the reaction mixture was left to stir for 10 minutes. Then, the resulting organolithium was quenched with different electrophiles. The racemic *N*-Boc-2-phenyl-2-substituted benzazepines **120a–f** were obtained in good to excellent yields (Scheme 76).




**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).

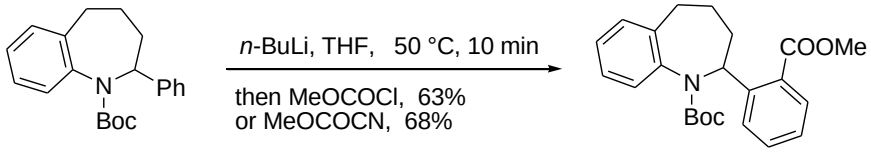
Trapping with carbonyl electrophiles such as acetone and benzaldehyde did not form alcohol products. Instead, the cyclic carbamates **120e** and **120f** were formed in good yields respectively. The stereochemistry of compound **120f** was determined by X-ray crystallography, after separating by column 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.




**120f**

**Figure 27**

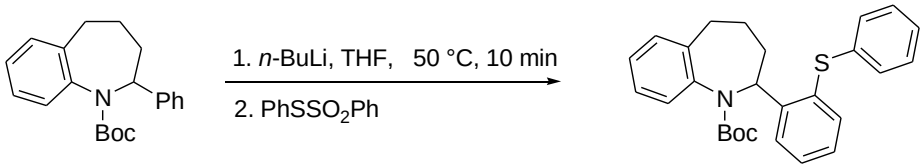
Interestingly, *ortho*-substituted products were formed when the organolithium intermediate was reacted with alkyl cyano- or chloroformates which was the same as that observed with *N*-Boc-2-phenylazepane **71**. The lithiation of *N*-Boc-2-phenylbenzazepine **96** followed by the addition of methyl cyanoformate or methyl chloroformate as electrophiles gave *ortho*-substituted product **127a** in a good yield of 63–68% (Scheme 77).




**96** **127a**

**Scheme 77**

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 ºC, followed by the addition of *S*-phenyl benzenethiosulfonate gave 85% yield of *ortho*-substituted product **127b** (Scheme 78).

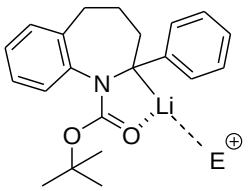



**96** **127b**, 85%

**Scheme 78**

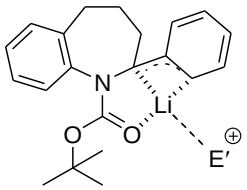
As explained earlier in chapter 2, some electrophiles have different regioselectivity in the reaction with the organolithium intermediate to form $\alpha$-substituted products or *ortho*-substituted products. The regioselectivity depends on the nature of lithium co-ordination. The lithium atom could co-ordinate in an $\eta^1$ arrangement to give complex **119**, which would form $\alpha$-substituted products. Alternatively, an $\eta^3$ complex could form where the lithium atom

co-ordinates to the *alpha*, *ipso* and *ortho* carbons forming *ortho*-substituted products (Scheme 79).




**119**

$\eta^1$- organolithium complex




**128**

$\eta^3$-organolithium complex

**Scheme 79**

### 3.3.1.4 Variable temperature $^1$H NMR spectroscopy study

It was interesting to see if the energy barrier to the rotation of the Boc group could be determined for *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 *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 ºC. The region δ = 5.50–2.50 ppm is shown in Figure 28 with the ratio of rotamers being approximately 1:0.8.

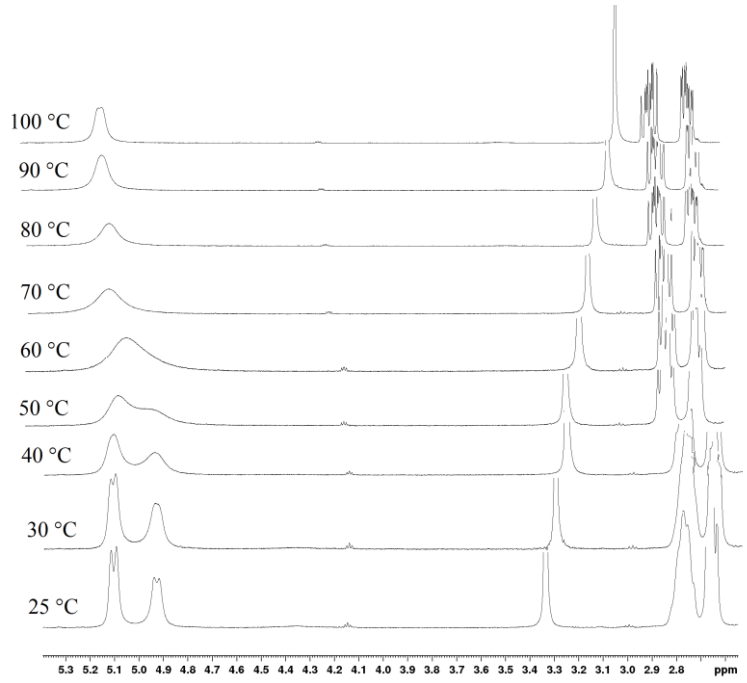
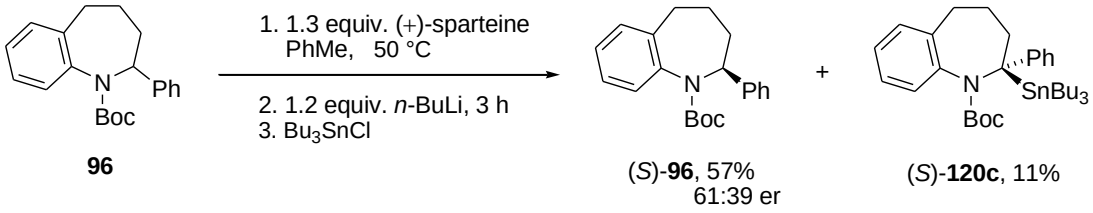



**Figure 28: Variable temperature $^1$H NMR spectroscopy of *N*-Boc-2-phenylbenzazepine 96**

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 J $K^{-1}$ $mol^{-1}$ and $\Delta H^{\ddagger}$ = 55.8 kJ $mol^{-1}$, giving a barrier of rotation $\Delta G^{\ddagger}$ = 62.0 kJ $mol^{-1}$ at –78 ºC and 62.9 kJ $mol^{-1}$ at –50 ºC. These activation parameters gave a rotation rate of 1 x $10^{-4}$ $s^{-1}$ and a rotational half-life of $t_{1/2}$ = 2 h at –78 °C. The half-life for rotation of the Boc group was estimated at –50 °C to be $t_{1/2}$ = 2 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 ºC, 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*)-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]




**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 ºC (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).

| Entry | Equiv.of *n*-BuLi | Equiv.of (+)-sp | Yield (%) and er of RSM 107 | Yield (%) of product | time | Addition of *n*-BuLi |
|---|---|---|---|---|---|---|
| **1** | 1.3 | 1.5 | 80%, (55:45) | 10% | 3 h | premix |
| **2** | 1.3 | 1.5 | 70%, (57:43) | 27% | 3 h | *n*-BuLi last |
| **3** | 1.5 | 2.5 | 65%, (57:43) | 19% | 5 h | premix |
| **4** | 2.3 | 2.8 | 85%, (55:45) | 0% | 4 h | premix |
| **5** | 1.2 | 1.3 | 57%, (60:40) | 11% | 3 h | *n*-BuLi last |
| **6** | 0.8 | 1.0 | 87%, (54:46) | 11% | 3 h | *n*-BuLi last |

**Table 6: Kinetic resolution conditions at –50 ºC**

Changing the temperature to –78 ºC (Table 7) gave in general the same results as those obtained at –50 ºC. 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).

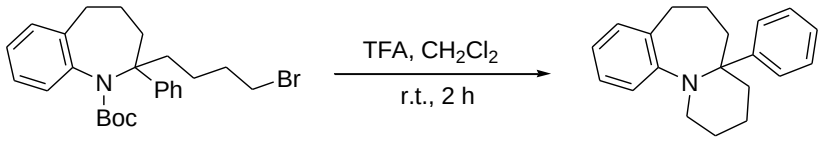
| Entry | Equiv.of *n*-BuLi | Equiv.of (+)-sp | Yield (%) and er of RSM 107 | Yield (%) of product | time | Addition of *n*-BuLi |
|---|---|---|---|---|---|---|
| **1** | 1.3 | 1.5 | 80%, (55:45) | 10% | 3 h | premix |
| **2** | 1.3 | 1.5 | 70%, (52:48) | 27% | 5 h | *n*-BuLi last |
| **3** | 1.5 | 2.5 | 65%, (61:39) | 19% | 5 h | premix |
| **4** | 2.3 | 2.8 | 85%, (55:45) | 10% | 4 h | premix |
| **5** | 1.2 | 1.3 | 60%, (59:41) | 11% | 3 h | *n*-BuLi last |
| **6** | 0.8 | 1.0 | 87%, (54:46) | 10% | 3 h | *n*-BuLi last |

**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

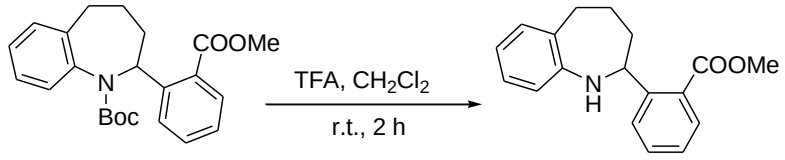
It was interesting to investigate the deprotection conditions of 2,2-disubstituted benzazepine derivatives. Previously, treating 2,2-disubstituted azepane **73b** with 1 equiv. of TFA in $CH_2Cl_2$ at room temperature did not give the desired product. In contrast, the deprotection 2,2-disubstituted benzazepine **120b** using 30% TFA in $CH_2Cl_2$ at room temperature gave 88% yield of the desired product without finding any problems in comparison with the analogous azepane derivatives (Scheme 81).




**120b** **129**, 88%

**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 $CH_2Cl_2$ 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.



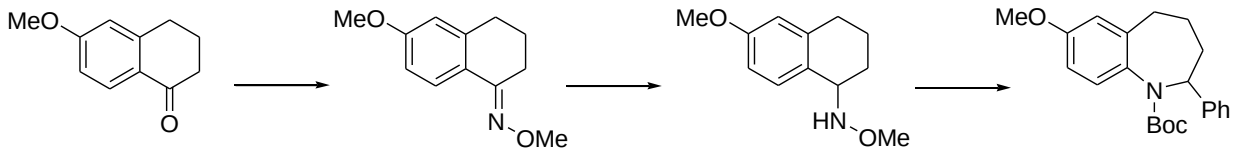

**127a** **130**, 86%

**Scheme 82**

### 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.

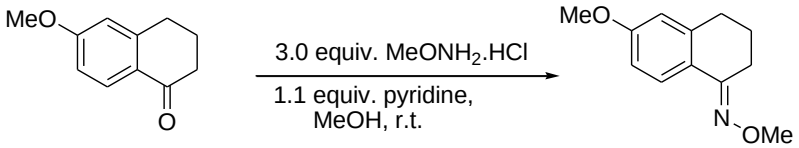



**100** **131** **115** **97**

**Scheme 83**

The first two steps were the common synthetic route of amine synthesis by imine formation and reduction using a literature method.[108] 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 $^1$H 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.[109]

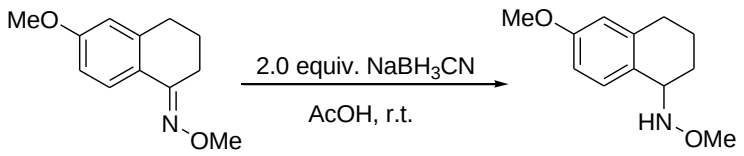



**100** **131**, 91%

**Scheme 84**

No stereochemistry of product **131** was given in the literature about which isomer formed.[108] It could not be a mixture of two isomers because the $^{1}$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 *ortho*-substituent.

By following the literature,[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.



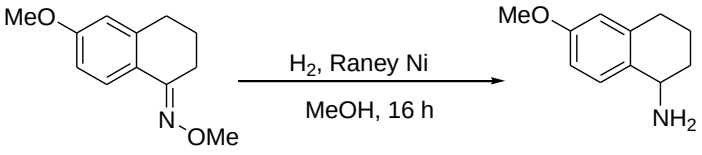

**131** **115**, 28%

**Scheme 85**

| Entry | Reducing Agent | Temp./ ºC | Time/ h | Yield % |
|---|---|---|---|---|
| **1** | 2 eq. $NaBH(OAc)_3$, AcOH | 24 | 6 | 0 |
| **2** | 4 eq. $NaBH(OAc)_3$, AcOH | 120 | 12 | 0 |
| **3** | 4 eq. $NaBH_4$, EtOH | 24 | 12 | 0 |
| **4** | 1.4 eq. DIBAL, THF | –78 | 12 | 0 |
| **5** | $H_2$, Raney Nickel, 1 atm, MeOH | 24 | 12 | 0 |
| **6** | 1.25 eq. $NaBH_3CN$, MeOH, HCl | 24 | 24 | 63 |

**Table 8**

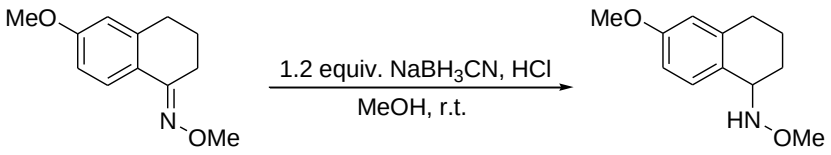
As shown in Table 7, different reducing agents were used by a final year undergraduate student assisting with this project. Using sodium triacetoxyborohydride $NaBH(OAc)_3$ instead of sodium cyanoborohydride did not give a product in either acetic acid or ethanol (entries 1,2). The same problem was found 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 $^1H$ NMR and $^{13}C$ NMR spectrum (entry 5 and scheme 86).[109]




**131** **132**, 88%

**Scheme 86**

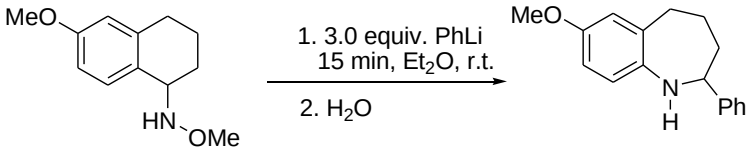
The best conditions were achieved when sodium cyanoborohydride was used as the reducing agent. As shown in entry 6, a 63% yield of amine **115** was obtained (Scheme 87) when oxime **131** was treated with sodium cyanoborohydride in methanol, followed by acidification of the solution with HCl. This method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




**131** **115**, 63%

**Scheme 87**

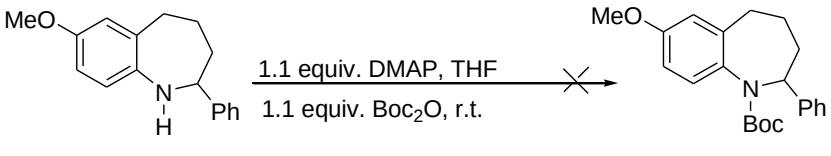
Next, following a literature method,[105] adding phenyl lithium to amine **115** gave 55% yield of 2-phenyl-7-methoxybenzazepine **133** (Scheme 88) *via* a rearrangement-addition reaction. The mechanism for this process was explained previously in section 3.2.3 (Scheme 68).




**115** **133**, 55%

**Scheme 88**

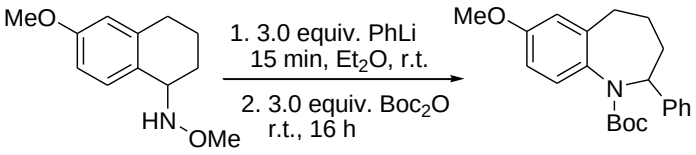
The final step was incorporation of the Boc group by adding $Boc_2O$ to 2-phenyl-7-methoxybenzazepine **133** in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 89). Unfortunately, this procedure did not form the desired product.




**133** **97**, 0%

**Scheme 89**

Our target product was carbamate **97** not amine **133**, therefore some changes were applied to the original procedure found in the literature.[105] Instead of using a protic reagent to quench the reaction in Scheme 88, $Boc_2O$ 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).




**115** **97**, 77%

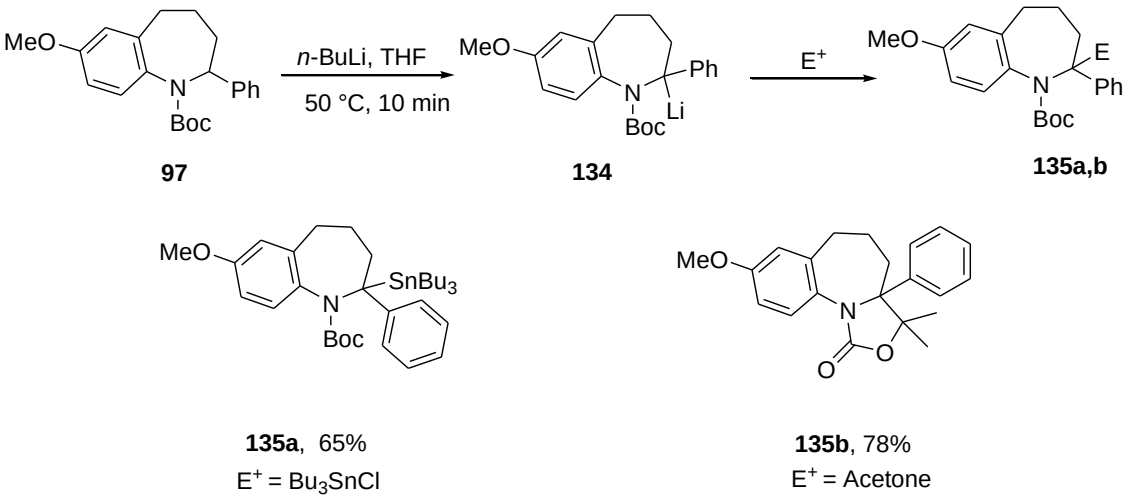
**Scheme 90**

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 ºC 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.



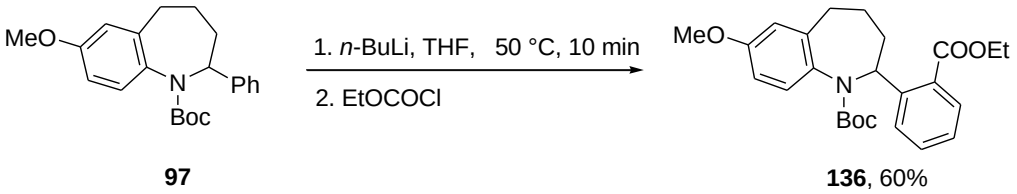

**97** **134** **135a,b**

**135a**, 65%
$E^+ = Bu_3SnCl$

**135b**, 78%
$E^+$ = Acetone

**Scheme 91**

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.

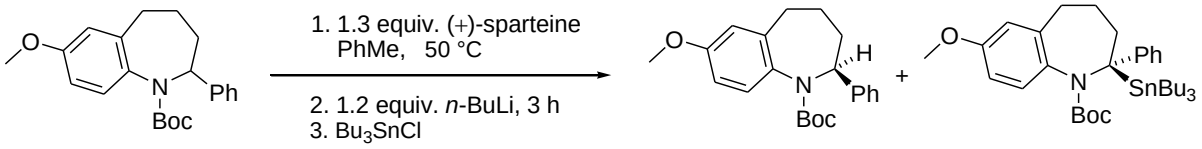



**97** **136**, 60%

**Scheme 92**

### 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 ºC, followed by the addition of 1.2 equivalents of *n*-BuLi. After three hours, tri-*n*-butyltin chloride was added (Scheme 93).




**97** (*S*)-**97**,46% 57:43 er (*S*)-**135a**, 43%

**Scheme 93**

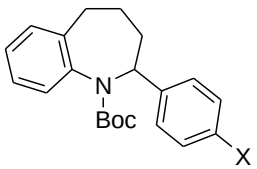
## 3.4 Conclusions and future work

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 °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.




X = F, Cl, $OCH_3$

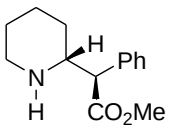
**Figure 29**

# *Chapter 4*

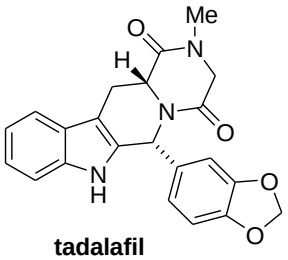
# Synthesis and Lithiation–Substitution of *N*-Boc-2-alkenylpiperidines and *N*-Boc-2- alkynylpiperidines

## 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.[110] 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]



**methylphenidate**



**tadalafil**

**Figure 30**

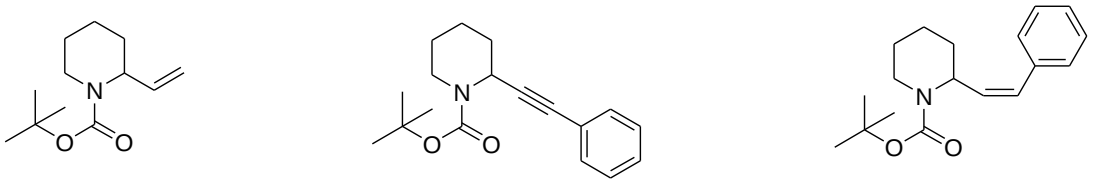
Various chiral piperidine alkaloids contain alkene or alkyne chains substituted in the 2-position and these have been challenging targets of total synthesis.[113] This chapter describes research on the synthesis of 2-alkenyl or alkynyl substituted piperidines and in particular, a focus on electrophilic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

## 4.2 Lithiation chemistry to synthesise 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 $\alpha$-positions (*i.e.* C2 or C6).[47,66,115–119] Our group has been using lithiation chemistry to synthesise 2,2-disubstituted *N*-Boc-piperidines.[57,60,65] As shown earlier (Chapter 1, Section 1.5), different examples of 2,2-disubstitued piperidines were synthesised successfully.[57,65] The incorporation of a carbonyl group attached to the nitrogen atom activates the compound by increasing the $\alpha$-proton's acidity. In addition, the acidity of the $\alpha$-proton can be considerably enhanced by having a vinyl or aryl substituent in the $\alpha$-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).



**136** **137** **138**

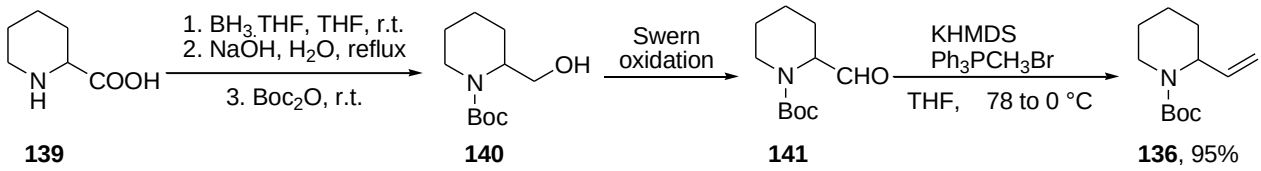
**Scheme 94**

## 4.3 Results and discussion

## 4.3.1. *N*-Boc-2-vinylpiperidine 136

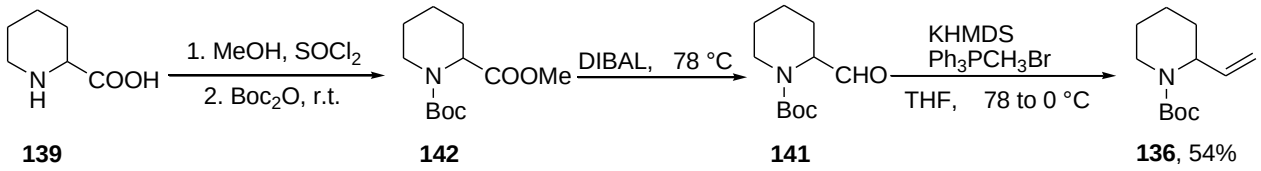
### 4.3.1.1 Synthesis of *N*-Boc-2-vinylpiperidine 136

*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.[120–123] 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).[121,123] As outlined in scheme 96, this method was reported to be successful to give an excellent yield of 95%.[121] Pipecolinic acid **139** was firstly reduced with borane. Then, the resulting amino alcohol was protected by $Boc_2O$ in a one pot reaction to give **140** which was oxidized by the Swern procedure[124] (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**.



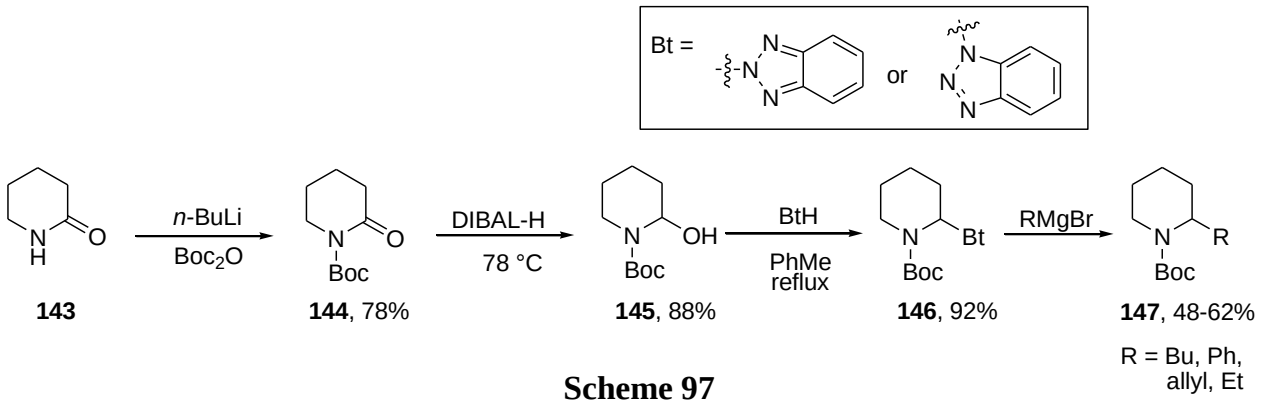

**Scheme 95**

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.[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).



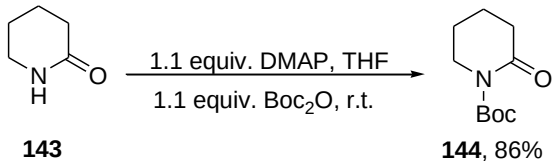

**Scheme 96**

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**.[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 97**

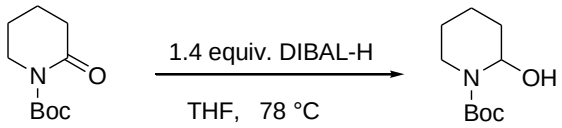
Boc protection of δ-valerolactam **143** (commercially available) was attempted using 4-dimethylaminopyridine (DMAP) alongside $Boc_2O$ to give the protected compound **144** with a yield of 86% which was a slight increase compared to the literature (Scheme 98).[83]




**143** **144**, 86%

**Scheme 98**

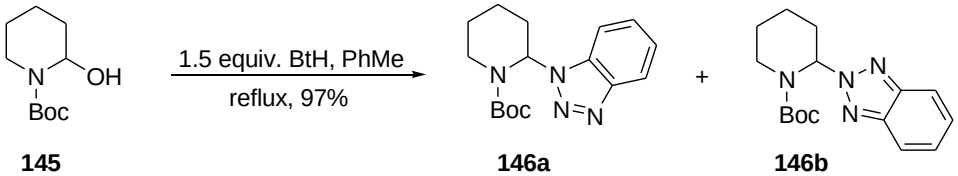
Reduction of the amide moiety of lactam **144** was achieved by treating it with DIBAL-H at –78 ºC to give the desired product **145** in 83% yield, which was slightly lower than the yield obtained in the literature (Scheme 99).[83]




**144** **145**, 83%

**Scheme 99**

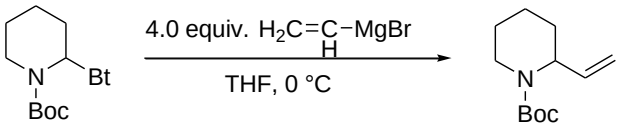
The third step was a substitution reaction of lactamol **145** with benzotriazole to give an excellent yield of **146** as a mixture of two isomers in ratio 1.0:0.6 according to the $^1H$ NMR spectrum. This yield was an increase on that achieved in the literature and the two isomers were not isolated separately as they both behave in the same manner when displaced in the next step (Scheme 100).[83]




**145** **146a** **146b**

**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).




**146** **136**, 27%

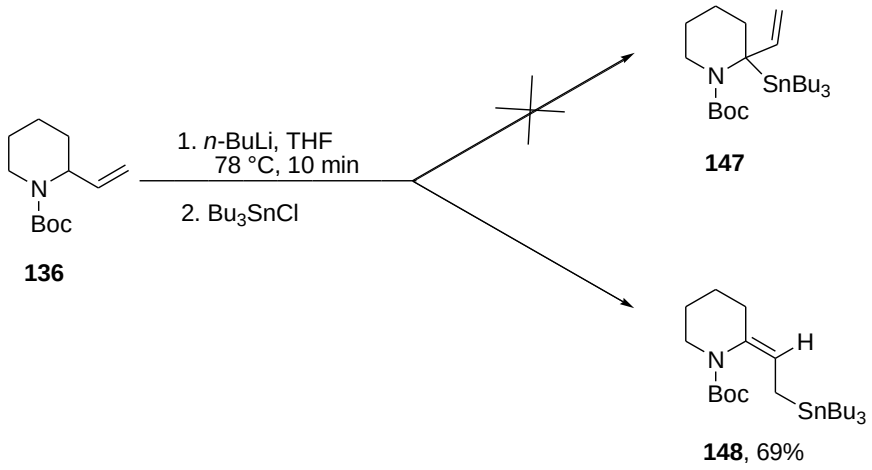
**Scheme 101**

Different conditions were applied to try and improve the yield, but all attempts were futile. For example, using a mixture of $Et_2O$:THF 9:1 as mentioned in the literature did not give any increase in the yield. Also, using neat $Et_2O$ 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 ºC 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

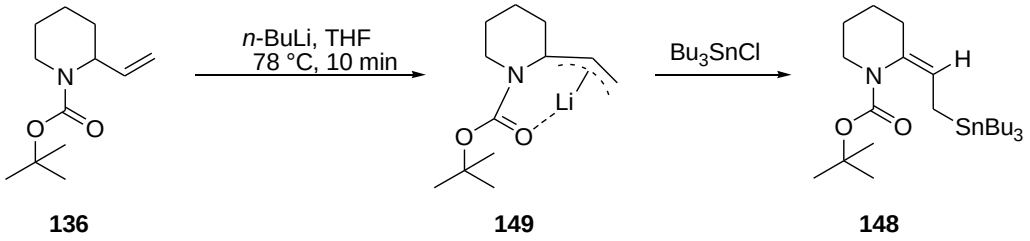
With *N*-Boc-2-vinylpiperidine **136** in hand, a racemic lithiation–substitution was attempted by using tributyltin chloride as the electrophile. *N*-Boc-2-vinylpiperidine **136** was deprotonated at –78 ºC with *n*-BuLi in THF and stirred for 10 minutes before tributyltin chloride was added. The Boc 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 *α*-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).




**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).

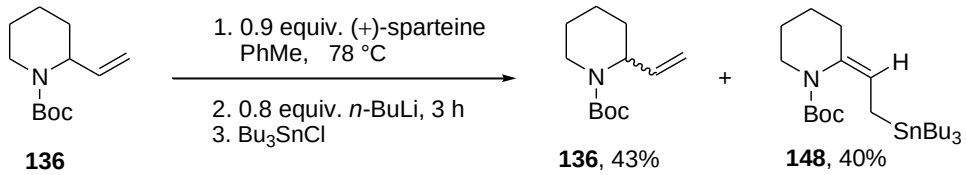



**Scheme 103**

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**

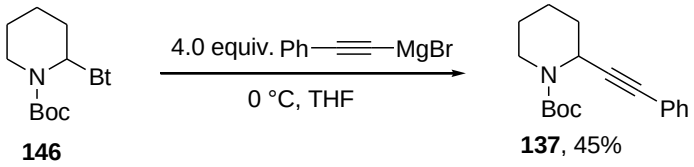
Therefore, it was difficult to carry out further investigations on this substrate because it was synthesised in a poor yield and it was difficult to separate the enantiomers by chiral HPLC.

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

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

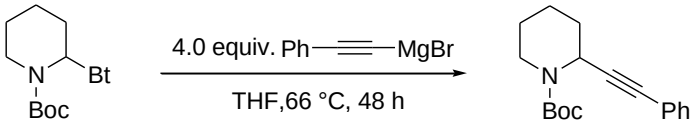
Even though the lithiation–substitution on the substrates discussed above gave mostly disappointing results, it was still considered that other 2-unsaturated substituted piperidines could have reactivity towards lithiation–substitution chemistry.

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**

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.



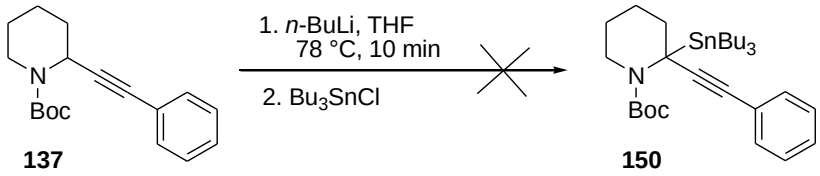

**146** **137**, 70%

**Scheme 106**

### 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.

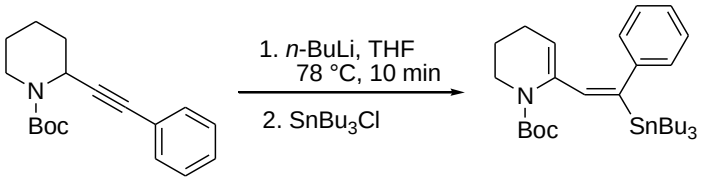
Tributyltin chloride was the first electrophile used in lithiation–substitution reactions and it was surprising that the expected 2,2-disubstituted piperidine **150** was not formed (Scheme 107).




**137** **150**

**Scheme 107**

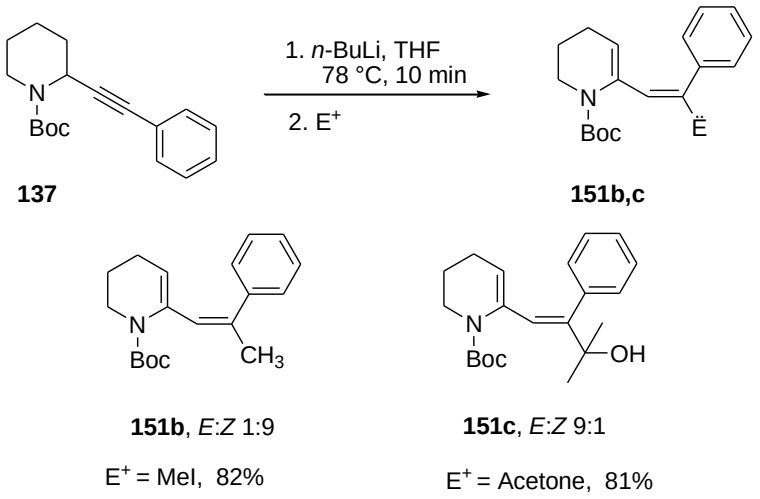
The $^{1}$H NMR spectrum of the formed product was shown to have two alkene protons, one of them appeared as a singlet at around 6.7 ppm while the other was a triplet at around 5.1 ppm. The $^{13}$C NMR spectrum showed a number of CH peaks in the chemical shift area characterized by unsaturated carbons 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).




**137** (*E*)-**151a**, 74%

**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.




**137** **151b,c**

**151b**, *E*:*Z* 1:9

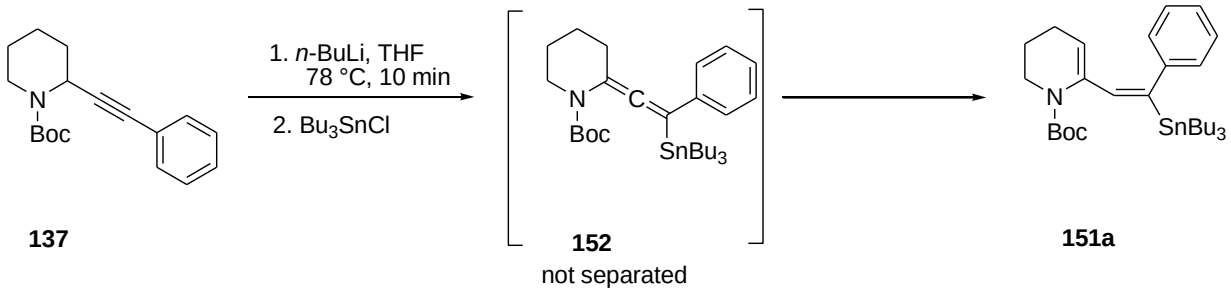
$E^+$ = MeI, 82%

**151c**, *E*:*Z* 9:1

$E^+$ = Acetone, 81%

**Scheme 109**

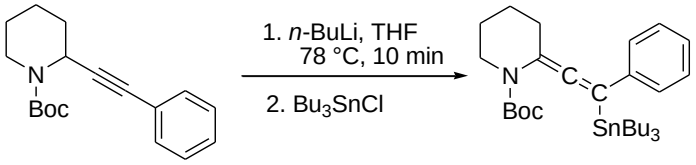
Interestingly, when checking the $^{1}$H NMR spectrum of the crude reaction mixture of the reaction that formed compound **151a**, it was found that there were no proton peaks between 6.7 and 5.1 ppm as found in pure **151a**. However, when the reaction mixture was purified by column chromatography, 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**.




**137** **152** not separated **151a**

**Scheme 110**

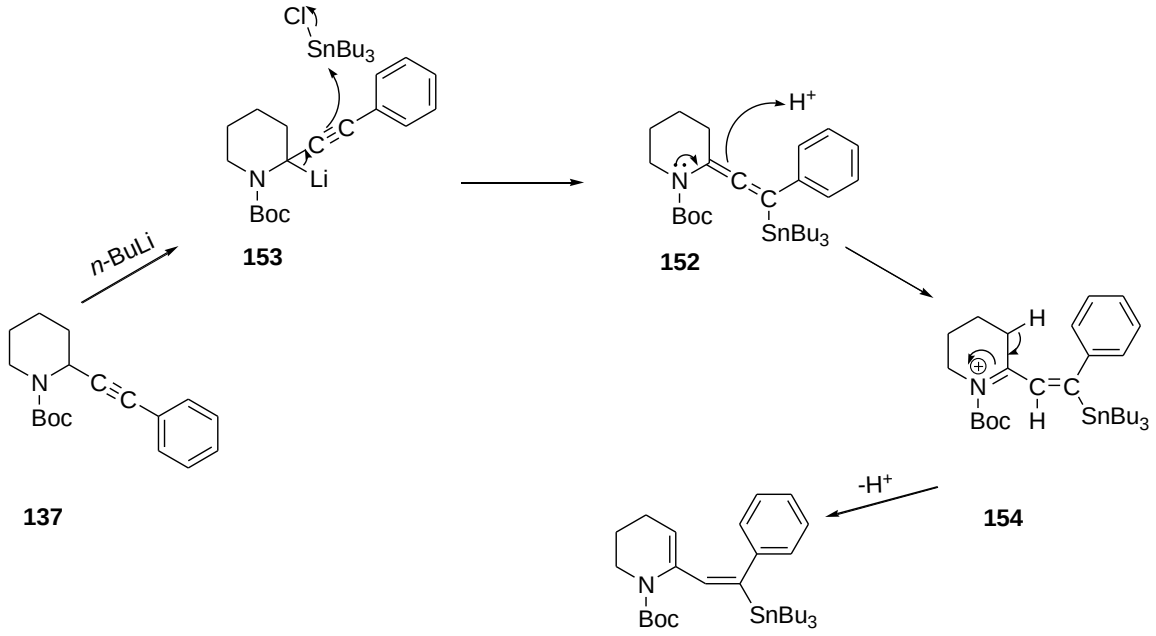
This suggested that the conjugated diene **151a** was more stable than allene **152**. In an attempt to separate the allene **152**, it was decided to basify the silica gel used as the stationary phase in column chromatography by adding triethylamine. This method was successful and allene **152** was 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**.




**137** **152**, 55%

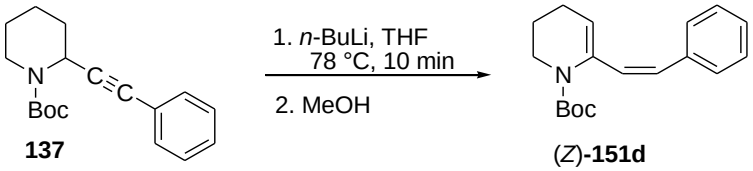
**Scheme 111**

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**.




**Scheme 112**

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 113**

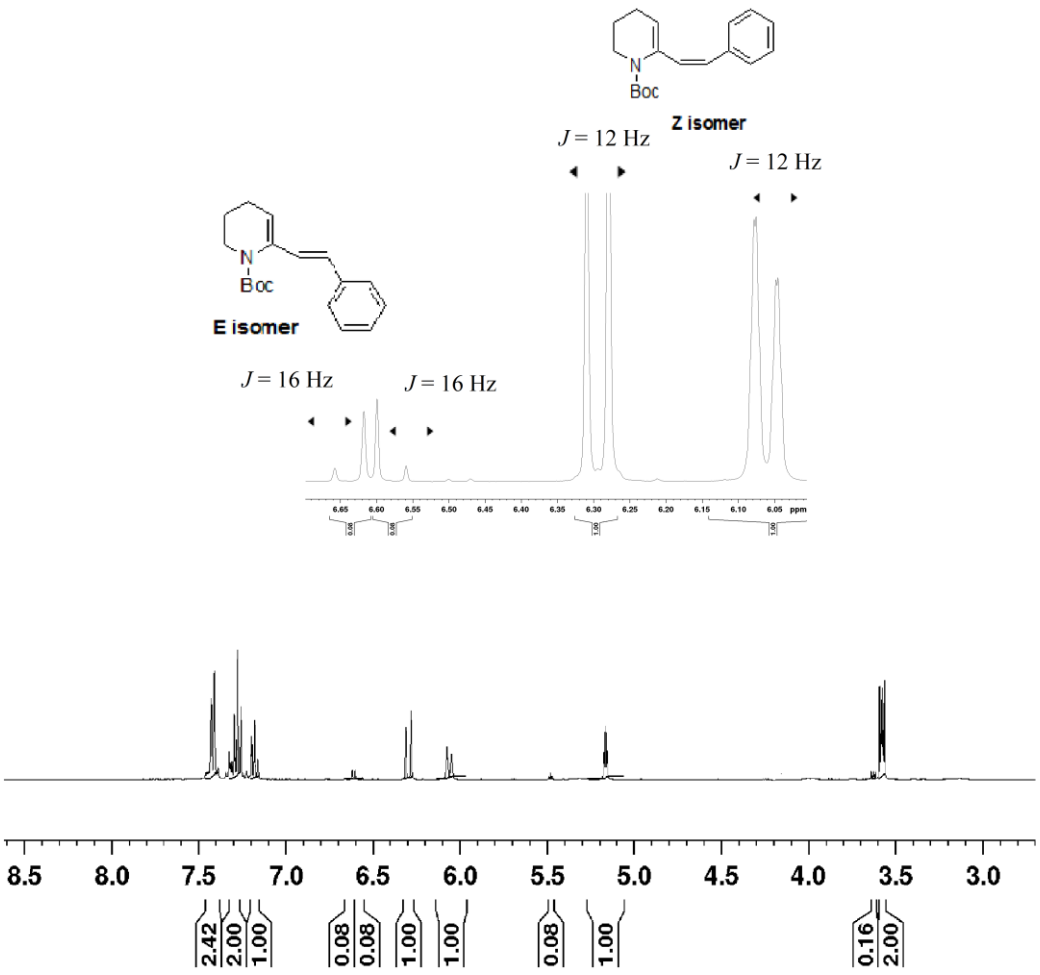
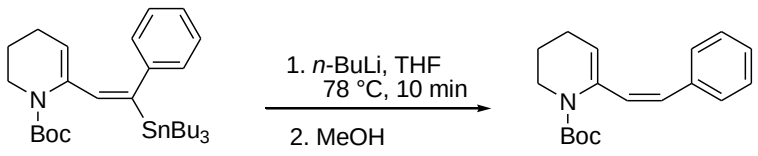



**Figure 31**

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).




(*E*)-**151a** (*Z*)-**151d**

**Scheme 114**

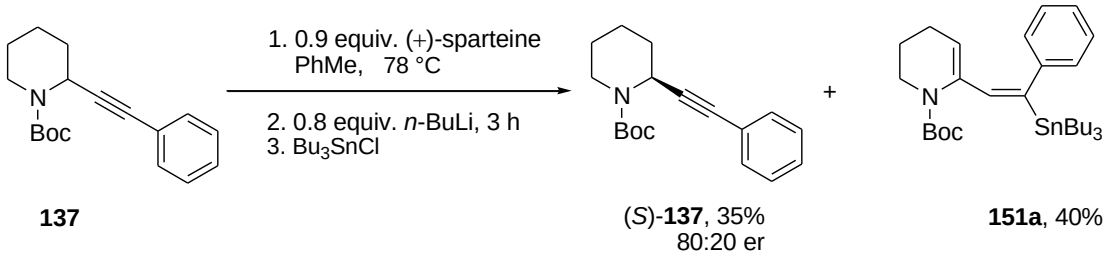
According to the $^{1}$H NMR spectrum, this method effected the synthesis of *Z*-isomer **151d** as the major product. Based on the expected reaction of the organolithium with retention of configuration, the product **151a** would be the *E*-isomer[35,125] and this suggested that the

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).




**137** (*S*)-**137**, 35% 80:20 er **151a**, 40%

**Scheme 115**

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

**Table 9**

Generally, the enantioselectivities were disappointing. The best enantiomeric ratio of recovered starting material was 80:20 with 35% yield, by adding *n*-BuLi last to a mixture of **137** and (+)-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*-BuLi/(+)-sparteine as the 'chiral base' gave 10% yield of RSM with poor enantioselectivity (entry 2). Reducing the number of *n*-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*-BuLi led to low yield and poor enantioselectivity (entry 5).

It was disappointing that the enantioselectivity of the kinetic resolutions of *N*-Boc-2-alkynylpiperidine were not as good as *N*-Boc-2-phenylpiperidine. The er of the kinetic resolutions depends on the difference in energy between *n*-BuLi/sparteine removing the *α*-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 **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 *α*-position being linear, so this might mean the molecule prefers to be in a conformation where *n*-BuLi/sparteine is able to remove the *α*-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*-BuLi/(+)-sparteine might be able to remove the proton from either enantiomer which would lower the enantioselectivity.

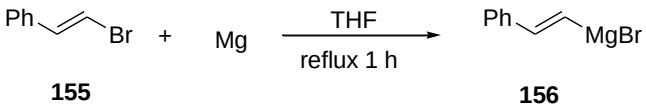
## 4.3.3 *N*-Boc-2-[(Z)-2-phenylethenyl]piperidine 138

### 4.3.3.1 Synthesis *N*-Boc-2-[(Z)-2-phenylethenyl]piperidine 138

It was interesting to try and synthesise more 2-substituted piperidine derivatives to use in lithition–substitution reactions. *N*-Boc-2-[(Z)-2-phenylethenyl]piperidine **138** was chosen because the *α*-carbon in this substrate is connected to a C=C, an $sp^2$ hybridised carbon which was similar to the 2-arylpiperidines. We thought that the presence of a bulky *β*-arylethenyl group would promote better selectivity than the alkynyl group. Also, this type of linkage was attractive because *β*-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 **136** and **137** by adding 2-phenylethenylmagnesium bromide **156** to *N*-Boc-2-

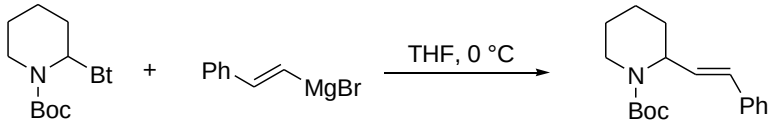
benzotriazolylpiperidine **146** (Scheme 117). Firstly, it was necessary to prepare the Grignard reagent because it was not commercially available. This was achieved by adding *β*-bromostyrene **155** to magnesium (Scheme 116).




**155** **156**

**Scheme 116**

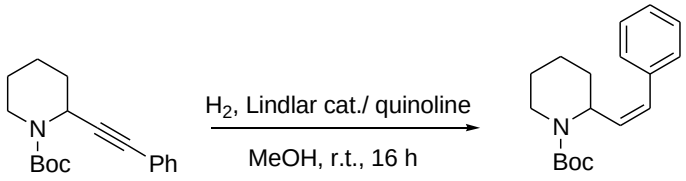
Then *N*-Boc-2-benzotriazolylpiperidine **146** was added to Grignard reagent **156** to give the desired product **138** (Scheme 117). Unfortunately, only about 10% yield was formed of a mixture of isomers of **138** with ratio *E*:*Z* 3:1. This low yield could be attributed to the formation of Grignard 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.




**146** **156** **138**, 10%
*E*:*Z*, 3:1

**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.

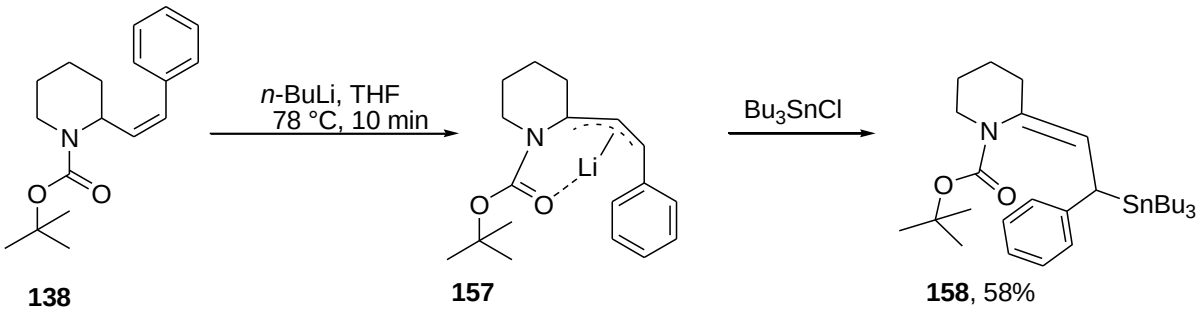



**137** **138**, 73%

**Scheme 118**

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

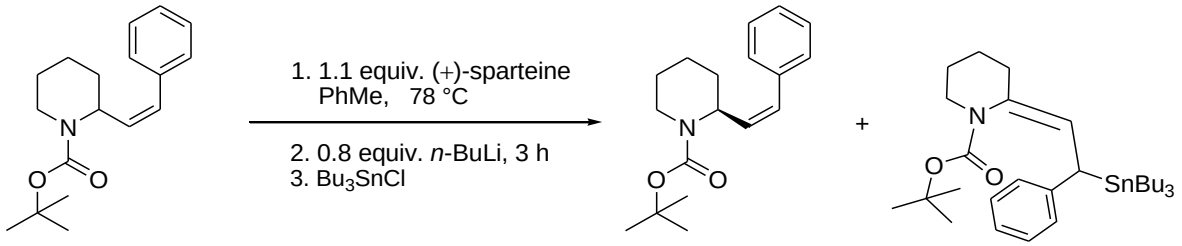
The initial lithiation–substitution was carried out by adding *n*-BuLi to carbamate **138** in THF at –78 °C. The reaction mixture was stirred for 10 minutes before trapping the organolithium intermediate with tributyltin chloride to give product **158** in 58% yield. Similar to *N*-Boc-2-vinylpiperidine **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).




**138** **157** **158**, 58%

**Scheme 119**

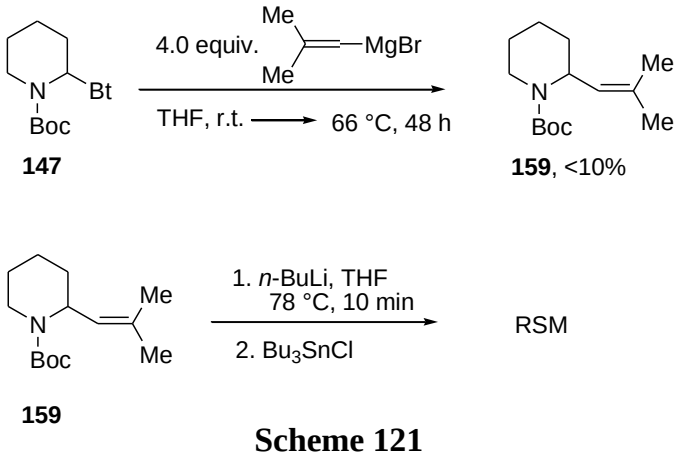
In order to test whether this compound had enantioselectivity in kinetic resolutions, just one trial kinetic resolution was attempted by adding *n*-BuLi to a mixture of **138** and (+)-sparteine in toluene at –78 °C. After 3 hours, tributyltin chloride was added. The starting material was recovered in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




**138** (*S*)-**138**, 45% 79:21 er **158**, 38%

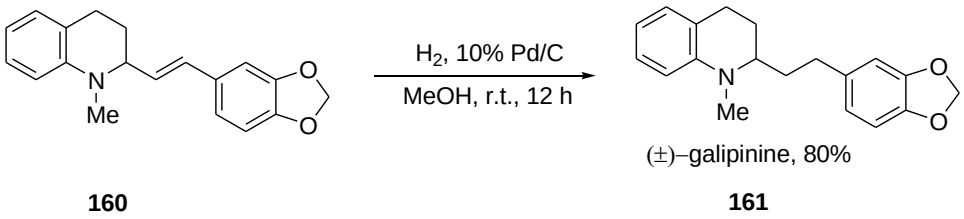
**Scheme 120**

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 °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).



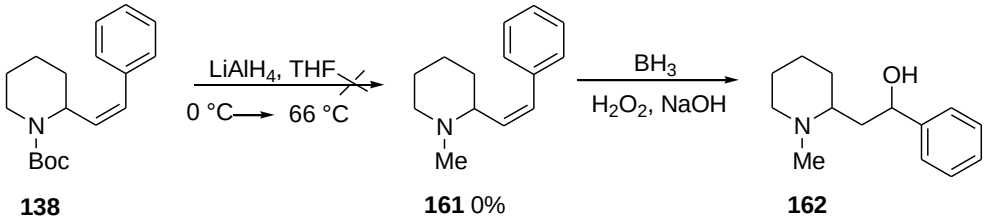

**Scheme 121**

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).[126]




**Scheme 122**

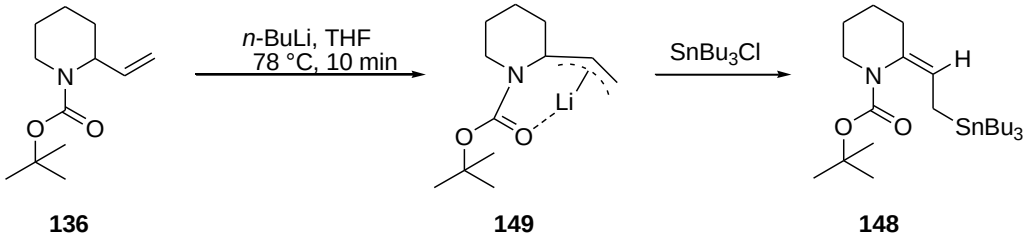
This chemistry could be carried out by Boc group reduction, then a regioselective hydroboration–oxidation reaction of the double bond as indicated in Scheme 123. However, reduction of the Boc group by using $LiAlH_4$ was disappointing and amine **162** was not formed.[127] Although, the reaction was 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 ºC failed to give a desired product, only the starting material was recovered.




**Scheme 123**

## 4.4 Conclusions and future work

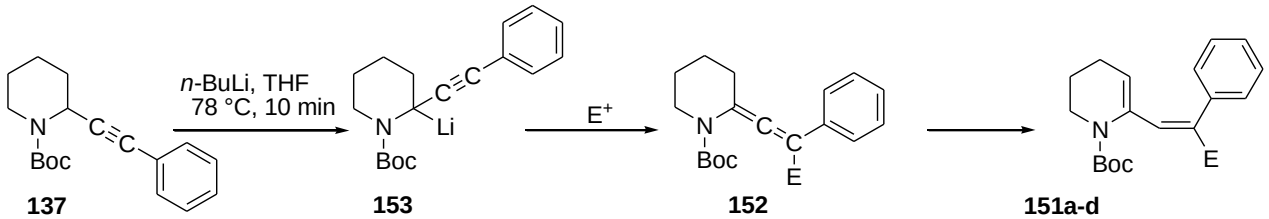
In conclusion, 2-alkenyl and alkynylpiperidine derivatives were synthesised in four steps, starting from cheap, commercially available compounds using literature methods. *N*-Boc-2-vinylpiperidine **136** was successfully synthesised but a poor yield of product **136** was obtained. A racemic lithiation–substitution was attempted by using *n*-BuLi at –78 ºC in THF to give *N*-Boc (2Z)-2-[2-(tributylstannyl)ethylidene]piperidine **148** *via* $\eta^3$ intermediate **149** (Scheme 124). The limitation for this substrate was inability to separate the formed products after the reaction with different electrophiles, $Bu_3SnCl$ 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.




**136** **149** **148**

**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 $\alpha$-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).

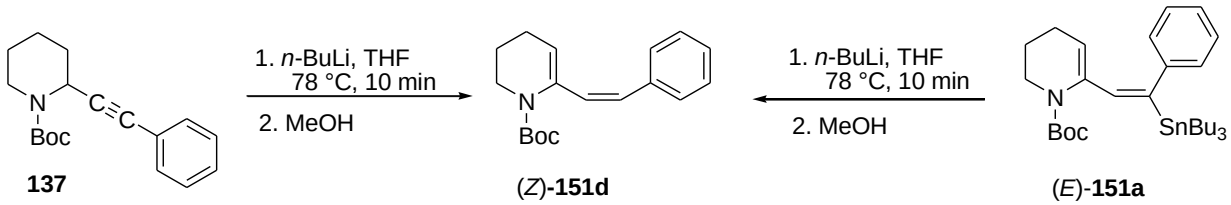



**137** **153** **152** **151a-d**

(*E*)-**151a**, $E^+ = SnBu_3Cl$, 74%
**151b**, *E*:*Z* 1:9, $E^+$ = MeI, 82%
**151c**, *E*:*Z* 9:1, $E^+$ = Acetone, 81%
**151d**, *E*:*Z* 1:12, $E^+$ = MeOH, 91%

**Scheme 125**

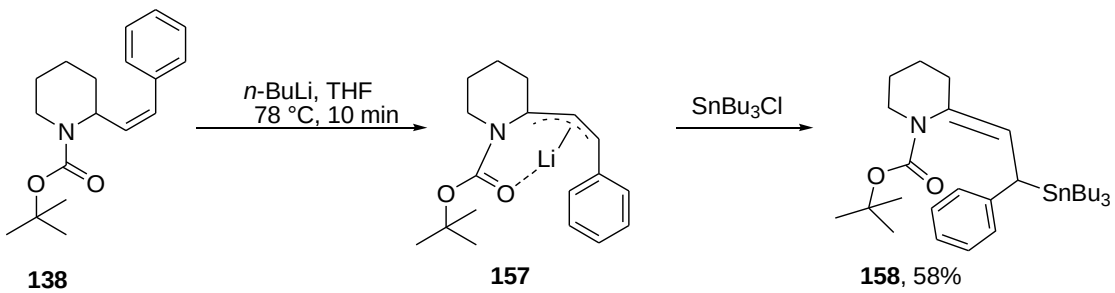
However, the stereochemistry of the products resulting from quenches by methyl iodide **151b** and acetone **151c** were not verified. The product resulting from quenching by tributyltin chloride **151a** was proven by a different method. Two experiments were attempted to confirm that the *E*-isomer 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 *α*-carbon to a linear group like the alkynyl group can reduce the selectivity of the abstraction of the *α*-proton by a 'chiral base' compared with 2-arylpiperidines.




**137** (*Z*)-**151d** (*E*)-**151a**

**Scheme 126**

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 *α*-carbon like in the 2-arylpiperidines. The initial lithiation–substitution by using *n*-BuLi gave a product which formed *via* an $\eta^3$ 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'.




**138** **157** **158**, 58%

**Scheme 127**

*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 ºC 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 $CaH_2$, *n*-BuLi was titrated before use.[128] (+)-Sparteine was freshly distilled by Kugelrohr distillation. Thin layer chromatography was performed on Merck silica gel $60F_{254}$ plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was performed using DAVISIL or Geduran silica gel (40-63 micron mesh). $^1$H 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. $^{13}$C 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**

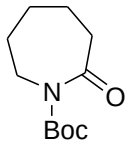
To a solution of *tert*-butyl 2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate **96** (100 mg, 0.309 mmol) in dry THF (2 mL) at –50 ºC under nitrogen, was added *n*-BuLi (0.154 mL, 0.370 mmol, 2.4 M in hexane). After stirring for 10 minutes, the electrophile (0.927 mmol) was added. The mixture 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

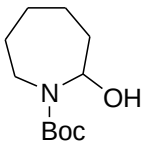
## 5.3 Experimental Details

### *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 $NaHCO_3$ 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 $CH_2Cl_2$–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 $\nu_{max}$ ATR/$cm^{-1}$ 2980, 2935, 2865, 1765 (C=O), 1700 (C=O), 1140; $^1$H NMR (400 MHz, $CDCl_3$) δ = 3.77–3.72 (2H, m, $NCH_2$), 2.65–2.60 (2H, m, 2 × CH), 1.79–1.68 (6H, m, 6 × CH), 1.51 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 174.7 (C=O), 151.8 (C=O), 81.6 (C), 45.1 ($CH_2$), 38.4 ($CH_2$), 28.2 ($CH_2$), 27.6 ($CH_2$), 27.0 ($CH_3$), 22.4 ($CH_2$); HRMS (ES) Found: $MNa^+$, 236.1260. $C_{11}H_{19}NO_3Na$ requires $MNa^+$, 236.1257; LRMS *m/z* (ES) 236 (15%, $MNa^+$), 158 (100, $MNa^+$–Boc+H). Data in accordance with the literature.[129]

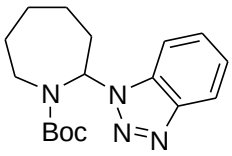
### *tert*-Butyl 2-Hydroxyazepane-1-carboxylate (85)



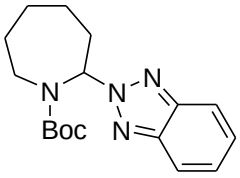

To a solution of carbamate **84** (10.0 g, 46.9 mmol) in dry THF (100 mL) at –78 ºC was added DIBAL-H (59.7 mL, 59.7 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at –78 ºC under nitrogen for 1 h, before gradually warming to room temperature over a further 1 h. The reaction was 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 $MgSO_4$ 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; $R_f$ 0.32 [$CH_2Cl_2$–MeOH (90:10)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 3430, 2980, 2935, 2855, 1675 (C=O), 1160; $^1$H NMR (400 MHz, $CDCl_3$, 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); $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.3 (C=O), 154.0 (C=O), 79.3 (C), 79.2 (C), 78.9 (CH), 78.6 (CH), 40.3 ($CH_2$), 39.8 ($CH_2$), 33.4 ($CH_2$), 33.1 ($CH_2$), 28.6 ($CH_2$), 28.5 ($CH_2$), 28.3 ($CH_2$), 28.2 ($CH_2$), 27.4 ($CH_3$), 27.3 ($CH_3$), 21.9 ($CH_2$), 21.8 ($CH_2$); HRMS (ES) Found: $MNa^+$, 238.1418. $C_{11}H_{21}NO_3Na$ 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-Benzo[d][1,2,3]triazol-1-yl)azepane-1-carboxylate (86a,b)**




**86a**

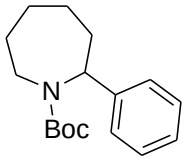



**86b**

To a solution of carbamate **85** (4.0 g, 18.5 mmol) in toluene (100 mL) was added benzotriazole (3.3 g, 28.0 mmol) and $MgSO_4$ (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 $NaCO_3$ solution (3 × 20 mL) and saturated brine solution (3 × 20 mL). The organic layers were dried over $MgSO_4$, 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; $R_f$ 0.64, 0.68 [petrol-EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2970, 2930, 2860, 1690 (C=O), 1160, 1110; $^1$H NMR (400 MHz, $CDCl_3$, 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), 4.25–3.87 (0.65H, m, CH), 3.69–3.53 (1H, m, CH), 3.49–3.39 (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); $^{13}$C NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 31.7 ($CH_2$), 28.5 ($CH_2$), 27.2 ($CH_3$), 27.1 ($CH_2$), 22.8 ($CH_2$); HRMS (ES) Found: $MNa^+$, 339.1791. $C_{17}H_{24}N_4O_2Na$ requires $MNa^+$, 339.1791; LRMS *m/z* (ES) 339 (10%, $MNa^+$), 142 (100, $MH^+$–*t*-Bu+H, –$C_6H_4N_3$).

**_tert_-Butyl 2-Phenylazepane-1-carboxylate (71)**



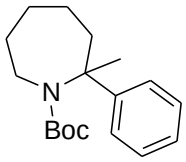

To a solution of carbamate **86a,b** (4.2 g, 15.2 mmol) in dry $Et_2O$ (90 mL) and dry THF (10 mL) at 0 ºC was added phenylmagnesium bromide solution (20.3 mL, 20.3 mmol, 3 M in $Et_2O$) dropwise. The reaction mixture was stirred under argon for 20 h, slowly warming to room temperature, then diluted with a saturated solution of $NH_4Cl$ (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 **71** (3.60 g, 54%) as an amorphous white solid, m.p. 41–42 °C, (reported as oil lit.)[83]; $R_f$ 0.56 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2970, 2925, 2850, 1690 (C=O), 1150; $^1$H NMR (400 MHz, $CDCl_3$, 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); $^{13}$C NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 42.0 ($CH_2$), 35.3 ($CH_2$), 34.5 ($CH_2$), 28.7 ($CH_2$), 28.6 ($CH_2$), 28.5 ($CH_2$),

28.4 ($CH_2$), 27.5 ($CH_3$), 27.3 ($CH_3$), 25.4 ($CH_2$), 24.5 ($CH_2$); HRMS (ES) Found: $MH^+$, 276.1958. $C_{17}H_{25}NO_2$ 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 ºC. 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 $\nu_{C=O}$ 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%).

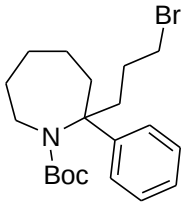
***tert*-Butyl 2-Methyl-2-phenylazepane-1-carboxylate (73a)**




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; $R_f$ 0.56 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2970, 2930, 2855, 1680 (C=O), 1155; $^1$H NMR (400 MHz, $CDCl_3$) 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, $CH_3$, 3 × CH), 1.66–1.52 (4H, m, 4 × CH), 1.05 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 44.9 ($CH_2$), 31.0 ($CH_2$), 29.1 ($CH_2$), 28.0 ($CH_3$), 27.0 ($CH_3$),

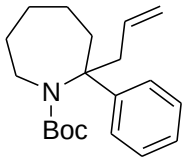
23.5 ($CH_2$); HRMS (ES) Found: $MH^+$, 290.2113. $C_{18}H_{28}NO_2$ requires $MH^+$, 290.2115; LRMS *m/z* (ES) 290 (5%, $MH^+$), 234 (100, $MH^+$–*t*-Bu+H).

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



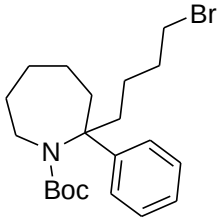

Using general procedure **A**, carbamate **71** (100 mg, 0.36 mmol), *n*-BuLi (0.189 mL, 0.44 mmol, 2.4 M in hexanes) and 1,3-dibromopropane (0.11 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **73b** (131 mg, 92%) as an amorphous white solid; m.p. 88–90 ºC; $R_f$ 0.58 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2975, 2935, 2860, 1685 (C=O), 1230, $^1$H NMR (400 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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. $C_{20}H_{31}{}^{79}BrNO_2$ requires $MH^+$, 396.1533; Found: $MH^+$, 398.1515. $C_{20}H_{31}{}^{81}BrNO_2$ 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)**




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 $\nu_{max}$ 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, C*H*=$CH_2$), 5.23–5.15 (2H, m, CH=C*H*$_2$), 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).

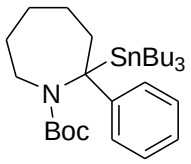
***tert*-Butyl 2-(4-Bromobutyl)-2-phenylazepane-1-carboxylate (73d)**




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 $\nu_{max}$ 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 ×

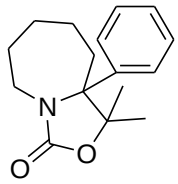
CH), 7.19–7.14 (1H, m, CH), 4.55–4.42 (1H, m, NCH), 3.52–3.41 (2H, m, $BrCH_2$), 3.07–2.94 (1H, m, NCH), 2.57–2.46 (1H, m, CH), 2.38–2.29 (1H, m, CH), 2.04 (1H, td, *J* = 12.5, 4.0 Hz, CH), 1.99–1.87 (3H, m, CH), 1.76–1.55 (4H, m, 4 × CH), 1.48–1.36 (3H, m, 3 × CH), 1.34–1.27 (1H, m, CH), 1.04 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 41.7 ($CH_2$), 39.2 ($CH_2$), 32.5 ($CH_2$), 32.3 ($CH_2$), 29.8 ($CH_2$), 28.1 ($CH_2$), 26.9 ($CH_3$), 22.4 ($CH_2$), 21.6 ($CH_2$); HRMS (ES) Found: $MH^+$, 412.1668. $C_{21}H_{33}{}^{81}BrNO_2$ requires $MH^+$, 412.1671; Found: $MH^+$, 410.1681. $C_{21}H_{33}{}^{79}BrNO_2$ requires $MH^+$, 410.1689; LRMS *m/z* (ES) 412 (100%, $MH^+$), 410 (100, $MH^+$).

**_tert_-Butyl 2-(Tributylstannyl)-2-phenylazepane-1-carboxylate (73e)**



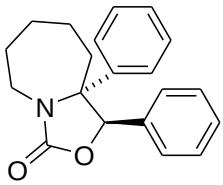

Using general procedure **A**, carbamate **71** (100 mg, 0.36 mmol), *n*-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and tributyltin chloride (0.29 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **73e** (153 mg, 75%) as a clear oil; $R_f$ 0.74 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2955, 2925, 2855, 1660 (C=O), 1155; $^1$H NMR (400 MHz, $CDCl_3$) 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, 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 × $CH_2$), 0.85 (9H, t, *J* = 7.0 Hz, 3 × $CH_3$), 0.75–0.58 (6H, m, 3 × $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 37.1 ($CH_2$), 28.4 ($CH_2$), 28.0 ($CH_2$), 27.9 ($CH_2$), 27.4 ($CH_3$), 26.7 ($CH_2$), 23.6 ($CH_2$) 12.8 ($CH_2$), 12.7 ($CH_3$); HRMS (ES) Found: $MNa^+$, 588.2864. $C_{29}H_{51}{}^{120}SnNO_2Na$ requires $MNa^+$, 588.2839; Found: $MNa^+$, 586.2872. $C_{29}H_{51}{}^{118}SnNO_2Na$ requires $MNa^+$, 586.2860; LRMS *m/z* (ES) 588 (100%, $MNa^+$), 586 (80, $MNa^+$), 508 (45, $MH^+$–*t*-Bu+H), 452 (50, $MH^+$–$C_4H_9$+H).

**1,1-Dimethyl-9a-phenyl-tetrahydro-5H-[1,3]oxazolo[3,4-a]azepin-3-one (73f)**

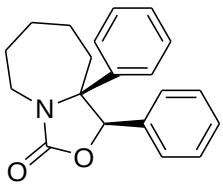


Using general procedure **A**, carbamate **4** (100 mg, 0.36 mmol), *n*-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and acetone (0.07 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **4e** (60 mg, 67%) as a clear oil; $R_f$ 0.4 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2980, 2935, 2865, 1735, 1065; $^1$H NMR (400 MHz, $CDCl_3$) 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, $CH_3$), 1.42–1.30 (2H, m, 2 × CH), 0.80 (3H, s, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 35.4 ($CH_2$), 27.8 ($CH_2$), 25.8 ($CH_3$), 25.0 ($CH_2$), 22.9 ($CH_2$), 22.6 ($CH_3$); HRMS (ES) Found: $MH^+$, 260.1642. $C_{16}H_{22}NO_2$ 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)**



***trans*-73g**



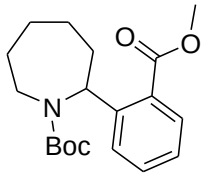
***cis*-73g**

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 ºC; $R_f$ 0.45 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 3065, 2925, 2850, 1750, 1390, 1040; $^1$H 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); $^{13}$C 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 ºC; $R_f$ 0.42 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 3090, 2940, 2850, 1735, 1400, 1020; $^1$H 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, NCH), 2.81–2.68 (2H, m, NCH, CH), 2.10–1.71 (6H, m, 6 × CH ), 1.37–1.29 (1H, m, CH); $^{13}$C 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)**

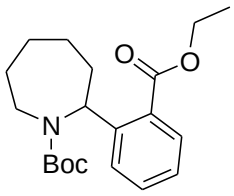



Using general procedure **A**, carbamate **71** (100 mg, 0.36 mmol), *n*-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.08 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **87a** (78 mg, 65%) as an amorphous white solid; m.p. 82–84 ºC; $R_f$ 0.41 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR / cm$^{-1}$ 2975, 2925, 2850, 1715 (C=O), 1685 (C=O), 1155; $^1$H 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),

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)

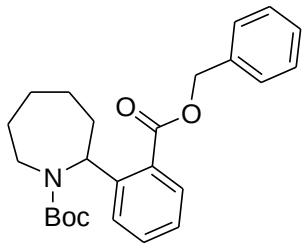



Using general procedure **A**, carbamate **71** (100 mg, 0.36 mmol), *n*-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and ethyl cyanoformate (0.107 mL, 1.09 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **87b** (80 mg, 64%) as an amorphous white solid; m.p. 71–72 ºC; $R_f$ 0.42 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ 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, $CDCl_3$, rotamers) δ = 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 ($CH_2$), 60.8 ($CH_2$), 58.7 (CH), 57.8 (CH), 44.5 ($CH_2$), 44.1 ($CH_2$), 35.9 ($CH_2$), 35.6 ($CH_2$), 31.0 ($CH_2$), 29.7 ($CH_2$), 29.3 ($CH_2$), 29.1 ($CH_2$), 28.5 ($CH_3$), 28.0 ($CH_3$), 27.8 ($CH_2$), 27.7 ($CH_2$), 14.3 ($CH_3$), 14.0 ($CH_3$); HRMS (ES) Found: $MH^+$, 348.2175. $C_{20}H_{30}NO_4$ 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)**



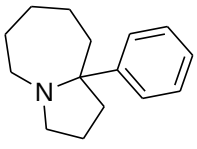

Using general procedure **A**, carbamate **71** (100 mg, 0.36 mmol), *n*-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexanes) and benzyl cyanoformate (0.15 mL, 1.09 mmol) gave, after flash column chromatography on silica, gel eluting with petrol–EtOAc (95:5), the carbamate **87c** (90 mg, 64%) as an amorphous white solid; m.p. 94–96 ºC; $R_f$ 0.43 [petrol–EtOAc (75:25)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2980, 2920, 2855, 1705 (C=O), 1672 (C=O), 1151; $^1$H NMR (400 MHz, $CDCl_3$, rotamers) δ = 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, PhC*H*$_2$), 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, $CDCl_3$, rotamers) δ = 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

(CH), 130.4 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (C), 128.1 (C), 128.0 (CH), 127.8 (CH), 126.2 (CH), 126.1 (CH), 125.5 (CH), 125.3 (CH), 79.2 (C), 77.2 (C), 66.8 ($CH_2$), 66.6 ($CH_2$), 58.6 (CH), 57.7 (CH), 44.5 ($CH_2$), 44.1 ($CH_2$), 35.9 ($CH_2$), 35.6 ($CH_2$), 31.0 ($CH_2$), 30.6 ($CH_2$), 29.7 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 28.5 ($CH_2$), 28.3 ($CH_3$ ), 28.0 ($CH_3$ ); HRMS (ES) Found: $MH^+$, 410.2327. $C_{25}H_{32}NO_4$ requires $MH^+$, 410.3226; LRMS *m/z* (ES) 410 (15%, $MH^+$), 354 (15, $MH^+$–*t*-Bu+H), 310 (100, $MH^+$–Boc+H).

**Kinetic Resolution of *tert*-Butyl 2-Phenylazepane-1-carboxylate 71 in Presence of (+)-Sparteine (Scheme 58)**

*n*-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*-Boc-2-phenylazepane **71** (100 mg, 0.36 mmol) in dry toluene (6 mL) at –5 °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 × 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 12.1 min; $[\alpha]_D^{22}$ –23.4 (3.2, $CHCl_3$), 66:34 er.

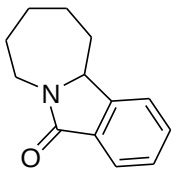
**Octahydro-9a-Phenyl-1H-pyrrolo[1,2-a]azepane (94)**




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 $MgSO_4$ 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 $\nu_{max}$ ATR/cm$^{-1}$ 2980, 2890, 2750, 1150; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 151.7 (C), 127.6 (CH), 126.6 (CH), 125.2 (CH), 68.7 (C), 54.0 ($CH_2$), 50.0 ($CH_2$), 43.4 ($CH_2$), 40.5 ($CH_2$), 30.6 ($CH_2$), 26.5 ($CH_2$), 24.0 ($CH_2$), 23.5 ($CH_2$); HRMS (ES) Found: $MH^+$, 216.1751. $C_{15}H_{22}N$ requires $MH^+$, 216.1747; LRMS *m/z* (ES) 216 (100%, $MH^+$).

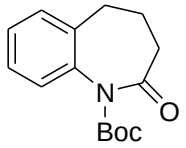
**7,8,9,10,11,11a-Hexahydroazepino[2,1-a]isoindol-5-one (95)**




To a solution of *tert*-butyl 2-(2-(methoxycarbonyl)phenyl)azepane-1-carboxylate **87a** (60 mg, 0.18 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (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 $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (95:5), to give the tricyclic lactam **95** (31 mg, 86%) as needles; m.p. 70–72 ºC; $R_f$ 0.15 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2930, 2920, 2850, 1660 (C=O); $^1$H NMR (400 MHz, $CDCl_3$) 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),

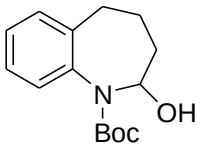
2.34–2.25 (1H, m, CH), 2.02–1.90 (1H, m, CH), 1.84–1.72 (3H, m, 3 × CH), 1.67–1.51 (3H, m, 3 × CH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 168.7 (C=O), 146.3 (C), 132.6 (C), 131.2 (CH), 128.0 (CH), 123.1 (CH), 121.9 (CH), 61.4 (CH), 43.5 ($CH_2$), 34.6 ($CH_2$), 29.5 ($CH_2$), 26.9 ($CH_2$), 26.1 ($CH_2$); HRMS (ES) Found: $MH^+$, 202.1229. $C_{13}H_{16}NO$ 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)**

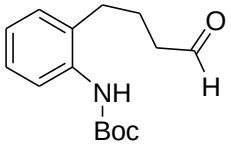



To a solution of 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one **99** (3.0 g, 18.6 mmol) and *N*,*N*-dimethylpyridin-4-amine (2.5 g, 20.4 mmol) in dry THF (50 mL) at room temperature was added di-*tert*-butyl dicarbonate (4.7 g, 20.4 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature 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 $NaHCO_3$ 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 $CH_2Cl_2$–MeOH (95:5), gave the carbamate **124** (4.5 g, 93%) as an amorphous white solid; m.p. 110–112 ºC; $R_f$ 0.26 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/ $cm^{-1}$ 2980, 2930, 2860, 1765 (C=O), 1715 (C=O), 1145; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 29.3 ($CH_2$), 27.8 ($CH_3$), 27.5 ($CH_2$); HRMS (ES) Found: $MH^+$, 262.1443. $C_{15}H_{20}NO_3$ 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)**




**125a**



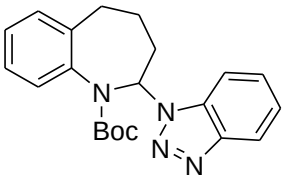

**125b**

To a solution of carbamate **124** (4.0 g, 15.3 mmol) in dry THF (50 mL) at –78 ºC was added DIBAL-H (21.4 mL, 21.4 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at –78 ºC 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 $MgSO_4$, and the solvent was removed under vacuum. Purification by flash silica chromatography, eluting with $CH_2Cl_2$–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); $R_f$ 0.50 (alcohol), 0.75 (aldehyde) [$CH_2Cl_2$–EtOAc (90:10)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 3450, 3360, 2970, 2980, 2940, 2870, 1710 (C=O), 1680 (C=O), 1160; $^1$H NMR (400 MHz, $CDCl_3$, 1:0.7 mixture of two isomer) δ = 9.82 (0.7H, t, *J* = 1.0 Hz, C*H*O), 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); $^{13}$C NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 30.5 ($CH_2$), 29.6 ($CH_2$), 29.4 ($CH_2$), 28.3 ($CH_3$), 28.2 ($CH_3$), 21.9 ($CH_2$), 21.1 ($CH_2$); HRMS (ES) Found: $MNa^+$, 286.1417. $C_{15}H_{21}NO_3Na$ 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: $^1$H NMR (400 MHz, $CDCl_3$) δ = 9.83 (1H, br s, C*H*O), 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); $^{13}$C NMR (100 MHz,

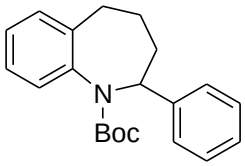
$CDCl_3$) δ = 202.3 (C=O), 153.5 (C=O), 136.0 (C), 131.0 (C), 129.4 (CH), 127.1 (CH), 123.9 (CH), 122.0 (CH), 80.3 (C), 43.0 ($CH_2$), 30.5 ($CH_2$), 28.3 ($CH_3$), 22.0 ($CH_2$).

**_tert_-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 $MgSO_4$ (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 $NaCO_3$ solution (3 × 20 mL) and saturated brine solution (3 × 20 mL). The organic layers were dried ($MgSO_4$), 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; $R_f$ 0.45 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 3025, 2970, 1690 (C=O), 1360, 1210; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 29.5 ($CH_2$), 29.0 ($CH_2$), 28.0 ($CH_3$); HRMS (ES) Found: $MNa^+$, 387.1793. $C_{21}H_{24}N_4O_2Na$, 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)**



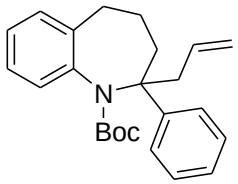

To a solution of carbamate **126** (4.0 g, 10.9 mmol) in dry $Et_2O$ (90 mL) and dry THF (10 mL) at 0 °C was added phenylmagnesium bromide solution (14.6 mL, 43.9 mmol, 3 M in $Et_2O$) dropwise. The reaction mixture was stirred under argon for 20 h, slowly warming to room temperature, then diluted with a saturated solution of $NH_4Cl$ (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 (95:5), gave the carbamate **96** (2.48 g, 70%) as needles, m.p. 110–112 ºC; $R_f$ 0.65 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2980, 2945, 2855, 1690 (C=O), 1160; $^1$H NMR (400 MHz, $CDCl_3$, 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); $^{13}$C NMR (100 MHz, $CDCl_3$, 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), 128.5 (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 ($CH_2$), 31.1 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 28.2 ($CH_3$), 28.1 ($CH_3$), 23.6 ($CH_2$), 23.0 ($CH_2$); HRMS (ES) Found: $MNa^+$, 346.1779. $C_{21}H_{25}NO_2Na$ 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$^{-1}$

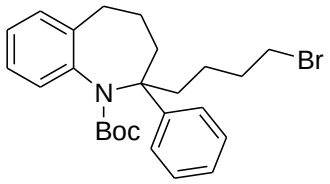
observed which was assigned to $\nu_{C=O}$ of lithiated intermediate **119**). The reaction was quenched with MeOH (1 mL), then purified by flash column chromatography, eluting with petrol–EtOAc (97:3), to afford pure starting material (250 mg, 61 %).

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



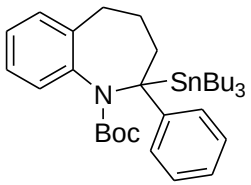

Using general procedure **B**, carbamate **96** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and allyl bromide (0.08 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **120a** (94 mg, 85 %) as a clear oil; $R_f$ 0.68 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2965, 2925, 2850, 1695 (C=O), 1260, 1090; $^1$H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.77–7.53 (1H, m, CH), 7.41–7.19 (8H, m, 8 × CH), 5.36–5.00 (1H, m, C*H*=$CH_2$), 4.99–4.58 (2H, m, CH=C*H*$_2$), 3.03–2.83 (1H, m, CH), 2.73–2.62 (1H, m, CH), 2.54–2.12 (3H, m, 3 × 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, $CDCl_3$) δ = 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 ($CH_2$), 23.0 ($CH_2$), 22.1 ($CH_2$); HRMS (ES) Found: $MH^+$, 364.2272. $C_{24}H_{30}NO_2$ 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)**




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; $R_f$ 0.34 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2950, 2925, 2860, 1700 (C=O), 1160; $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.12 (9H, m, 9 × CH), 3.17–3.05 (2H, m, $BrCH_2$), 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); $^{13}$C NMR (100 MHz, $CDCl_3$, one $CH_2$ 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 ($CH_2$), 33.7 ($CH_2$), 33.3 ($CH_2$), 32.8 ($CH_2$), 29.7 ($CH_2$), 27.9 ($CH_3$), 22.4 ($CH_2$); HRMS (ES) Found: $MNa^+$, 480.1507. $C_{25}H_{32}{}^{79}BrNO_2Na$ requires $MNa^+$, 480.1509; Found: $MNa^+$, 482.1489. $C_{25}H_{32}{}^{81}BrNO_2Na$ requires $MNa^+$, 482.1492; LRMS *m/z* (ES) 482 (10%, $MNa^+$), 480 (10, $MNa^+$), 404 (100, $MH^+$–*t*-Bu+H), 402 (100, $MH^+$–*t*-Bu+H).

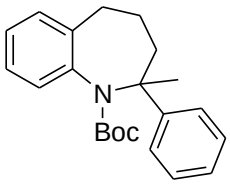
***tert*-Butyl 2-(Tributylstannyl))-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate (120c)**




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; $R_f$ 0.75 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2955,

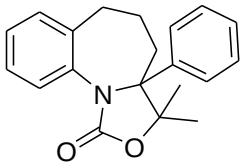
2920, 2860, 1670 (C=O), 1135; $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.24–6.94 (9H, m, 9 × CH), 2.99–2.86 (1H, m, CH), 2.60 (1H, dt, *J* = 9.0, 4.5 Hz, CH), 2.55–2.45 (1H, m, CH), 1.92–1.82 (2H, m, 2 × CH), 1.47–1.19 (22H, m, *t*-Bu, CH, 3 × $CH_2CH_2$), 0.87 (9H, t, *J* = 7.0 Hz, 3 × $CH_3$), 0.83–0.65 (6H, m, 3 × $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 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. $C_{33}H_{51}NO_2{}^{120}Sn$ Na requires $MNa^+$, 636.2839; Found: $MNa^+$, 634.2863. $C_{33}H_{51}NO_2{}^{118}Sn$ 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)



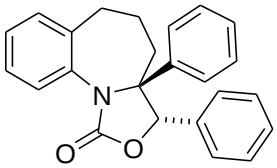

Using general procedure **B**, carbamate **96** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and iodomethane (0.06 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **120d** (62 mg, 60%) as a yellow oil; $R_f$ 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) δ = 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) δ = 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), 128.9 (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[8.4.0.0$^{2,6}$]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; $R_f$ 0.37 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2965, 2925, 2855, 1745 (C=O), 1165; $^1$H NMR (400 MHz, $CDCl_3$) 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, $CH_3$), 1.36–1.30 (1H, m, CH), 1.02 (3H, s, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 35.9 ($CH_2$), 26.2 ($CH_3$), 21.1 ($CH_3$), 21.0 ($CH_2$); HRMS (ES) Found: $MH^+$, 308.1648. $C_{20}H_{22}NO_2$ requires $MH^+$, 308.1645; LRMS *m/z* (ES) 330 (10%, $MNa^+$), 308 (100, $MH^+$).

**5,6-Diphenyl-4-Oxa-2-azatricyclo[8.4.0.0$^{2,6}$]tetradeca-1(10),11,13-trien-3-one (120f)**

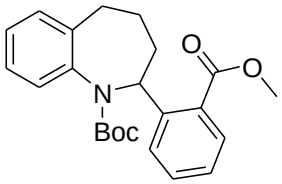


***trans*-120f**

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; $R_f$ 0.43, 0.24 [petrol–EtOAc (70:300)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 3065, 2925, 2850, 1750, 1390, 1040; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR

(101 MHz, $CDCl_3$) 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 ($CH_2$), 33.6 ($CH_2$), 20.5 ($CH_2$); HRMS (ES) Found: $MH^+$, 356.1645. $C_{24}H_{22}NO_2$ 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)**

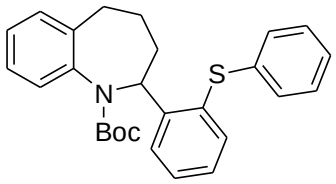



Using general procedure **B**, carbamate **96** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.07 mL, 0.91 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **127a** (71 mg, 68%) as a yellow oil; $R_f$ 0.43 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2975, 2940, 2860, 1720 (C=O), 1695 (C=O) ; $^1H$ NMR (400 MHz, $CDCl_3$, 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, $CH_3$), 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); $^{13}C$ NMR (100 MHz, $CDCl_3$, 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), 130.6 (CH), 130.1 (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), 80.2 (C), 80.1 (C), 57.2 (CH), 56.6 (CH), 52.3 ($OCH_3$), 52.0 ($OCH_3$), 31.8 ($CH_2$), 31.5 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 28.2 ($CH_3$), 27.9 ($CH_3$), 23.9 ($CH_2$), 23.8 ($CH_2$); HRMS (ES) Found: $MH^+$, 382.1942. $C_{23}H_{28}NO_4$ 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)



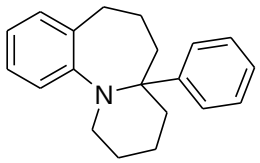

Using general procedure **B**, carbamate **96** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37mmol, 2.4 M in hexanes) and *S*-phenyl benzenethiosulfonate (0.23 mL, 0.93 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **127b** (110 mg, 85%) as an amorphous white solid; m.p. 94–96 ºC; $R_f$ 0.42 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ 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. $C_{27}H_{30}NO_2S$ 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; $[\alpha]_D^{23}$ –15.0 (1.0, $CHCl_3$), 61:39 er.

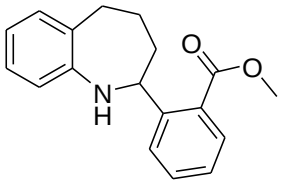
**11-Phenyl-1-azatricyclo[9.4.0.0$^{2,7}$]pentadeca-2(7),3,5-triene (129)**




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 $CH_2Cl_2$ (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) $CH_2Cl_2$. Aqueous NaOH (5 mL, 2 M) was added and the mixture was stirred vigorously for 15 min. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by flash silica chromatography, eluting with petrol–EtOAc (95:5), to give the bicyclic product **129** (53 mg, 88%) as a brown oil; $R_f$ 0.46 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2990, 2875, 2750, 1150; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 40.7 ($CH_2$), 30.6 ($CH_2$), 29.7 ($CH_2$),

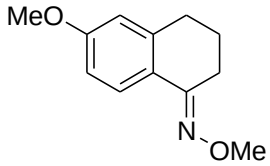
26.2 ($CH_2$), 21.3 ($CH_2$), 19.8 ($CH_2$); HRMS (ES) Found: $MH^+$, 278.1906. $C_{20}H_{24}N$ requires $MH^+$, 278.1903; LRMS *m/z* (ES) 278 (100%, $MH^+$).

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



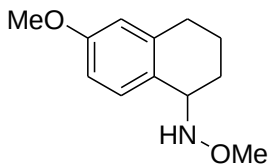

To a solution of *tert*-butyl 2-(2-(methoxycarbonyl)phenyl)-2,3,4,5-tetrahydrobenzo[b]azepine -1-carboxylate **127a** (100 mg, 0.26 mmol) in $CH_2Cl_2$ (1 mL) was added trifluoroacetic acid (0.20 mL, 2.62 mmol) and the mixture was allowed to stir for 1 h at room temperature. After this time, the acid was evaporated, and the crude mixture was diluted with (2 mL) $CH_2Cl_2$. 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 $\nu_{max}$ ATR/$cm^{-1}$ 3350, 2960, 2920, 1700 (C=O); $^1$H NMR (400 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 *m/z* (ES) 282 (100%, $MH^+$), 250 (15, $MH^+$–$OCH_3$).

**(1E)-*N*,6-Dimethoxy-3,4-dihydro-2H-naphthalen-1-imine (131)**




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 $CH_2Cl_2$ (3 × 150 mL). The organic layers were washed with water (300 mL) and dried over $Na_2SO_4$. The solvent was removed under vacuum to give the oxime **131** (5.19 g, 91%) as a brown oil;[108] $R_f$ 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$^+$–$OCH_3$).

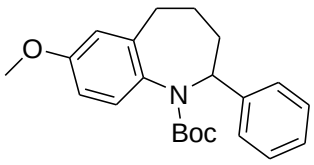
***N*,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine (115)**




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 $CH_2Cl_2$ (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 $\nu_{max}$ ATR/cm$^{-1}$ 2940, 3400, 1610; $^1$H NMR (400 MHz, $CDCl_3$) δ = 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), 2.08–1.96 (1H, m, CH), 1.84–1.71 (2H, m, 2 × CH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 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%, $M^+$–$NHOCH_3$).

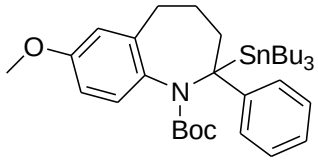
**_tert_-Butyl 2,3,4,5-Tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate (97)**




To a solution *N*,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine **115** (322 mg, 1.60 mmol) in dry $Et_2O$ (10 mL) at 0 ºC was added phenyllithium solution (2.50 mL, 4.80 mmol, 1.9 M in $Et_2O$) dropwise. The reaction mixture was stirred under argon for 2 h, after that a solution of $Boc_2O$ (1.00 g, 4.80 mmol) in $Et_2O$ (10 mL) was added dropwise. The solution was warmed to room temperature and was stirred overnight. $Et_2O$ (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 °C; $R_f$ 0.26 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2930, 1690 (C=O), 1600, 1245, 1150; $^1$H NMR (400 MHz, $CDCl_3$, rotamers) δ = 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

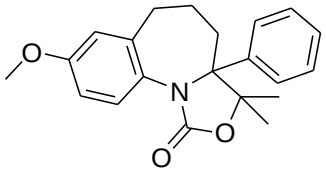
(2H, m, 2 × CH), 1.56–1.47 (1H, m, CH), 1.33 (4H, s, *t*-Bu), 1.31 (5H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers) δ = 158.5 (C), 158.2 (C), 155.1 (C=O), 155.0 (C=O), 138.8 (C), 138.5 (C), 132.2 (C), 132.0 (C), 131.5 (C), 131.4 (C), 130.7 (CH), 130.5 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 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 ($OCH_3$), 55.3 ($OCH_3$), 32.0 ($CH_2$), 31.0 ($CH_2$), 30.1 ($CH_2$), 29.9 ($CH_2$), 28.3 ($CH_3$), 28.2 ($CH_3$), 23.6 ($CH_2$), 22.9 ($CH_2$); HRMS (ES) $MNa^+$, 376.1885. $C_{22}H_{27}NO_3Na$ requires $MNa^+$, 376.1883; LRMS *m/z* (ES) 376 (5%, $MNa^+$), 298 (100, $MH^+$–*t*-Bu+H).

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



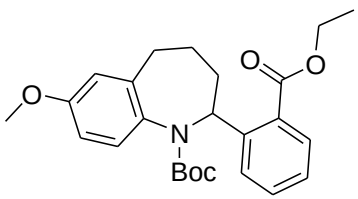

Using general procedure **C**, carbamate **132** (100 mg, 0.28 mmol), *n*-BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) and tributyltin chloride (0.22 mL, 0.84 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **134a** (118 mg, 65%) as a white solid; m.p. 86–88 ºC; $R_f$ 0.53 [petrol–EtOAc (90:10)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2955, 1670 (C=O), 1495, 1170; $^1$H NMR (400 MHz, $CDCl_3$) 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, $OCH_3$), 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 × $CH_2$), 1.28–1.21 (6H, m, 3 × $CH_2$), 0.86 (9H, t, *J* = 7.0 Hz, 3 × $CH_3$), 0.82–0.63 (6H, m, 3 × $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_3$), 30.3 ($CH_2$), 29.0 ($CH_2$), 28.3 ($CH_3$), 27.7 ($CH_2$), 23.7 ($CH_2$), 23.0 ($CH_2$), 13.7 ($CH_3$), 13.4 ($CH_2$); HRMS (ES) Found: $MNa^+$, 666.2972. $C_{34}H_{53}NO_3{}^{120}SnNa$ requires $MNa^+$, 666.2945; Found: $MNa^+$, 664.3000. $C_{34}H_{53}NO_3{}^{118}SnNa$ requires $MNa^+$, 664.2940; LRMS *m/z* (ES) 666 (100%, $MNa^+$), 664 (80, $MNa^+$).

**12-methoxy-5,5-dimethyl-6-phenyl-4-oxa-2-azatricyclo[8.4.0.0$^{2,6}$]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 ºC; $R_f$ 0.26 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2935, 1750 (C=O), 1610, 1270, 1160; $^1$H NMR (400 MHz, $CDCl_3$) 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, $OCH_3$), 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, $CH_3$), 1.35–1.30 (1H, m, CH), 1.01 (3H, s, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($OCH_3$), 36.4 ($CH_2$), 36.1 ($CH_2$), 26.1 ($CH_3$), 21.2 ($CH_2$), 21.0 ($CH_3$); HRMS (ES) Found: $MH^+$, 338.1757. $C_{21}H_{24}NO_3$ 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)**



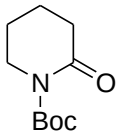
Using general procedure **C**, carbamate **132** (100 mg, 0.28 mmol), *n*-BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) and ethyl chloroformate (0.08 mL, 0.84 mmol) gave, after flash column chromatography on silica gel, eluting with petrol–EtOAc (70:30), the carbamate **134c** (72 mg, 60%) as a brown oil; $R_f$ 0.52 [petrol–EtOAc (70:30)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2980, 1695 (C=O), 1500, 1270, 1160; $^1$H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.91 (1H, d, *J* =

8.0 Hz, CH), 7.59–7.57 (1H, m, CH), 7.52–7.48 (1H, m, CH), 7.23–7.20 (1H, m, CH), 6.99–6.88 (1H, m, CH), 6.78–6.74 (1H, m, CH), 6.68–6.57 (1H, m, CH), 5.94 (0.25H, d, *J* = 12.0 Hz, NCH), 5.77 (0.75H, d, *J* = 12.0 Hz, NCH), 4.45–4.37 (2H, m, $OCH_2$), 3.84 (2.25H, s, $OCH_3$), 3.79 (0.75H, s, $OCH_3$), 3.00–2.93 (1H, m, CH), 2.64–2.58 (1H, m, CH), 2.56–2.43 (1H, m, CH), 2.39–2.20 (1H, m, CH), 1.97–1.86 (2H, m, 2 × CH), 1.44 (3H, t, *J* = 7.0, Hz, $CH_3$), 1.35 (3H, s, *t*-Bu), 1.18 (6H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers) δ = 167.2 (C=O), 166.6 (C=O), 158.3 (C), 157.9 (C), 155.0 (C=O), 154.7 (C=O), 150.4 (C), 149.6 (C), 138.5 (C), 138.2 (C), 132.3 (CH), 132.2 (CH), 130.8 (C), 130.7 (C), 130.1 (CH), 130.0 (CH), 129.4 (C), 129.3 (C), 127.4 (CH), 127.3 (CH), 127.0 (CH), 126.5 (CH), 125.9 (CH), 125.6 (CH), 113.9 (CH), 113.5 (CH), 111.7 (CH), 111.0 (CH), 80.1 (C), 79.5 (C), 61.1 ($OCH_2$), 60.8 ($OCH_2$), 57.0 (NCH), 56.4 (NCH), 55.4 ($OCH_3$), 55.3 ($OCH_3$), 31.8 ($CH_2$), 31.5 ($CH_2$), 29.9 ($CH_2$), 29.7 ($CH_2$), 28.2 ($CH_3$), 27.9 ($CH_3$), 23.9 ($CH_2$), 23.8 ($CH_2$), 14.3 ($CH_3$), 14.1 ($CH_3$); HRMS (ES) Found: $MH^+$, 426.2282. $C_{25}H_{32}NO_5$ requires $MH^+$, 426.2275; LRMS *m/z* (ES) 426 (25%, $MH^+$), 370 (100, $MH^+$–*t*-Bu+H), 326 (60, $MH^+$–Boc+H).

**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)**

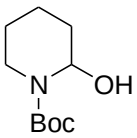
*n*-BuLi (0.14 mL, 0.34 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (86 mg, 0.37 mmol) and *N*-Boc-2-phenyl-7-methoxybenzazepine **97** (100 mg, 0.28 mmol) in dry toluene (6 mL) at –50 °C. After 3 h, tributyltin chloride (0.23 mL, 0.85 mmol) was added. The mixture 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, $CHCl_3$), 57:43 er.

***tert*-Butyl 2-Oxopiperidine-1-carboxylate (145)**




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-*tert*-butyl dicarbonate (12.74 g, 55.5 mmol) in dry THF (30 mL). The reaction mixture was stirred at 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 $\nu_{max}$ ATR/$cm^{-1}$ 2980, 2955, 2895, 1770 (C=O), 1700 (C=O), 1130; $^1$H NMR (400 MHz, $CDCl_3$) δ = 3.68–3.46 (2H, m, $NCH_2$), 2.62–2.26 (2H, m, 2 × CH), 1.86 –1.65 (4H, m, 4 × CH), 1.44 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 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%, $MH^+$–*t*-Bu+H). Data in accordance with the literature.[130]

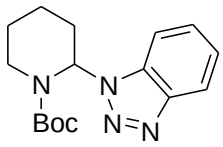
***tert*-Butyl 2-Hydroxypiperidine-1-carboxylate (146)**

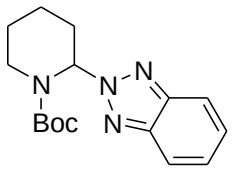



To a solution of carbamate **145** (8.60 g, 43.1 mmol) in dry THF (120 mL) at –78 ºC was added DIBAL-H (60.4 mL, 60.4 mmol, 1 M in cyclohexane) dropwise. The reaction mixture was stirred at –78 ºC under nitrogen for 1 h, before gradually warming to room temperature over a further 1 h. The reaction was 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; $R_f$ 0.44 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 3420 (OH), 2980, 2940, 2860, 1670 (C=O), 1160; 1H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 155.5 (C=O), 80.1 (C), 74.7 (CH), 39.3 ($CH_2$), 30.4 ($CH_2$), 28.4 ($CH_3$), 24.7 ($CH_2$), 17.7 ($CH_2$); HRMS (ES) Found: $MNa^+$, 224.1261. $C_{10}H_{19}NO_3Na$ 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)**

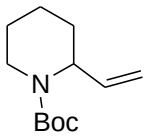



To a solution of carbamate **146** (7.00 g, 34.8 mmol) in toluene (100 mL) was added benzotriazole (6.21 g, 52.2 mmol) and $MgSO_4$ (1.0 g). The reaction mixture was heated to reflux for 18 h then allowed to cool to room temperature, before washing with saturated aqueous $NaCO_3$ solution (3 × 30 mL) and saturated brine solution (3 × 30 mL). The organic layer was dried over $MgSO_4$ 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; $R_f$ 0.42, 0.60 [petrol-EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2970, 2930, 2860, 1690 (C=O), 1160, 1110; $^1$H NMR (400 MHz, $CDCl_3$, 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); $^{13}$C NMR (100 MHz, $CDCl_3$,

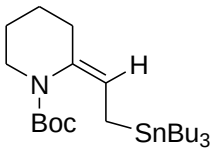
mixture of isomers) δ = 155.4 (C=O), 154.3 (C=O), 145.6 (C), 144.0 (C), 132.7 (C), 131.6 (C), 127.3 (CH), 126.1 (CH) 123.9 (CH), 119.6 (CH), 118.4 (CH), 110.7 (CH), 105.6 (CH), 105.1 (CH), 81.1 (C), 80.9 (C), 66.5 (CH), 64.2 (CH), 41.4 ($CH_2$), 40.2 ($CH_2$), 29.2 ($CH_2$), 28.7 ($CH_2$), 28.3 ($CH_3$), 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. $C_{16}H_{22}N_4O_2Na$ requires $MNa^+$, 325.1640; LRMS *m/z* (ES) 128 (100%, $MH^+$–*t*-Bu+H, $C_6H_4N_3$). Data in accordance with the literature.[130]

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




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 $NH_4Cl$ (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 $\nu_{max}$ 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, C*H*=$CH_2$), 5.18 (1H, dt, *J* = 10.5, 1.5 Hz, CH=C$H_2$), 5.04 (1H, dt, *J* = 16.0, 1.5 Hz, CH=C$H_2$), 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. $C_{12}H_{21}NO_2Na$ requires $MNa^+$, 234.1465; LRMS *m/z* (ES) 156 (100%, $MH^+$–*t*-Bu+H). Data in accordance with the literature.[131]

***tert*-Butyl (2Z)-[2-(Tributylstannyl)ethylidene]piperidine-1-carboxylate (149)**



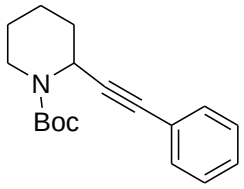

To a solution of *tert*-butyl 2-ethenylpiperidine-1-carboxylate **136** (100 mg, 0.47 mmol) in dry THF (2 mL) at –50 ºC under nitrogen, was added *n*-BuLi (0.25 mL, 0.57 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.45 mL, 1.42 mmol) was added. The mixture was allowed 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–$Et_2O$ (98:2), gave the carbamate **149** (164 mg, 69%) as a yellow oil; $R_f$ 0.72 [petrol–$Et_2O$ (60:40)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2960, 2920, 2850, 1695 (C=O), 1660 (C=C); $^1$H NMR (400 MHz, $CDCl_3$, 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); $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers, one $CH_3$ 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 ($CH_2$), 46.1 ($CH_2$), 33.3 ($CH_2$), 32.9 ($CH_2$), 29.6 ($CH_2$), 29.1 ($CH_2$), 28.4 ($CH_3$), 27.8 ($CH_2$), 27.3 ($CH_2$), 26.8 ($CH_2$), 26.5 ($CH_2$), 26.0 ($CH_2$), 25.7 ($CH_2$), 19.1 ($CH_2$), 17.5 ($CH_2$), 13.7 ($CH_3$), 13.6 ($CH_3$), 9.8 ($CH_2$), 9.3 ($CH_2$); HRMS (ES) Found: $MH^+$, 502.2716. $C_{24}H_{48}NO_2{}^{120}Sn$ requires $MH^+$, 502.2707; Found: $MH^+$, 500.2733. $C_{24}H_{48}NO_2{}^{118}Sn$ 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

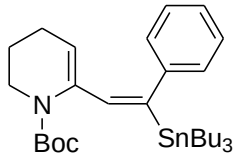
petrol/EtOAc (97:2), gave the recovered starting material **136** (43 mg, 43%) as colourless oil; data as above; the enantiomeric ratio was not determined.

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



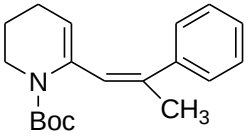

To a solution of carbamate **147a,b** (4.00 g, 13.2 mmol) in dry THF (40 mL) at 0 ºC was added phenylethynylmagnesium bromide (52.95 mL, 52.95 mmol, 1 M in THF) dropwise. The reaction mixture was stirred under argon for 1 h at room temperature, then heated at 66 ºC for 48 h, then cooled to room temperature, diluted with a saturated solution of $NH_4Cl$ (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 (95:5), gave the carbamate **137** (2.65 g, 70%) as needles, m.p. 82–84 °C (reported as oil[131]); $R_f$ 0.60 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2975, 2940, 2860, 1690 (C=O), 1405, 1155; $^1$H NMR (400 MHz, $CDCl_3$) 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); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 30.7 ($CH_2$), 28.4 ($CH_3$), 25.4 ($CH_2$), 20.1 ($CH_2$); HRMS (ES) Found: $MNa^+$, 308.1627. $C_{18}H_{23}NO_2Na$ 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.[131]

***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 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, eluting with petrol–EtOAc (97:3), to give the carbamate **151a** (149 mg, 74%) as a yellow oil; $R_f$ 0.65 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2955, 2930, 2870, 1690 (C=O), 1635 (C=C), 1160; $^1$H NMR (400 MHz, $CDCl_3$) 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 × $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 29.1 ($CH_2$), 28.5 ($CH_3$), 27.4 ($CH_2$), 23.8 ($CH_2$), 23.4 ($CH_2$), 13.6 ($CH_3$), 11.9 ($CH_2$); HRMS (ES) Found: MNa$^+$, 598.2700. $C_{30}H_{49}NO_2{}^{120}SnNa$ requires MNa$^+$, 598.2683; Found: MNa$^+$, 596.2708. $C_{30}H_{49}NO_2{}^{118}SnNa$ requires MNa$^+$, 596.2708; LRMS *m/z* (ES) 598 (45%, MNa$^+$), 596 (30, MNa$^+$), 356 (100).

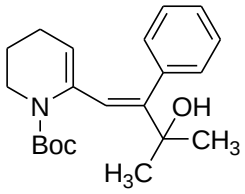
**tert-Butyl 2-[(1Z)-2-phenylprop-1-en-1-yl]-5,6-dihydro-4H-pyridine-1-carboxylate (151b)**




To a solution of carbamate **137** (100 mg, 0.35 mmol) in dry THF (2 mL) at –78 ºC 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; $R_f$ 0.53 [petrol–$Et_2O$ (60:40)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2980, 2925, 2860, 1700 (C=O), 1600 (C=C), 1160; $^1H$ NMR (400 MHz, $CDCl_3$, 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, $CH_3$), 2.10 (2.7H, s, $CH_3$), 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); $^{13}C$ NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 28.4 ($CH_3$), 25.4 ($CH_3$), 23.2 ($CH_2$), 23.1 ($CH_2$); HRMS (ES) Found: $MH^+$, 322.1780. $C_{19}H_{25}NO_2Na$ requires $MNa^+$, 322.1778; LRMS *m/z* (ES) 322 (5%, $MH^+$), 244 (100, $MH^+$–*t*-Bu+H).

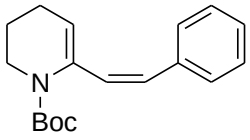
**tert-Butyl 2-[(1*E*)-3-Hydroxy-3-methyl-2-phenylbut-1-en-1-yl]-5,6-dihydro-4H-pyridine-1-carboxylate (151c)**




To a solution of carbamate **137** (100 mg, 0.35 mmol) in dry THF (2 mL) at –78 ºC 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; $R_f$ 0.33 [petrol–EtOAc (60:40)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 3385, 2980, 2920, 2850, 1690 (C=O), 1640 (C=C),1155; $^1H$ NMR (400 MHz, $CDCl_3$, 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, $CH_3$), 1.39 (5.4H, s, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 29.4 ($CH_3$), 28.5 ($CH_3$), 25.6 ($CH_2$), 23.0 ($CH_2$); HRMS (ES) Found: $MH^+$, 344.4600. $C_{21}H_{30}NO_3$ 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)**



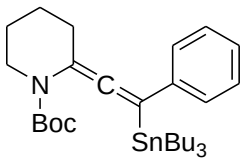

To a solution of carbamate **137** (100 mg, 0.35 mmol), *n*-BuLi (0.175 mL, 0.42 mmol, 2.4 M in hexanes) at –78 ºC, after 10 min MeOH (1mL) was added. The reaction mixture was allowed to warm to room temp. and then was stirred at room temperature under nitrogen for 16 h. Purification by flash silica chromatography, eluting with petrol–EtOAc (97:3), gave the carbamate **151d** (91 mg, 91%) as yellow oil; $R_f$ 0.55 [petrol–$Et_2O$ (60:40)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2960, 2920, 2865, 1695 (C=O), 1610 (C=C), 1160; $^1H$ NMR (400 MHz, $CDCl_3$, 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); $^{13}C$ NMR (100 MHz, $CDCl_3$, 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 ($CH_2$), 28.2 ($CH_3$), 23.2 ($CH_2$), 23.1 ($CH_2$); HRMS (ES) Found: $MH^+$, 286.1802. $C_{18}H_{24}NO_2$ 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 ºC 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)

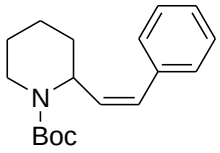



To a solution of carbamate **137** (100 mg, 0.35 mmol) in dry THF (2 mL) at –78 ºC under nitrogen was added *n*-BuLi (0.18 mL, 0.42 mmol, 2.4 M in hexanes). After stirring for 10 minutes, tributyltin chloride (0.28 mL, 1.05 mmol) was added. The mixture was allowed to warm gradually to room temperature 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–$Et_3N$ (97:2:1), to give the carbamate **152** (110 mg, 55%) as an unstable yellow oil; $R_f$ 0.63 [petrol–EtOAc (80:20)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2960, 2920, 1695 (C=O), 1645 (C=C), 1150; $^1$H NMR (400 MHz, $CDCl_3$) 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 × $CH_2$), 1.24 (9H, m, *t*-Bu), 1.15–0.99 (6H, m, 3 × $CH_2$), 0.94–0.79 (15H, m, 3 × $CH_3$, 3 × $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) 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 ($CH_2$), 30.6 ($CH_2$), 29.0 ($CH_2$) , 28.5 ($CH_3$), 27.3 ($CH_2$), 25.7 ($CH_2$), 25.5 ($CH_2$), 13.8 ($CH_3$), 11.2 ($CH_2$); HRMS (ES) Found: $MH^+$, 598.4300. $C_{30}H_{49}NO_2{}^{120}SnNa$ requires $MNa^+$, 598.2810; Found: $MH^+$, 596.4310. $C_{30}H_{49}NO_2{}^{118}SnNa$ 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; $[\alpha]_D^{23}$ –4.8 (3.75, $CHCl_3$), 80:20 er.

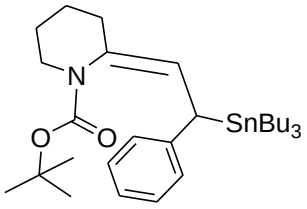
***tert*-Butyl 2-[(Z)-2-phenylethenyl]piperidine-1-carboxylate (138)**




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/$CH_2Cl_2$ (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–$Et_2O$ (70:30)]; FT-IR $\nu_{max}$ ATR/$cm^{-1}$ 2970, 2935, 2860, 1695 (C=O), 1615 (C=C), 1400; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.37–7.27 (4H, m, 4 × 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, m, 2 × CH), 1.70–1.63 (2H, m, 2 × CH), 1.51–1.44 (2H,

m, 2 × CH), 1.25 (9H, m, *t*-Bu); $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 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 ºC 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–$Et_2O$ (80:20)];FT-IR $\nu_{max}$ ATR/cm$^{-1}$ 2960, 2925, 1690 (C=O), 1640 (C=C), 1160; $^1$H NMR (400 MHz, $CDCl_3$, rotamers) δ = 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, $CDCl_3$) δ = 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)**

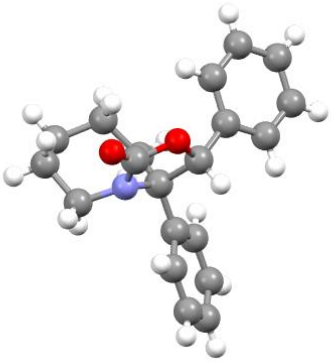
*n*-BuLi (0.11 mL, 0.28 mmol, 2.5 M in hexane) was added dropwise to a stirred solution of (+)-sparteine (89 mg, 0.38 mmol) and *N*-Boc-2-[(Z)-2-phenylethenyl]piperidine **138** (100 mg, 0.35 mmol) in dry toluene (6 mL) at –78 °C. After 3 h, tributyltin chloride (0.28 mL, 1.04 mmol) was added. The mixture 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; $[\alpha]_D^{23}$ –46.6 (0.75, $CHCl_3$), 79:21 er.

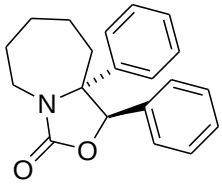
# *Chapter 7*

# *Appendices*

## Appendix 6.1: X-ray crystal structures

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





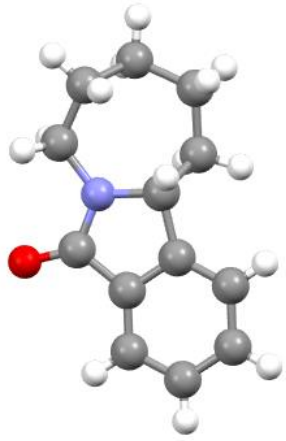

**73g**

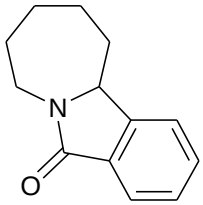
**Table 1 Crystal data and structure refinement for oic287v_0m.**

| | | |
|---|---|---|
| Identification code | oic287v_0m | |
| Empirical formula | $C_{20}H_{21}NO_2$ | |
| Formula weight | 307.38 | |
| Temperature/K | 100.02 | |
| Crystal system | monoclinic | |
| Space group | $P2_1/n$ | |
| Unit cell dimensions | a = 7.1861(4) Aº | α = 90º |
| | b = 12.9276(7) Aº | β = 94.003(2)º |
| | c = 17.0022(9) Aº | γ = 90º |
| Volume | 1575.63(15) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.296 $g/cm^3$ | |
| Absorption coefficient | 0.658 $mm^{-1}$ | |
| F(000) | 656.0 | |
| Crystal size | 0.232 × 0.227 × 0.05 $mm^3$ | |
| Wavelength | 1.54178 Å | |

| | |
|---|---|
| Theta range for data collection | 8.6 to 133.306º |
| Index ranges | $-8 \leq h \leq 8, -15 \leq k \leq 15, -20 \leq l \leq 20$ |
| Reflections collected | 25185 |
| Independent reflections | 2782 [R(int) = 0.0287, R(sigma) = 0.0150] |
| Data/restraints/parameters | 2782/0/208 |
| Goodness-of-fit on $F^2$ | 1.067 |
| Final R indexes [I>=2sigma (I)] | $R_1$ = 0.0347, $wR_2$ = 0.0847 |
| Final R indexes [all data] | $R_1$ = 0.0365, $wR_2$ = 0.0861 |
| Largest diff. peak and hole | 0.29/-0.23 e $Å^{-3}$ |

**Appendix 6.1b**: X-ray crystal structure determination data of compound **95**





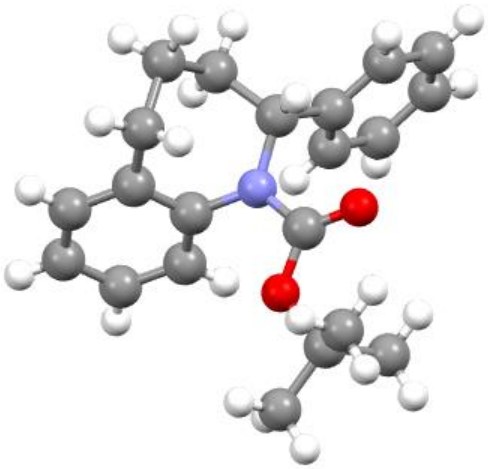

**95**

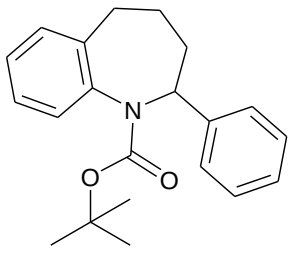
**Table 1 Crystal data and structure refinement for oic297v_2_0m.**

| | | |
|---|---|---|
| Identification code | oic297v_2_0m | |
| Empirical formula | $C_{13}H_{15}NO$ | |
| Formula weight | 201.26 | |
| Temperature/K | 99.99 K | |
| Crystal system | triclinic | |
| Space group | P1 | |
| Unit cell dimensions | a = 5.9056(3) Aº | α = 92.980(2)º |
| | b = 7.7414(3) Aº | β = 99.128(3)º |
| | c = 11.8446(5) Aº | γ = 93.940(2)º |

| | |
|---|---|
| Volume | 1575.63(15) $Å^3$ |
| Z | 2 |
| Density (calculated) | 1.256 $g/cm^3$ |
| Absorption coefficient | 0.622 $mm^{-1}$ |
| F(000) | 216.0 |
| Crystal size | 0.15 × 0.1 × 0.05 $mm^3$ |
| Wavelength | 1.54178 Å |
| Theta range for data collection | 7.574 to 133.35 |
| Index ranges | $-7 \leq h \leq 7, -9 \leq k \leq 9, -14 \leq l \leq 14$ |
| Reflections collected | 13872 |
| Independent reflections | 3613 [R(int) = 0.0553, R(sigma) = 0.0489] |
| Data/restraints/parameters | 3613/3/272 |
| Goodness-of-fit on $F^2$ | 1.086 |
| Final R indexes [I>=2sigma (I)] | $R_1$ = 0.0378, $wR_2$ = 0.0707 |
| Final R indexes [all data] | $R_1$ = 0.0470, $wR_2$ = 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**





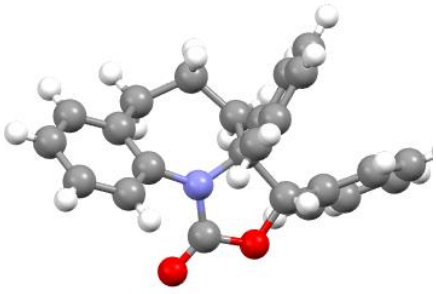

**96**

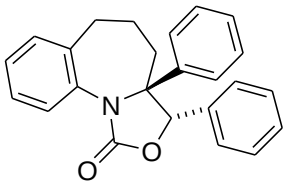
**Table 1 Crystal data and structure refinement for OIC296v_0m.**

| | |
|---|---|
| Identification code | OIC296v_0m |
| Empirical formula | $C_{21}H_{25}NO_2$ |

| | | |
|---|---|---|
| Formula weight | 323.42 | |
| Temperature/K | 100.03 | |
| Crystal system | triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 10.3272(7) Aº | α = 75.953(4)º |
| | b = 13.2567(9) Aº | β = 73.968(4)º |
| | c = 14.5809(11) Aº | γ = 73.587(4)º |
| Volume | 1810.8(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.186 $g/cm^3$ | |
| Absorption coefficient | 0.593 $mm^{-1}$ | |
| F(000) | 696.0 | |
| Crystal size | 0.28 × 0.13 × 0.04 $mm^3$ | |
| Wavelength | λ = 1.54178 Å | |
| Theta range for data collection | 6.41 to 133.576 | |
| Index ranges | $-12 \leq h \leq 12$, $-15 \leq k \leq 15$, $-17 \leq l \leq 17$ | |
| Reflections collected | 22283 | |
| Independent reflections | 6354 [$R_{int}$ = 0.1083, $R_{sigma}$ = 0.0969] | |
| Data/restraints/parameters | 6354/0/440 | |
| Goodness-of-fit on $F^2$ | 1.022 | |
| Final R indexes [I>=2sigma (I)] | $R_1$ = 0.0569, $wR_2$ = 0.1263 | |
| Final R indexes [all data] | $R_1$ = 0.1050, $wR_2$ = 0.1503 | |
| Largest diff. peak and hole | 0.28/-0.26 e $Å^{-3}$ | |

**Appendix 6.1d**: X-ray crystal structure determination data of compound *trans*-**120f**






**120f**

**Table 1 Crystal data and structure refinement for oic298k_0m.**

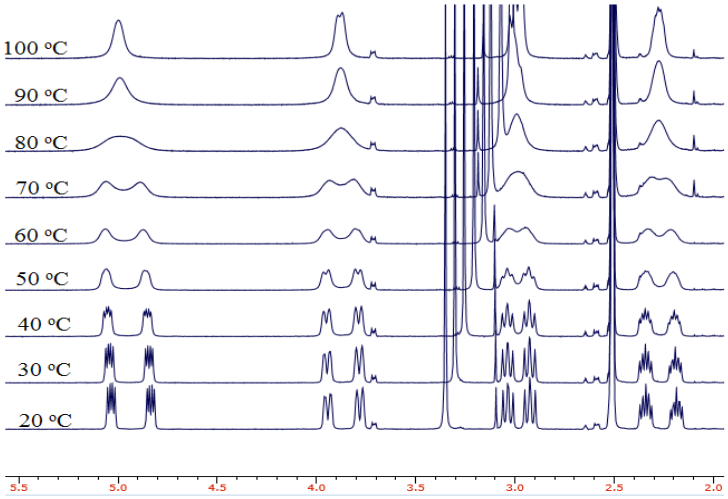
| | | |
|---|---|---|
| Identification code | oic298k_0m | |
| Empirical formula | $C_{24}H_{21}NO_2$ | |
| Formula weight | 355.42 | |
| Temperature/K | 100 | |
| Crystal system | triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 7.9010(17) Aº | α = 104.496(5)º |
| | b = 9.1178(19) Aº | β = 103.712(5)º |
| | c = 13.496(3) Aº | γ = 101.491(5)º |
| Volume | 879.2(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.343 $g/cm^3$ | |
| Absorption coefficient | 0.085 $mm^{-1}$ | |
| F(000) | 376.0 | |
| Crystal size | 0.18 × 0.178 × 0.177 $mm^3$ | |
| Wavelength | 0.71073 Å | |
| Theta range for data collection | 3.27 to 55.096º | |
| Index ranges | $-10 \leq h \leq 10$, $-11 \leq k \leq 11$, $-17 \leq l \leq 17$ | |
| Reflections collected | 21148 | |
| Independent reflections | 3970 [$R_{int}$ = 0.0713, $R_{sigma}$ = 0.0680] | |
| Data/restraints/parameters | 3970/0/245 | |
| Goodness-of-fit on $F^2$ | 1.014 | |
| Final R indexes [I>=2sigma (I)] | $R_1$ = 0.0497, $wR_2$ = 0.0994 | |
| Final R indexes [all data] | $R_1$ = 0.0926, $wR_2$ = 0.1158 | |
| Largest diff. peak and hole | 0.29/-0.26 e $Å^{-3}$ | |

## 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:

$k = \pi\ \Delta\nu_o^2 / 2[(\Delta\nu_{1/2})^e - (\Delta\nu_A)^o{}_{1/2}]$

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.

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

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

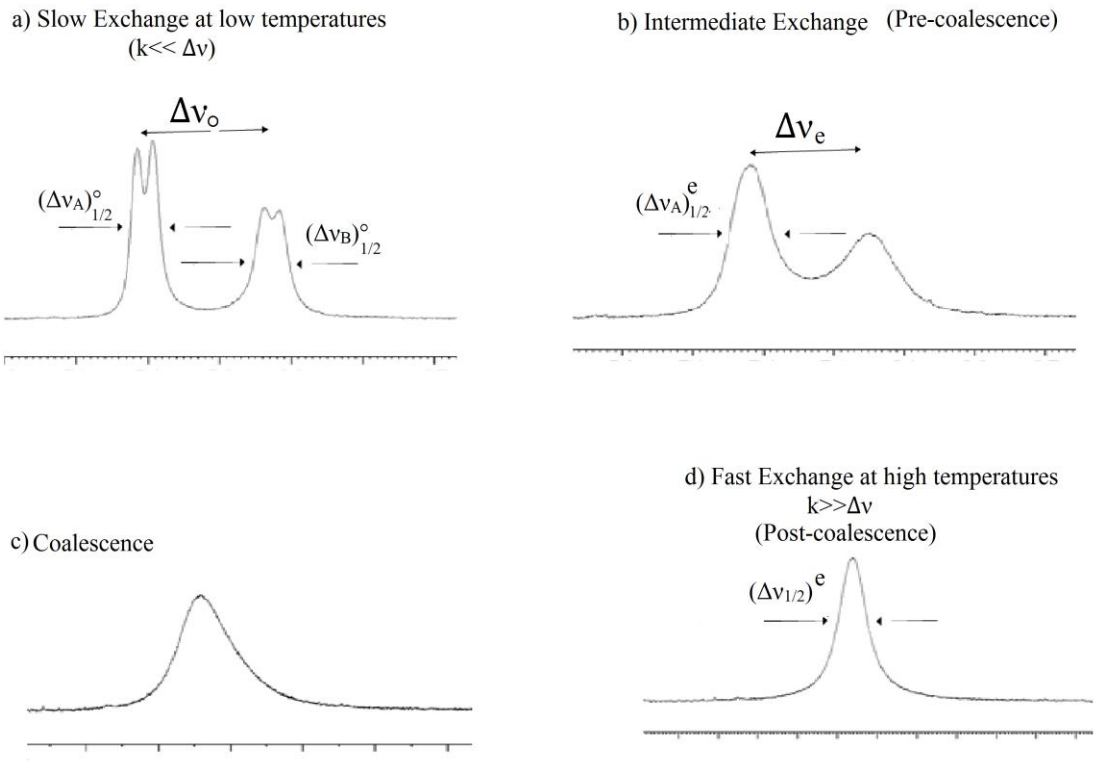


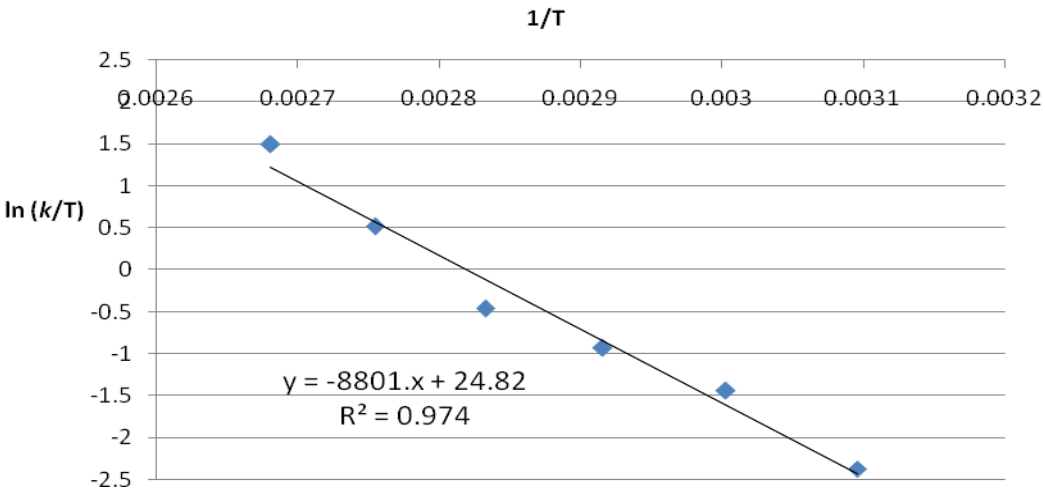

**Figure A**

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

| T/K | 1/T | $\Delta\nu_o$ | $\Delta\nu_e$ | *k* | ln(*k*/T) |
|---|---|---|---|---|---|
| **313** | 0.003195 | 99.58 | 100.6149 | – | – |
| **323** | 0.003096 | 99.58 | 98.6525 | 30.1618 | -2.371076 |
| **333** | 0.003003 | 99.58 | 92.9989 | 79.0650 | -1.437872 |
| **343** | 0.002915 | 99.58 | 78.9393 | 134.7905 | -0.934009 |
| **353** | 0.002833 | 99.58 | | 221.7861 | -0.4647548 |
| **363** | 0.002755 | 99.58 | 46.7697[a] | 609.3444 | 0.5179807 |
| **373** | 0.002681 | 99.58 | 30.5727[a] | 1662.974 | 1.4947846 |

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 kJ/mol and $\Delta S^{\ddagger}$ = 8.8 J/K·mol

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

$\Delta G^{\ddagger}$ = 70.8 kJ/mol at –5 °C, that equates to k = 8.7 x $10^{-2}$ $s^{-1}$, $t_{1/2}$ = 8 s

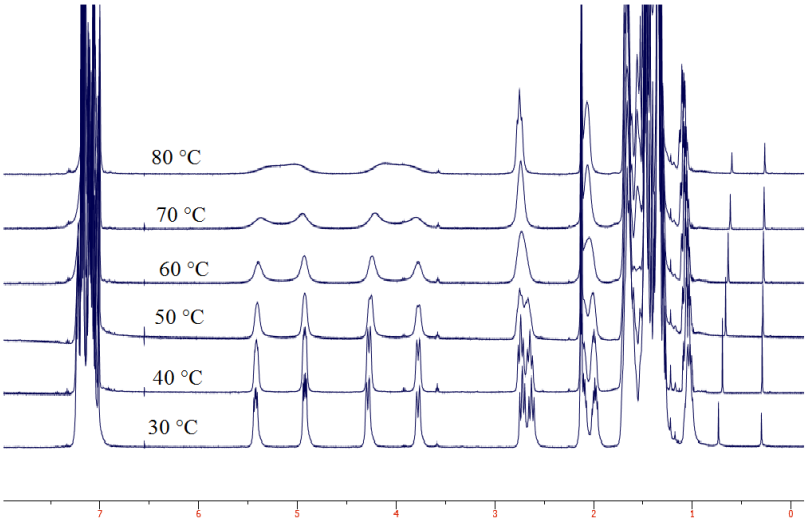
$\Delta G^{\ddagger}$ = 71.5 kJ/mol at –78 °C, that equates to k = 2.9 x $10^{-7}$ $s^{-1}$, $t_{1/2}$ = 28 d

These values are consistent with the slow rotation and lithiation at –78 °C, as shown by the ReactIR plots (figure 15, 17, chapter 2)

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

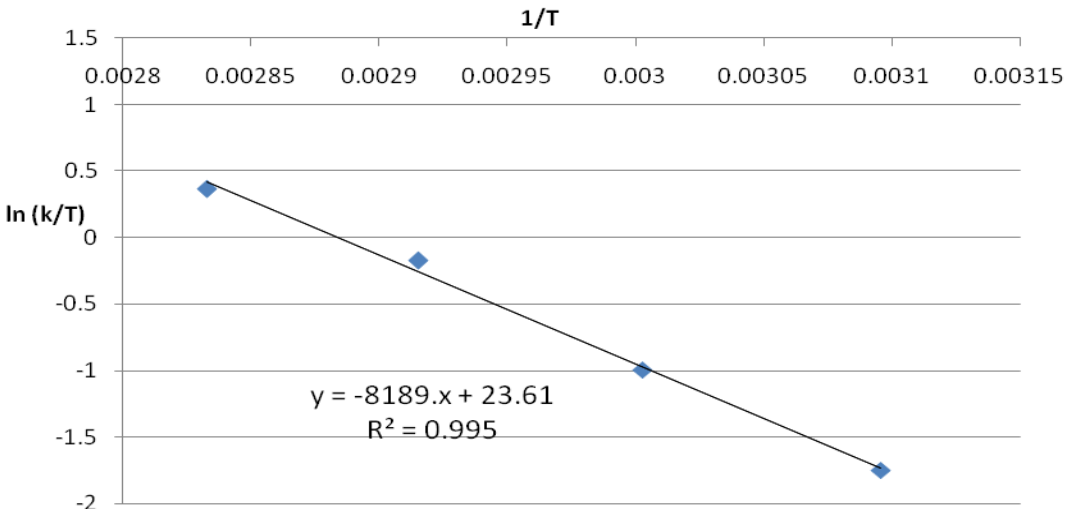
**NMR in toluene-$d_8$**

A sample of *N*-Boc-2-phenylazepane **71** (28 mg, 0.10 mmol) in toluene-$d_8$ (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, *e.g.* around 5 ppm, at about 80 °C.




Using the signals at 2.53 and 2.63 ppm

| T/K | 1/T | $\Delta\nu_o$ | $\Delta\nu_e$ | *k* | ln(*k*/T) |
|---|---|---|---|---|---|
| **323** | 0.003096 | 47.138 | 39.8051 | 56.09229 | -1.75065 |
| **333** | 0.003003 | 47.138 | 51.9397 | 123.1366 | -0.99485 |
| **343** | 0.002915 | 47.138 | 35.6782 | 288.8429 | -0.17185 |
| **353** | 0.002833 | 47.138 | 30.45 | 509.1147 | 0.366205 |




From the Eyring plot:

$\Delta H^{\ddagger}$ = 68.1 kJ/mol and $\Delta S^{\ddagger}$ = –1.2 J/K·mol

These values provide:

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

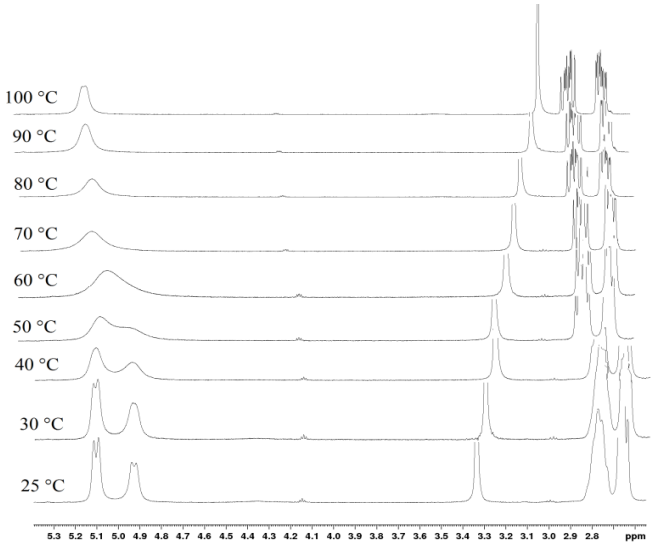
$\Delta G^{\ddagger}$ = 67.9 kJ/mol at –78 °C, that equates to $k$ = 2.7 x $10^{-6}$ $s^{-1}$, $t_{1/2}$ = 72 h

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**

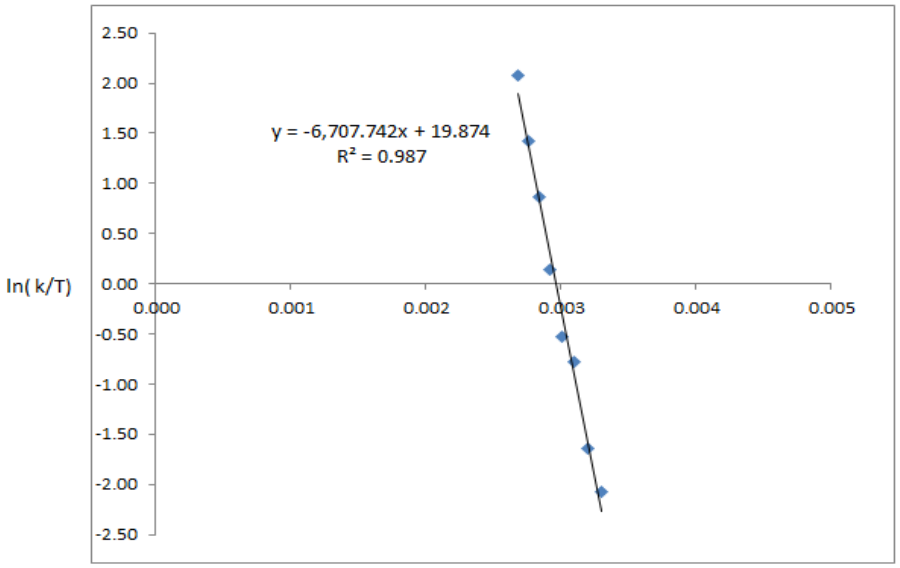
**NMR in DMSO-d$_6$**

A sample of *N*-Boc-2- phenylbenzazepine **96** (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 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**

| T/K | 1/T | $\Delta\nu_o$ | $\Delta\nu_e$ | *k* | ln(*k*/T) |
|---|---|---|---|---|---|
| **298** | 0.003356 | 88.65 | 88.65 | 0 | – |
| **303** | 0.003300 | 88.65 | 86.97 | 38.157 | -2.07202 |
| **313** | 0.003195 | 88.65 | 84.35 | 60.589 | 1.64209 |
| **323** | 0.003096 | 88.65 | 58.45 | 148.062 | -0.78002 |
| **333** | 0.003003 | 88.65 | 40.45 | 196.931 | -0.52529 |
| **343** | 0.002915 | 88.65 | | 396.550 | 0.14507 |
| **353** | 0.002833 | 88.65 | | 836.922 | 0.86326 |
| **363** | 0.002755 | 88.65 | | 1498.131 | 1.41757 |
| **373** | 0.002681 | 88.65 | | 2996.262 | 2.08354 |



From the Eyring plot:

$\Delta H^{\ddagger}$ = 55.77 kJ/mol and $\Delta S^{\ddagger}$ = –32.31 J/K·mol

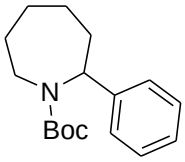
These values provide:

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

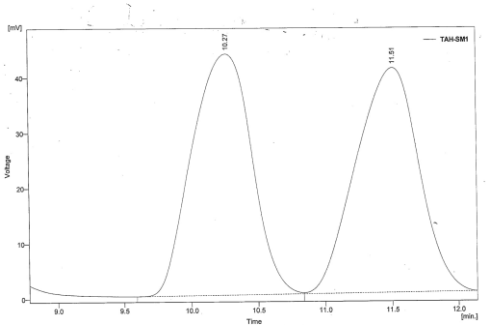
$\Delta G^{\ddagger}$ = 62.07 kJ/mol at –78 °C, that equates to $k$ = 1.0 x $10^{-4}$ $s^{-1}$, $t_{1/2}$ = 120 min

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

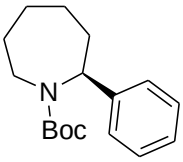



*rac*-**71**

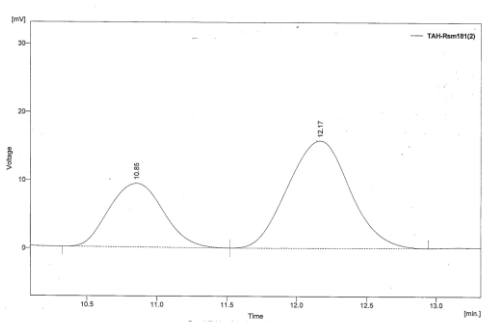



(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 10.267 | 1353.076 | 50.4 |
| 2 | 11.510 | 1331.002 | 49.6 |
| | total | 2684.078 | 100.0 |

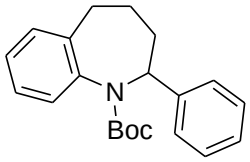



(*S*)-**71**



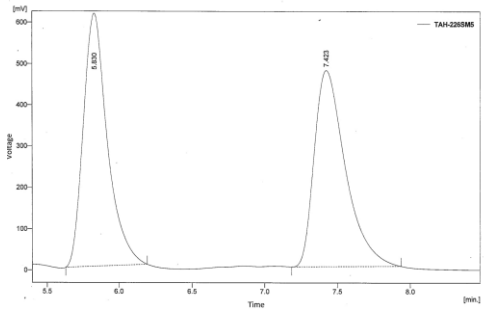

(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 10.853 | 250.618 | 34.0 |
| 2 | 12.167 | 485.950 | 66.0 |
| | total | 12676.206 | 100.0 |

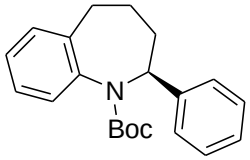



*rac*-**96**

(Cellulose-2)

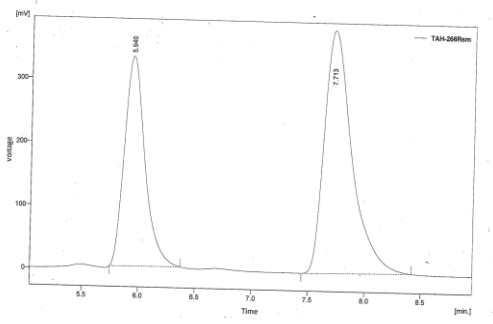



| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 5.830 | 7114.468 | 50.2 |
| 2 | 7.423 | 7061.618 | 49.8 |
| | total | 14176.085 | 100.0 |

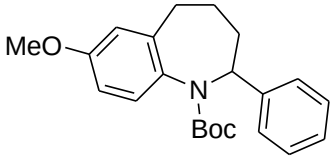



(*S*)-**96**

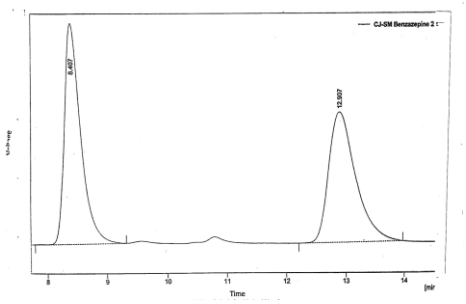
(Cellulose-2)




| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 5.940 | 4170.300 | 39.0 |
| 2 | 7.713 | 6521.836 | 61.0 |
| | total | 10692.136 | 100.0 |

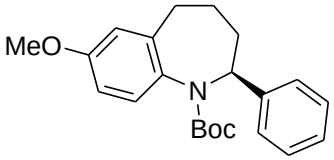



*rac*-**97**

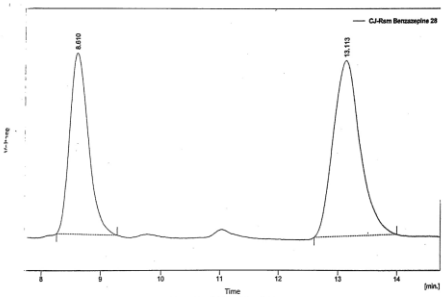



(Cellulose-2)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 8.407 | 1423.824 | 50.4 |
| 2 | 12.907 | 1399.959 | 49.6 |
| | total | 2823.782 | 100.0 |

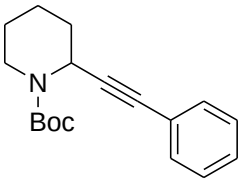



(*S*)-**97**

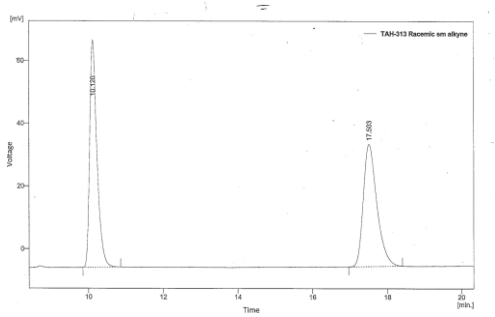



(Cellulose-2)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 8.610 | 337.649 | 42.0 |
| 2 | 13.113 | 471.315 | 58.0 |
| | total | 808.964 | 100.0 |

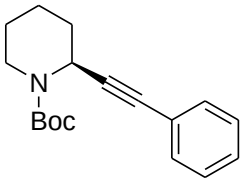



*rac*-**137**

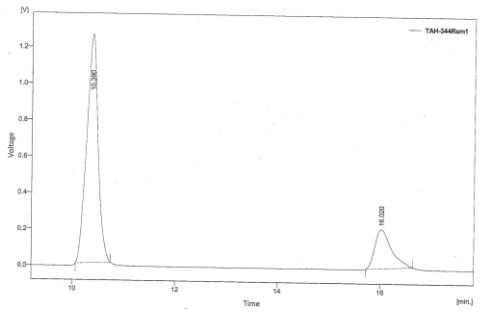



(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 10.120 | 985.263 | 50.0 |
| 2 | 17.503 | 983.863 | 50.0 |
| | total | 1969.126 | 100.0 |

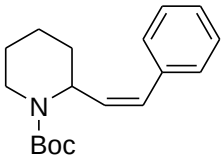



(*S*)-**137**

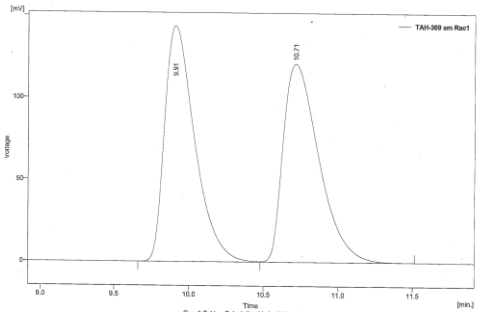



(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 10.390 | 19375.660 | 80.0 |
| 2 | 16.020 | 4843.630 | 20.0 |
| | total | 24219.290 | 100.0 |

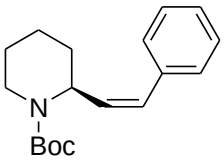



*rac*-**138**

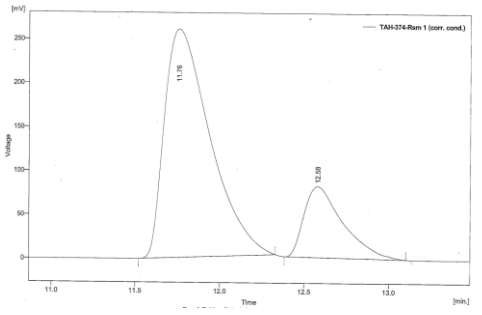



(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 9.907 | 2019.459 | 50.0 |
| 2 | 10.713 | 2019.577 | 50.0 |
| | total | 4039.036 | 100.0 |




(*S*)-**138**




(Cellulose-1)

| | $R_t$/min | Area/ mV.s | Area/% |
|---|---|---|---|
| 1 | 11.757 | 4895.406 | 79.0 |
| 2 | 12.580 | 1300.552 | 21.0 |
| | total | 6195.958 | 100.0 |

# *Chapter 6*

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