A Combined Synthetic, *In situ* IR Spectroscopic and Computational Investigation of the Lithiation-Trapping Reactions of N-Boc Heterocycles

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Abstract

This thesis describes some novel aspects of the α-lithiation-trapping of N-Boc heterocycles, including computational DFT modelling of the lithiation and kinetic studies of both the lithiation and trapping reactions of N-Boc heterocycles.

Chapter 2 details the use of in situ IR spectroscopy to monitor the progress of the α-lithiation reactions of a wide variety of N-Boc heterocycle substrates with vastly different reactivities. Different s-BuLi/ligand combinations were also found to have a dramatic effect on the rate of lithiation. Kinetic analysis of the in situ IR spectroscopic data enabled the rates of lithiation to be quantified which allowed the construction of a reactivity order for N-Boc heterocycles that were investigated.

In Chapter 3, the α-lithiation reactions of the N-Boc heterocycles studied in Chapter 2 were modelled with DFT. Many of the reactivity differences of the N-Boc heterocycles that were uncovered by the experimental investigation were accounted for by the DFT modelling. Correlation of the experimental and computational results allowed the reactivities of unknown N-Boc heterocycles to be predicted using only DFT modelling.

Chapter 4 describes the investigation of the rates of trapping of lithiated N-Boc heterocycles using in situ IR spectroscopy. Kinetic analysis of the in situ IR spectroscopic data revealed some remarkable differences in the rates of trapping for a small selection of different N-Boc heterocycles and electrophiles.

Chapter 5 reports the use of synthesis, in situ IR spectroscopic analysis and DFT modelling to investigate how the electrophile and ligand employed can affect the diastereoselectivity of the lithiation-trapping of a 3,4-disubstituted N-Boc pyrrolidine.
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Disc 1 is attached to the inside back cover of this thesis
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Author’s Declaration

The research presented in this thesis is, to the best of my knowledge, original except where due reference has been made to other authors and/or co-workers. This work has not previously been presented for an award at this, or any other, University.

Adam Islip
Chapter 1: Introduction

Nitrogen heterocycles, including pyrrolidines, piperidines and piperazines are important structural motifs in both nature and pharmaceutical compounds. For example, 44 of the “Top 200 selling pharmaceuticals in US retail sales of 2015” contain either a pyrrolidine, piperidine, morpholine or piperazine subunit. The racemic and asymmetric synthesis of 2-substituted N-Boc heterocycles has become widespread using the N-Boc α-lithiation protocol pioneered by Beak.\textsuperscript{2,3}

Since Beak’s first publication in 1989, much research has been carried out investigating different N-Boc heterocycle substrates, various ligands and a variety of electrophiles to trap the lithiated intermediates. This has enabled the synthesis of a large variety of different substituted N-Boc heterocycles. In this thesis, synthetic, in situ IR spectroscopy and computational DFT modelling techniques have been used to investigate, find optimal conditions and better understand the α-lithiation reactions of N-Boc heterocycles.

Recently, interest in the 2,3,4-trisubstituted pyrrolidine motif has developed and such a motif can be accessed enantioselectively and diastereoselectively using α-lithiation chemistry.\textsuperscript{4} Subsequent trapping with an appropriate electrophile would give a functionalised heterocycle fragment which could then be further reacted to form the desired compound. This 2,3,4-trisubstituted pyrrolidine motif is present in drug compounds such as Boceprevir\textsuperscript{5} developed by Schering-Plough (now Merck) and Telaprevir\textsuperscript{6} developed by Vertex Pharmaceuticals, both of which are protease inhibitors used to treat hepatitis C (Figure 1.1).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Figure1.png}
\caption{Boceprevir and Telaprevir protease inhibitors}
\end{figure}
1.1 Directed α-Lithiation - The Complex Induced Proximity Effect

The α-deprotonation of N-Boc heterocycles occurs for one key reason – the directing effect afforded by the carbamate that is attached to the N-heterocycle. This type of directing effect has been used in synthetic organolithium chemistry for several decades and was coined the ‘Complex Induced Proximity Effect’ (CIPE) by Beak and Meyers in 1986. Beak and Meyers proposed a general mechanism for the CIPE whereby the Lewis basic directing group attached to the heteroatom (in this case nitrogen) of substrate 1 can reversibly coordinate to the organolithium reagent to form prelithiation complex 2 (Scheme 1.1). This prelithiation complex places the organolithium in close proximity to the α-protons which facilitates the α-deprotonation of 2, forming α-lithiated intermediate 3. Lithiated intermediate 3 is dipole-stabilised, as the positive charge in resonance form 3b can stabilise the adjacent carbanion. Upon addition of an electrophile (E+), lithiated intermediate 3 undergoes trapping to form trapped product 4.

**Scheme 1.1. General mechanism for the CIPE directed α-lithiation to a heteroatom**

The directing effect offered by the CIPE can also strongly influence the regioselectivity of the lithiation of a substrate. For example, lithiation of benzyl lactam 5 with n-BuLi at −78 °C resulted in exclusive formation of α-lithiated lactam 6, rather than the thermodynamically favoured enolate 7 (Scheme 1.2).

**Scheme 1.2. Regioselective α-lithiation of lactam 5**

Many different types of directing groups have been employed to enable the α-lithiation of amines. These directing groups need to be Lewis basic to allow coordination of the organolithium species involved and resistant to nucleophilic attack from the alkyllithium...
reagents used. Some of the directing groups that have been utilised are amides (used by Beak,\textsuperscript{8–15}), formamidines (reported by Meyers\textsuperscript{16–19}), nitrosoamines (reported by Seebach\textsuperscript{20,21}) and ureas (used by Metallinos)\textsuperscript{22,23} (Figure 1.2).

![Figure 1.2. Directing groups used to direct \(\alpha\)-lithiation of amines](image)

Carbamates can also be used to direct lithiation \(\alpha\) to an amine and the first \(\alpha\)-lithiation of a carbamate was reported by Seebach in 1978.\textsuperscript{24} Treatment of hindered aryl carbamate 8 with \(s\)-BuLi/TMEDA resulted in lithiation \(\alpha\) to nitrogen and subsequent trapping with \(n\)-C\textsubscript{8}H\textsubscript{17}I provided the respective alkylated carbamate in 87\% yield (Scheme 1.3). Both the lithiation and trapping reactions of 8 were conducted at 0 °C. In general, low temperatures (usually between 0 °C and –100 °C) are required for the lithiation and trapping steps to prevent side reactions and decomposition of the lithiated intermediate.

Scheme 1.3. Directed \(\alpha\)-lithiation of carbamate 8

Some years later, Beak reported the directed \(\alpha\)-lithiation of cyclic amines using a tert-butoxycarbonyl (Boc) carbamate to direct the lithiation in his seminal 1989 publication.\textsuperscript{2} This methodology has two key advantages. First, the Boc group is a common amine protecting group, so installation of the Boc group is well known and reagents are commerically available. Second, the Boc group is easy to remove with acids such as TFA or HCl, so further functionalisation of the amine can be carried out after \(\alpha\)-functionalisation. The use of the Boc group as a director for the \(\alpha\)-lithiation reactions of \(N\)-Boc heterocycles relevant to the work described in this thesis will be discussed in the next section of this overview.
1.2 Lithiation-Trapping Reactions of N-Boc Heterocycles

1.2.1 N-Boc pyrrolidine and N-Boc piperidine

The first α-lithiation-trapping reactions of N-Boc pyrrolidine 9 and N-Boc piperidine 10 were reported by Beak in 1989.\textsuperscript{2} Both heterocycles were treated with s-BuLi/TMEDA at –78 °C in Et\textsubscript{2}O for 3 h and then Me\textsubscript{3}SiCl was added to trap the lithiated intermediates. This afforded 2-silyl N-Boc pyrrolidine 11 and 2-silyl N-Boc piperidine 12 in 81% and 94% isolated yields respectively (Scheme 1.4).

Scheme 1.4. Racemic α-lithiation-trapping reactions of N-Boc pyrrolidine 9 and N-Boc piperidine 10

Later, the O’Brien group developed a ‘diamine-free’ lithiation for the α-lithiation of N-Boc heterocycles.\textsuperscript{25} Lithiation of N-Boc pyrrolidine 9 with s-BuLi/THF at –30 °C and subsequent trapping with Me\textsubscript{3}SiCl furnished 2-silyl N-Boc pyrrolidine 11 in 71% yield (Scheme 1.5). With this methodology, a variety of 2-substituted N-Boc pyrrolidines 11, 13-16 were synthesised in moderate to good yield ranging from 49-77%.

Scheme 1.5. ‘Diamine-free’ s-BuLi/THF lithiation-trapping of N-Boc pyrrolidine 9

When the s-BuLi/THF lithiation-trapping of N-Boc piperidine 10 was attempted, no trapped adducts were detected. It has been proven that alkyllithiums are less stable in THF than
Et₂O²⁶ and recent unpublished work in the O’Brien group had observed the s-BuLi mediated decomposition of THF at higher temperatures (> –30 °C).²⁷ As N-Boc piperidine 10 is significantly less reactive than N-Boc pyrrolidine 9, the decomposition of the THF solvent is likely the kinetically favoured reaction, meaning that no trapped adduct was observed.

The enantioselective s-BuLi/(−)-sparteine-mediated lithiation-trapping of N-Boc pyrrolidine 9 was communicated by Beak and Kerrick in 1991³ and reported in full in 1994.²⁸ Lithiation using s-BuLi and the chiral diamine (−)-sparteine, followed by trapping with Me₃SiCl gave (S)-11 in 87% yield and excellent 95:5 er (Scheme 1.6). The O’Brien group subsequently reported the synthesis of 2-silyl N-Boc pyrrolidine (R)-11 in 84% yield and 95:5 er using their chiral diamine, the (+)-sparteine surrogate 17, which behaves in an enantiocomplementary manner to (−)-sparteine (Scheme 1.6).²⁹ Throughout this thesis the degree of enantioselectivity exhibited in an asymmetric reaction will be quantified using enantiomeric ratios (er). This measure of enantioselectivity has been selected as it is mathematically more simple than enantiomeric excess (ee), making it easier for the reader to comprehend of the degree of enantioselectivity exhibited in a reaction.

**Scheme 1.6. Asymmetric lithiation-trapping of N-Boc pyrrolidine 9 with (−)-sparteine and (+)-17 chiral diamine ligands**

Altmann *et al.* has performed lithiations with both s-BuLi/(−)-sparteine and s-BuLi/(+)-17 to synthesise the natural products (+)- and (−)-hygroline 18.³⁰ The synthesis involved the asymmetric lithiation of N-Boc pyrrolidine 9 with either s-BuLi/(−)-sparteine or s-BuLi/(+)-17 and then subsequent trapping with chiral epoxides (R)- or (S)-19, followed by reduction with LiAlH₄ to give (+)- or (−)-hygroline 18 (Scheme 1.7).
The α-lithiation reactions of N-Boc pyrrolidine 9 with s-BuLi/(-)-sparteine or i-PrLi/(-)-sparteine have both been subjected to mechanistic investigation. In 1991, Beak conducted several lithiation-trapping reactions of N-Boc pyrrolidine 9 to determine whether the enantioselectivity observed with s-BuLi/(-)-sparteine arises from an enantioselective deprotonation or whether the enantioselectivity is afforded post-deprotonation. 3 Racemic 2-lithio N-Boc pyrrolidine rac-21 was generated by both s-BuLi deprotonation of N-Boc pyrrolidine 9 and tin-lithium exchange of 2-stannyl pyrrolidine 20. (-)-Sparteine was then added to the lithiated intermediate rac-21 followed by Me₃SiCl. The Me₃SiCl trapped adduct 11 from both reactions was obtained as a racemate (Scheme 1.8).

**Scheme 1.7. Synthesis of (+)- and (–)-hygroline via asymmetric lithiation trapping of N-Boc pyrrolidine 9**

**Scheme 1.8. Determination of the source of enantioselectivity of the s-BuLi/(-)-sparteine lithiation of N-Boc pyrrolidine 9**

Beak therefore concluded that the enantioselectivity afforded by (-)-sparteine must arise from an enantioselective deprotonation and does not occur post-deprotonation. O’Brien *et al.* have also shown that the enantioselectivity afforded with N-Boc piperidine 10 and s-...
BuLi/(+)-17 occurs by an enantioselective deprotonation using experiments similar to those used by Beak.\textsuperscript{31}

In 1995, Beak and Gallagher conducted a mechanistic investigation of the i-PrLi/(-)-sparteine lithiation of N-Boc pyrrolidine 9 using kinetic experiments.\textsuperscript{32} They noted that the lithiation had a zero-order dependence on the concentration of the i-PrLi/(-)-sparteine complex 22, the structure of which had been determined previously.\textsuperscript{33} This led them to propose that the rapid formation of a prelithiation complex occurs before the rate determining α-deprotonation, which accounted for the zero-order dependence of the alkyllithium (Scheme 1.9). Kinetic isotope experiments were also carried out and they confirmed that the second step of the α-lithiation where deprotonation occurs ($k_2$) and (S)-23 is formed was rate determining.

**Scheme 1.9. Proposed mechanism for the i-PrLi/(-)-sparteine α-lithiation of N-Boc pyrrolidine 9**

Three possible structures for the prelithiation complex were suggested: 24, 25 and 26 (Figure 1.3). Beak and Gallagher suggested that the prelithiation complex was unlikely to be 24 as the (-)-sparteine was far removed from N-Boc pyrrolidine 9 and would not likely be able to offer any enantiocontrol over α-lithiation from this distance.

**Figure 1.3. Proposed pre-lithiation complexes for the RLi/(-)-sparteine lithiation of N-Boc pyrrolidine 9**
Beak and Kerrick first reported the \( s\text{-BuLi}/(-)\text{-sparteine} \) lithiation-trapping of \( N\text{-Boc} \) piperidine \( 10 \) in 2002.\(^{34}\) Lithiation for 16 h and trapping with \( \text{Me}_3\text{SiCl} \) gave the desired 2-silyl \( N\text{-Boc} \) piperidine \( (S)\)-12 in a low ~8\% yield and moderate 87:13 er, with side-products 27 and 28 also isolated (Scheme 1.10). The slow rate of reaction between \( s\text{-BuLi}/(-)\text{-sparteine} \) and \( N\text{-Boc} \) piperidine \( 10 \) allows side reactions to occur. In particular, \( s\text{-BuLi} \) can perform a nucleophilic attack into the Boc carbonyl generating by-products 27 and 28.

**Scheme 1.10. Attempted \( s\text{-BuLi}/(-)\text{-sparteine} \) lithiation of \( N\text{-Boc} \) piperidine 10**

Coldham and O’Brien also attempted the asymmetric lithiation of \( N\text{-Boc} \) piperidine \( 10 \) using cyclohexyl diamine ligand \((R,R)\)-29 which had displayed high enantioselectivity for the lithiation of \( N\text{-Boc} \) pyrrolidine \( 9 \) (Scheme 1.11).\(^{35,36}\) Lithiation of \( N\text{-Boc} \) piperidine \( 10 \) with \( s\text{-BuLi}/(R,R)\)-29 and trapping with \( \text{Me}_3\text{SiCl} \) provided 2-silyl adduct \((S)\)-12 in only 13\% yield in 90:10 er. Comparison of this result with the 8\% yield of \((S)\)-12 obtained by Beak and Kerrick with \( s\text{-BuLi}/(-)\text{-sparteine} \) (see Scheme 1.10), shows that the \( s\text{-BuLi}/(R,R)\)-29 complex was more reactive and provided marginally higher enantioselectivity. However, the lithiation of \( N\text{-Boc} \) piperidine \( 10 \) with \( s\text{-BuLi}/(R,R)\)-29 still did not provide a synthetically useful method of preparing enantioenriched 2-substituted piperidines.

**Scheme 1.11. Asymmetric lithiation-trapping of \( N\text{-Boc} \) piperidine and \( N\text{-Boc} \) pyrrolidine 10 with \( s\text{-BuLi}/(R,R)\)-29**

Later, O’Brien reattempted the asymmetric lithiation of \( N\text{-Boc} \) piperidine \( 10 \) using \( s\text{-BuLi}/(+)\text{-sparteine surrogate} \) 17. This afforded 2-silyl piperidine \((R)\)-12 in good 73\% yield with moderate 86:14 er (Scheme 1.12).\(^{31}\) In contrast to the \( s\text{-BuLi}/(-)\text{-sparteine} \) lithiation of
N-Boc piperidine 10, the s-BuLi/(+)-sparteine surrogate lithiation gives a greatly improved yield which can be attributed to the more reactive s-BuLi/(+)-17 lithiating complex.

The O’Brien group have also presented a catalytic two-ligand enantioselective lithiation of N-Boc pyrrolidine 9, using the combination of a sub-stoichiometric amount of chiral ligand (−)-sparteine or (+)-17 and stoichiometric quantities of achiral diamine di-i-Pr bispidine 30. The presence of the achiral diamine allows the (−)-sparteine or (+)-17-complexed lithiated intermediate to exchange ligands with di-i-Pr bispidine 30, freeing the chiral ligand to carry out further lithiation cycles. Importantly, s-BuLi/di-i-Pr bispidine 30 has a slower rate of lithiation than s-BuLi/(−)-sparteine or s-BuLi/(+)-17, meaning that the chiral ligand lithiates the majority of the starting material, which gives the product in high er. Use of s-BuLi with 0.2 eq. of either (−)-sparteine or (+)-17 and 1.2 eq. of di-i-Pr bispidine 30 to lithiate N-Boc pyrrolidine 9 and trapping with Me_3SiCl gave 2-silyl pyrrolidines (S)- and (R)-11 in 76% and 66% yields respectively with er varying between 90:10 and 96:4 (Scheme 1.13).

The lithiation of N-Boc pyrrolidine 9 using the chiral ligands (−)-sparteine and (+)-17 has also been carried out in THF solvent. Earlier work by O’Brien indicated that the THF can act as ligand allowing racemic lithiation of N-Boc pyrrolidine 9 (see Scheme 1.5) and therefore it was uncertain whether enantioenrichment would be observed with the chiral
diamines. When the lithiation of \(N\)-Boc pyrrolidine 9 was conducted with \(s\text{-BuLi}/(-)\)-sparteine in THF, trapped products \(syn\)- and \(anti\)-31 were obtained as near-racemates (Scheme 1.14). When the same reaction was conducted using \(s\text{-BuLi}/(+)\)-17, the trapped adducts \(syn\) and \(anti\)-31 were obtained in 95:5 er.

**Scheme 1.14. \(s\text{-BuLi}/(-)\)-sparteine and \(s\text{-BuLi}/(+)\)-17 lithiation of \(N\)-Boc pyrrolidine 9 in THF solvent**

By using \(^{13}\text{C}\) and \(^{6}\text{Li}\) NMR spectroscopy, O’Brien noted that over 3.0 eq. of \((-)\)-sparteine were required for the \((-)\)-sparteine to displace the THF coordinated to the alkyllithium. This is likely the reason that \(s\text{-BuLi}/(-)\)-sparteine lithiation in THF provides only racemic product as the alkyllithium is preferentially coordinated to THF. On the other hand, addition of 1.0 eq. of \((+)\)-17 resulted in formation of a complex where the alkyllithium in coordinated to both \((+)\)-17 and a molecule of THF. This means that enantioselective lithiation will occur with 1.0 eq. of \((+)\)-17 and is why an asymmetric \(s\text{-BuLi}/(+)\)-17 lithiation can be carried out in THF.
1.2.2. 4-Substituted N-Boc piperidines

Several examples of the synthesis of 2,4-disubstituted N-Boc piperidines using α-lithiation-trapping chemistry have also been described.\textsuperscript{25,38–40} Beak and Lee reported the α-lithiation-trapping reactions of 4-phenyl, 4-\textit{t}-Bu and 4-ketal substituted N-Boc piperidines \textsuperscript{32, 33} and \textsuperscript{34,38} Lithiation of substituted piperidines \textsuperscript{32, 33} and \textsuperscript{34} with \textit{s}-BuLi/TMEDA followed by trapping with MeI or Me\textsubscript{2}SO\textsubscript{4} afforded methylated piperidines \textit{cis-35}, \textit{cis-36} and \textit{37} in good (71-83\%) yield (Scheme 1.15). It was noted that the products of the lithiation-trapping reactions of 4-phenyl and 4-\textit{t}-Bu piperidines \textsuperscript{32} and \textsuperscript{33} were both obtained as \textit{cis} diastereoisomers. This diastereoselectivity arises from the preference for equatorial α-lithiation which allows the CIPE to occur. In these 4-substituted piperidines, the equatorial α-proton will be \textit{cis} to the C4-substituent as this places the substituent in an energetically favoured equatorial position. Trapping then occurs with retention of the stereochemistry so only the \textit{cis} diastereomer was obtained.

\textbf{Scheme 1.15. Lithiation-trapping of 4-substituted N-Boc piperidines with rationale for the \textit{cis} selectivity observed}

Knochel \textit{et al.} have also prepared a range of different 2,4-disubstituted piperidines using a diastereoselective cross-coupling reaction between aryl iodides and substituted piperidinyl-zinc reagents, prepared by α-lithiation-transmetallation.\textsuperscript{39} The α-arylation of N-Boc pyrrolidines using α-lithiation-transmetalation and cross-coupling was reported earlier by Campos.\textsuperscript{41} Using this methodology, Knochel \textit{et al.} prepared a variety of 2-arylated piperidines using a selection of 4-substituted piperidines including 4-methyl, 4-phenyl and 4-OTIPS N-Boc piperidines \textsuperscript{38, 32} and \textsuperscript{39}. Zincation of these N-Boc piperidines with \textit{s}-BuLi/TMEDA then ZnCl\textsubscript{2} and subsequent Negishi coupling with RuPhos or SPhos with 4-
CF$_3$ substituted aryl iodide provided 2,4-disubstituted piperidines *cis*-40-42 in good to moderate yield (81-64%) and very good 97:3-95:5 drs (Scheme 1.16).

**Scheme 1.16. Diastereoselective cross-coupling of 4-substituted piperidines 38, 32 and 39**

Knochel suggested that the *cis* diastereoselectivity observed in the 2-aryl piperidines *cis*-40-42 was likely introduced during the lithiation of the piperidine substrates, as observed with Beak’s work (see Scheme 1.15). In the same communication, the synthesis of *trans*-2,6-disubstituted piperidine 44 by zincation and cross-coupling of 2-methyl N-Boc piperidine 43 was also attempted. However, none of the expected product *trans*-44 was obtained. Instead, 2,5-disubstituted piperidine *trans*-45 was isolated in 90% yield (Scheme 1.17). It was rationalised that β-hydride elimination of the organopalladium intermediate occurs. The PhPdL$_2$H complex that is formed, remains bound to the same side of the tetrahydropyridinyl ring and *syn* addition occurs which places the Pd at the less sterically hindered C-5 position. Reductive elimination would then afford the observed 2,5-disubstituted piperidine *trans*-45.

**Scheme 1.17. 1,2-Migration of Pd in the cross-coupling of 2-methyl N-Boc piperidine 43**
The asymmetric lithiation-trapping reactions of 4-phenyl and 4-ketal piperidines have been reported but both offered trapped products in only moderate yield and er.⁴⁻³ The lithiation of the 4-substituted piperidines was conducted with s-BuLi/(−)-sparteine and s-BuLi/(R,R)-2⁹, which Coldham and O’Brien had found provided the best enantioselectivity for the lithiation of N-Boc piperidine ¹⁰ (see Scheme 1.11). Lithiation of 4-phenyl N-Boc piperidine ³² and subsequent Me₃SiCl trapping provided only a 6% yield of the 2-silyl 4-phenyl piperidine *cis*-⁴⁶ in a moderate 78:22 er. The same lithiation-trapping of 4-ketal N-Boc piperidine ³⁴ provided none of the trapped silyl adduct ⁴⁷ (Scheme 1.18). When the reactions were repeated with the more reactive s-BuLi/(R,R)-²⁷ complex, 2-silyl piperidines ⁴⁶ and ⁴⁷ were obtained in improved 48% and 53% yields. The er of trapped products was variable, with 2-silyl 4-phenyl piperidine *cis*-⁴⁶ obtained in 87:13 er and 2-silyl 4-ketal piperidine ⁴⁷ obtained almost as a racemate (47:53 er).

Scheme 1.18. Asymmetric lithiation-trapping reactions of 4-phenyl and 4-ketal N-Boc piperidines ³² and ³⁴

Trapped adducts *cis*-⁴⁶ and ⁴⁷ were obtained in significantly higher yield than 2-silyl piperidine ¹², obtained by the lithiation-trapping of N-Boc piperidine ¹⁰ using the same conditions (13% yield, see Scheme 1.10). This suggested that these two 4-substituted piperidines have a higher reactivity than that of N-Boc piperidine ¹⁰. Competition experiments with 4-phenyl piperidine ³² and N-Boc piperidine ¹⁰ have also indicated that the lithiation of 4-phenyl piperidine ³² is more facile.⁴⁰

The α-lithiation-trapping of 4-chloro N-Boc piperidine ⁴⁸ was first reported by Beak in 1994 to synthesise bicyclic heterocycles.⁴² Lithiation of 4-chloro N-Boc piperidine ⁴⁸ with 2 eq. s-BuLi/TMEDA for 8 h and subsequent quenching of the reaction provided [3.1.0] azabicycle ⁴⁹ in 75% yield (Scheme 1.19). When an electrophile was added after the lithiation, a 2-substituted bicyclic pyrolidine was obtained. For example, the addition of Bu₃SnCl after lithiation afforded 2-stannyl bicycle ⁵⁰ in 70% yield. The mechanism for the bicycle formation likely involves intramolecular cyclisation of the lithiated intermediate ⁵¹,
which undergoes further lithiation to provide lithiated bicycle 52. If the lithiation is then quenched, bicyclic pyrrolidine 49 is generated, whereas if an electrophile such as Bu₃SnCl is added, a 2-trapped adduct such as 50 is formed. Similar syntheses of bicyclic heterocycles have been reported via lithiation of 4-O-nosyl and 4-O-tosyl N-Boc piperidines.\textsuperscript{34,43}

**Scheme 1.19. Bicycle formation via lithiation-trapping of 4-chloro N-Boc piperidine 48**

Rayner \textit{et al.} used the α-lithiation-trapping of 4-chloro N-Boc piperidine 48 to prepare enantiopure chiral sulfoxides which could then be converted into enantiopure Grignard reagents.\textsuperscript{44} The s-BuLi/(R,R)-29 lithiation of 4-chloro piperidine 48 and trapping with enantiopure sulfinate (S₅)-53 afforded (R,R,S₅)-54 in 51\% yield and 99:1 er and (S,S,S₅)-54 in 25\% yield and 87:13 er (Scheme 1.20). Sulfoxide/Mg exchange of (R,R,S₅)-54 formed Grignard (R,R)-55 which when trapped with ClCO₂Me provided ester (S,R)-56 in 89\% yield and 99:1 er.

**Scheme 1.20. Chiral Grignard preparation via synthesis of chiral sulfoxides**
1.2.3. \(N\)-Boc piperazines

There are many examples of racemic \(\alpha\)-lithiation-trapping reactions of \(N\)-Boc piperazines in the literature.\textsuperscript{25,45–50} The first of these was reported by Van den Hoogenband and Van Maarseveen in 2005, where \(N'\)-Bn and \(N'\)-Me \(N\)-Boc piperazines \textsuperscript{57} and \textsuperscript{58} were lithiated with \(s\)-BuLi/TMEDA and then trapped with Me\(_3\)SiCl and Bu\(_3\)SnCl.\textsuperscript{51} Trapping after lithiation with Bu\(_3\)SnCl provided both the \(N'\)-Bn and \(N'\)-Me stannanes \textsuperscript{61} and \textsuperscript{62} in good 71\% and 82\% yields respectively. The trapping of lithiated \(N'\)-Bn piperazine \textsuperscript{57} with Me\(_3\)SiCl also provided the desired 2-silyl piperidine \textsuperscript{59} in a good 68\% yield. However, when \(N'\)-Me piperazine \textsuperscript{58} was subjected to lithiation and trapping with Me\(_3\)SiCl, the desired 2-silyl piperazine \textsuperscript{60} was obtained in only 5\% yield (Scheme 1.21).

Scheme 1.21. Lithiation-trapping of \(N'\)-Bn piperazine \textsuperscript{57} and \(N'\)-Me piperazine \textsuperscript{58}

No explanation was offered as to why the 2-silyl piperazine \textsuperscript{60} was obtained in such low yield. However, in a recent paper, O’Brien \textit{et al.} repeated the \(s\)-BuLi/TMEDA lithiation and Me\(_3\)SiCl trapping of \(N'\)-Me piperazine \textsuperscript{58}.\textsuperscript{50} In their hands, none of the desired 2-silyl piperazine product \textsuperscript{60} was obtained. Instead, a mixture of fragmentation products \textsuperscript{63} and \textsuperscript{64} were obtained (Scheme 1.22).

Scheme 1.22. Repeated lithiation-trapping of \(N'\)-Me piperazine \textsuperscript{58} by O’Brien \textit{et al.}

O’Brien encountered this piperazine fragmentation in earlier work and proposed that the fragmentation occurs as the distal nitrogen reacts with the electrophile, generating an ammonium intermediate \textsuperscript{65} (Scheme 1.23).\textsuperscript{52} Subsequent \(\beta\)-elimination and cleavage of the weak N-Si bond during work-up would provide a vinylic carbamate as observed for the repeated lithiation-trapping of \(N'\)-Me piperazine \textsuperscript{63} in Scheme 1.22. A subsequent vinylic
lithiation and Me₃SiCl trapping of intermediate 63 would also account for the additional fragmentation product 64 observed.

**Scheme 1.23. Proposed mechanism of N'-Me piperazine 58 fragmentation**

This mechanism may also explain why the same fragmentation is not observed for the lithiation and Me₃SiCl trapping of N'-Bn piperazine 57. The greater steric bulk on the distal nitrogen afforded by the Bn group could perturb the attack of the distal nitrogen onto the bulky Me₃SiCl electrophile, meaning that fragmentation cannot occur. The high yield obtained for the Bu₃SnCl trapped N'-Me piperazine 59 in Scheme 1.21 may arise from the relative rates of Bu₃SnCl and Me₃SiCl trapping. Unpublished work by the O'Brien group has found that trapping with Bu₃SnCl is rapid whereas trapping reactions with chlorosilanes are known to be slow and work in this thesis has also confirmed this. Therefore, it is possible that with Bu₃SnCl the trapping process is faster than fragmentation so the desired 2-substituted piperazine is obtained. With the slow Me₃SiCl trapping, the fragmentation may be faster than trapping so only products of the fragmentation are obtained.

To date, there have only been two reports of the asymmetric lithiation-trapping reactions of an N-Boc piperazine. McDermott at AstraZeneca reported the lithiation of N'-t-Bu N-Boc piperazine 66 with s-BuLi/(-)-sparteine followed by trapping with CO₂ which afforded enantioenriched carboxylic acid (R)-67. The crude acid was subsequently coupled with benzyl piperazine which provided amide (R)-68 in 48% yield and 89:11 er (Scheme 1.24).

**Scheme 1.24. Asymmetric lithiation-trapping of N'-t-Bu N-Boc piperazine 66**

1. s-BuLi/(-)-sparteine, Et₂O, -78 °C, 5 h
2. CO₂

(R)-67

COOH

N

Boc

N

Boc

(CN)

68

48%, 89:11 er

Bn

(R)-68
More recently, O’Brien et al. have reported the asymmetric lithiation-trapping of piperazines with a wide range of different substituents on the distal nitrogen. They initially performed lithiation-trapping reactions of $N'$-Bn $N$-Boc piperazine 57 with $s$-BuLi/($-$)-sparteine and $s$-BuLi/($+$)-sparteine surrogate 17. However, for each of the lithiation-trapping reactions significant amounts of piperazine fragmentation occurred, as described in Scheme 1.22. As discussed earlier, they suggested that a bulkier substituent on the distal nitrogen would prevent this fragmentation by preventing the attack of the distal nitrogen onto the electrophile (see Scheme 1.23). Therefore, O’Brien et al. used a bulkier and enantiopure $N'$-$\alpha$-methyl benzyl piperazine (S)-69 which both prevented the fragmentation and introduced an additional stereocentre to the substrate. This additional stereocentre meant after the asymmetric lithiation-trapping the products were formed as diastereomers that can be more easily separated. The $\alpha$-methyl benzyl substituent can also be removed readily with $\alpha$-chloroethyl chloroformate allowing further functionalisation of the distal nitrogen after the lithiation-trapping. Lithiation of $N'$-$\alpha$-methyl benzyl piperazine (S)-69 with $s$-BuLi/$+$-17 and trapping with a range of electrophiles provided 2-substituted piperazines 70-75 in moderate to good 31%-94% yield and excellent to moderate dr (Scheme 1.25).

**Scheme 1.25. Lithiation-trapping of $N'$-$\alpha$-methyl benzyl piperazine (S)-69**

![Scheme 1.25. Lithiation-trapping of $N'$-$\alpha$-methyl benzyl piperazine (S)-69](image)
1.2.4. \(N\)-Boc morpholines

To date, the \(\alpha\)-lithiation of only one \(N\)-Boc morpholine has been reported in the literature.\(^5\) Bicyclic \(N\)-Boc morpholine 76 was subjected by Lautens to an enantioselective desymmetrisation using \(s\)-BuLi/(−)-sparteine, providing chiral trisubstituted azepane 78 (Scheme 1.26). At a reaction temperature of \(-78^\circ\text{C}\), azepane 78 was obtained in 46% yield and a moderate 73:27 er; at lower temperature (−105 °C), azepane 78 was obtained in improved yield and er (60%, 80:20 er). Lautens suggests that the mechanism of this reaction occurs via formation of a 2-lithio azepane intermediate 77 which then eliminates to form ring opened azepane 78.

**Scheme 1.26. Enantioselective desymmetrization of \(N\)-Boc morpholine 76**

![Scheme 1.26](image)

The only other \(\alpha\)-lithiation of a morpholine that has been reported is the lithiation of \(N\)-benzoyl morpholine 79 with LDA.\(^6\) After lithiation, the reaction was quenched with \(NH_2Cl_{(aq)}\) which provided ring opened alcohol 80 in 80% yield (Scheme 1.27). The mechanism for the ring opening is likely to be the same as that for the bicyclic morpholine in Scheme 1.26, where the \(\alpha\)-lithiation is followed by an elimination that forms ring-opened alcohol 80. Typically, strong alkylolithium bases such as \(s\)-BuLi are required to remove the \(\alpha\)-proton but in this case, the weaker LDA base is sufficient.

**Scheme 1.27. LDA/THF lithiation of \(N\)-benzoyl morpholine 79**

![Scheme 1.27](image)
1.2.5. Bicyclic N-Boc pyrrolidines

The α-lithiation-trapping reactions of bicyclic pyrrolidines has become more common, with many examples now available in the literature. One of the first α-lithiation-trapping reactions of a bicyclic N-Boc heterocycle was reported by Krow in 2002 in order to synthesise compounds to allow the study of conformational effects on collagen stability.\(^{61}\) \([2.1.1]-\)Aza bicycle 81 was subjected to lithiation with s-BuLi/TMEDA followed by trapping with CICO\(_2\)Me (Scheme 1.28). Lithiation of bicycle 81 can lead to the formation of two regioisomers, as it is possible to deprotonate either the methylene or bridgehead α-proton. When lithiation-trapping of 81 was conducted at \(-78{\,}^\circ\text{C}\), a 43:57 mixture of regioisomers 82 and 83 was obtained in an 81% combined yield. However, lithiation-trapping at 0 °C provided exclusive formation of regioisomer 82 in 70% yield.

**Scheme 1.28. Lithiation-trapping of bicyclic pyrrolidine 81**

Krow revisited the regioselectivity of the α-lithiation of bicyclic pyrrolidine 81 in a subsequent computational investigation of the regioselectivity.\(^{62}\) The computational modelling suggested that the energy barrier for rotamer interconversion is low at 0 °C, so rapid rotamer conversion occurs. This means exclusive deprotonation of the more acidic and kinetically preferred α-proton at the bridgehead occurs. On the other hand, at \(-78{\,}^\circ\text{C}\), the rotamer interconversion is slow thus the regioselectivity observed reflects the ratio of the rotamers. The α-lithiation of each rotamer occurs more readily than the interconversion of rotamers. Hence, a 43:57 mixture of regioisomers 82 and 83 is observed.

Researchers at AstraZeneca have also presented the α-lithiation-trapping of a similar but symmetrical bicyclic N-Boc pyrrolidine, in the development of a synthesis towards a potent glyT1 uptake inhibitor.\(^{63}\) The α-lithiation-trapping of bicyclic pyrrolidine 84 was conducted with s-BuLi/TMEDA followed by trapping with a range of electrophiles including CO\(_2\), DMF, MeI and Weinreb amide 89. The trapped adducts 85-88 were obtained in 53-90% yield (Scheme 1.29).
Using this α-lithiation methodology, 28 g of glyT1 uptake inhibitor 90 was synthesised in 28% overall yield from bicyclic N-Boc pyrrolidine 84 via a five-step synthesis (Scheme 1.30). s-BuLi/TMEDA lithiation of bicyclic pyrrolidine 84 and trapping with imine 91 provided intermediate (R,R)-92 in 50% yield and was conducted on a ~200 g scale. Subsequent hydrolysis of the sulfinamide 92 provided primary amine 93 in quantitative yield. Amide formation with 2,6-dimethylbenzoyl chloride and Boc group cleavage with HCl provided secondary amine 94, which was then subjected to Eschweiler-Clarke methylation to provide the desired inhibitor 90.

Scheme 1.30. Five-step synthesis of glyT1 uptake inhibitor 90
The α-lithiation-trapping of bicyclic 3,4-disubstituted N-Boc pyrrolidines was first reported by Johnson and Beak in 2002.\(^4\) The asymmetric \(s\)-BuLi/(−)‐sparteine lithiations of three 3,4-disubstituted \(N\)-Boc pyrrolidines \textit{syn-95}, \textit{syn-96} and \textit{syn-97} were investigated. For each of the disubstituted pyrrolidines, \(\text{Me}_3\text{SiCl}\) was used to trap the lithiated intermediate. These lithiation-trapping reactions afforded 2,3,4-trisubstituted pyrrolidines \textit{syn-anti-98-100} in moderate 46–50\% yield in good \textit{dr} and variable \textit{er} (Scheme 1.31).

**Scheme 1.31.** \(s\)-BuLi/(−)‐sparteine lithiation-trapping of 3,4-disubstituted \(N\)-Boc pyrrolidines \textit{syn-95}, \textit{syn-96} and \textit{syn-97}

For the \(s\)-BuLi/(−)‐sparteine-mediated asymmetric deprotonation of pyrrolidines \textit{syn-95-97}, the pro-\(S\) proton is removed as expected when using \(s\)-BuLi/(−)‐sparteine, as discussed in Section 1.2.1. Interestingly, the \textit{er} varies significantly between the three substrates, with the trapped adduct \textit{syn-anti-98} having the highest 87:13 \textit{er}. By the addition of only a double bond on the cyclohexane ring, this \textit{er} is eroded to 73:27. Diphenyl pyrrolidine \textit{syn-anti-100} was formed in only 58:42 \textit{er}. The \textit{ers} observed indicate that the substrate has significant control over the enantioselectivity of the lithiation reaction. High \textit{dr}s were observed for all
three of the 2,3,4-trisubstituted pyrrolidine products \textbf{98-100}; this is reasonable as it will be favourable to have the \( s \)-BuLi/(–)-sparteine lithiating complex attacking the proton \textit{anti} to the cyclohexyl ring to minimise steric interactions.

Beak and Johnson also carried out the \( s \)-BuLi/(–)-sparteine lithiation and Me\(_3\)SiCl trapping of C\(_2\)-symmetric \( N \)-Boc pyrrolidine \textit{anti-97}. This lithiation-trapping reaction afforded 2,3,4-trisubstituted \( N \)-Boc pyrrolidine \textit{anti-anti-100} in >95:5 dr and high 78\% yield (Scheme 1.32).

\textbf{Scheme 1.32.} \( s \)-BuLi/(–)-sparteine lithiation-trapping of 3,4-disubstituted \( N \)-Boc pyrrolidine \textit{anti-97}

For the lithiation-trapping of \textit{anti-97}, the \( \alpha \)-nitrogen selectivity is reversed and pro-\( R \) deprotonation, which is usually a higher energy process for \( s \)-BuLi/(–)-sparteine, occurred giving product \textit{anti-anti-100}. For a pro-\( S \) deprotonation of \textit{anti-97}, the phenyl substituent and \( s \)-BuLi/(–)-sparteine complex would need to be on the same face; these steric interactions may be significant enough to stop this occurring (Scheme 1.33.a). Alternatively, and more likely in our opinion, the selectivity observed in this reaction may arise from the trapping reaction with Me\(_3\)SiCl, where pro-\( S \) deprotonation of \textit{anti-97} does occur, giving the lithiated intermediate \textit{anti-syn-101} that would be expected with \( s \)-BuLi/(–)-sparteine. If Me\(_3\)SiCl trapping is slow or non-occurring, warming the reaction after adding the electrophile could lead to the lithiated intermediate becoming configurationally unstable before it is trapped. This would allow a dynamic kinetic resolution to be established where only the lithiated intermediate \textit{anti-anti-101} is trapped, giving trapped the product \textit{anti-anti-100} in the high dr observed (Scheme 1.33.b).
Scheme 1.33. Possible routes for the reversed selectivity observed for the \( s\)-BuLi/\((-\))-sparteine lithiation of \textit{anti}-\textbf{97}

The racemic and asymmetric \( \alpha \)-lithiation-trapping of another 3,4-disubstituted \( N \)-Boc pyrrolidine, was investigated by a process development group at Vertex Pharmaceuticals.\(^{64}\)

They proposed a series of disconnections for the blockbuster drug Telaprevir. By cleaving amide bonds, the target molecule can be simplified to five small molecular fragments (Scheme 1.34).

**Scheme 1.34. Proposed RSA for Telaprevir**

They noted that the 2,3,4-trisubstituted pyrrolidine fragment \( \textbf{102} \) could be synthesised using \( \alpha \)-lithiation chemistry from bicyclic pyrrolidine \( \textbf{103} \). First, lithiation of bicyclic pyrrolidine \( \textbf{103} \) was carried out asymmetrically with both \( s\)-BuLi/\((-\))-sparteine and \( s\)-BuLi/(\(+\))-sparteine surrogate \( \textbf{17} \), followed by trapping with CO\(_2\). Use of \( s\)-BuLi/\((-\))-sparteine gave 2,3,4-trisubstituted pyrrolidine \( \textbf{104} \) in \( >95\% \) conversion with 96:4 \( \text{dr} \) and 90:10 \( \text{er} \); \( s\)-BuLi/(\(+\))-
sparteine surrogate provided \textit{ent-104} in 44\% isolated yield with 92:8 dr and 94:6 er (Scheme 1.35).

**Scheme 1.35. Asymmetric lithiation-trapping of 3,4 disubstituted N-Boc pyrrolidine 103**

The group noted that the use of \textit{s-BuLi/\(+\)-sparteine surrogate 17} did provide promising results but decided to opt for a diastereoselective racemic lithiation followed by resolution. A racemic synthesis was decided upon due to the uncertainty of the availability of \textit{(+)-sparteine surrogate 17} which is synthesised using a plant-derived starting material \textit{(-)-cytisine}. \textit{(-)-Cytisine} has an uncertain supply which was deemed too high a risk for the production of the \textit{(+) -sparteine surrogate} in industrial quantities.

The racemic lithiation-trapping of bicyclic pyrrolidine \textit{103} with \textit{s-BuLi/di-n-Pr bispidine 105} and \textit{CO}_2 offered a 95:5 diastereomeric mixture of carboxylic acids \textit{anti-106} and \textit{syn-106} which were isolated in 86\% yield (Scheme 1.36). Bispidine \textit{105} was employed as the ligand as optimisation studies showed that this sterically bulkier ligand offered better diastereoselectivity and formed fewer side-products in the trapping reaction than less bulky ligands such as TMEDA. The lithiation forms product \textit{anti-106} preferentially as the less sterically hindered proton \textit{anti} to the pentane ring on the 3- and 4-positions of the pyrrolidine ring is presumably easier to lithiate by the bulky \textit{s-BuLi/105} complex.

**Scheme 1.36. \textit{s-BuLi/bispidine 105} lithiation-trapping of \textit{N-Boc pyrrolidine 103**
Subsequent resolution of the mixture of *anti*- and *syn*-106 using a chiral amine furnished the desired *anti*-106 salt in 99:1 er and 100:0 dr in 31% overall yield. After Boc cleavage and conversion of the carboxylate to a *tert*-butyl ester, key Telaprevir fragment 102 was formed in 27% overall yield from pyrrolidine 103 in >99.5:0.5 er and dr. This process has been used to manufacture 200 kg of this key intermediate.

The lithiation-trapping of a similar bicyclic *N*-Boc pyrrolidine 107 with a fused cyclopropane ring has also been reported. Lithiation of bicyclic pyrrolidine 107 was attempted using *s*-BuLi and diamine ligands TMEDA, di-*n*-Pr bispidine 105 and ({\texten-})-sparteine (Scheme 1.37). Use of TMEDA gave a crude product which contained a 77:2:21 mixture of *syn*-108, *anti*-108 and the 2,5-disubstituted adduct 109; the major product *syn*-108 was isolated in 69% yield. The use of diamine *di-n*-Pr bispidine 105 gave only pure *syn*-108 which was isolated in 74% yield. The *s*-BuLi/({\texten-})-sparteine lithiation of *N*-Boc pyrrolidine 107 followed by trapping with CO$_2$ gave carboxylic acid *syn*-110 in 32% yield and 87:13 er.

**Scheme 1.37. Lithiation-trapping reactions of bicyclic pyrrolidine 107**
The *syn* diastereoselectivity of the lithiation was unexpected as the *s*-BuLi/diamine must have attacked the α-proton on the same face on which the cyclopropyl ring is located. However, the conformational differences due to the cyclopropane substituent presumably accounts for this. Computational modelling was used to model the lithiated intermediate of *N*-Boc pyrrolidine 107 with the lithium and *di-n*-Pr bispidine 105. The energies calculated indicated that the *syn* complex was 3.90 kcal mol\(^{-1}\) lower in energy than the respective *anti* complex. However, only the lithiated intermediates have been modelled and the kinetic energy barriers for *syn* and *anti* lithiation have not been considered. Therefore, these calculations will only give an indication of the diastereoselectivity of lithiation if the transition state is product-like or if the lithiation is under thermodynamic control, which is not likely to be the case at \(-78 \, ^\circ\text{C}\).\(^{66}\) For a more rigorous computational study, modelling of the deprotonation by optimisation of ground states and transitions states for the α-deprotonation reaction needs to considered.

The examples presented in this overview of α-lithiation chemistry show the diversity of *N*-Boc heterocycles that can be subjected to α-functionalisation using Beak’s α-lithiation-trapping protocol. This overview has also shown that desired products can be obtained enantioselectively or diastereoselectively by simply changing the diamine employed in the lithiation. Many of the *N*-Boc heterocycles included in this review are included in the reactivity study detailed in Chapter 2 of this thesis. In many of the examples presented, the lithiating conditions are not optimised, and therefore long > 3 h reaction times have been used. Previous unpublished work in our group has shown that many of these substrates require < 1 h for complete lithiation rather than the several hours used. Knowledge of substrate reactivity would be particularly beneficial for large-scale reactions, where the maintenance of low temperatures for extended periods of time is not cost-effective.
1.3 *In situ* IR Spectroscopic Studies of Lithiation-Trapping Reactions

This section explores previous work where *in situ* IR spectroscopy has been used to monitor lithiation and trapping reactions. This has not only allowed determination of the end-point of the lithiation and trapping reactions but has been used to elucidate reaction mechanism and identify reaction intermediates.

1.3.1. *In situ* IR spectroscopic studies of lithiation reactions

One of the earliest examples of using *in situ* IR spectroscopy to monitor lithiation α to a heteroatom was reported by Beak and Smith in 1983. Amide 111 and s-BuLi were mixed in IR stopped flow apparatus and upon mixing, two IR absorptions were detected: the starting material amide 111 (ν_{C=O} = 1650 cm\(^{-1}\)) and the prelithiation complex 112 (ν_{C=O} = 1625 cm\(^{-1}\)) which forms reversibly at the start of the reaction. After mixing, these two absorptions disappeared and a new band appeared due to the formation of lithiated intermediate 113 (ν_{C=O} = 1588 cm\(^{-1}\)) (Scheme 1.38).

**Scheme 1.38. In situ IR stopped flow monitoring of the s-BuLi lithiation of amide 111 (ν_{C=O} measured in cyclohexane solvent)**

Subsequently in 1984, Smith monitored the lithiation of ketones, including phenyl ketone 114, with the same IR stopped flow apparatus. These lithiations were carried out using s-BuLi or n-BuLi in non-coordinating hydrocarbon solvents, where most of the alkyllithium will exist as aggregates (tetramer for s-BuLi and hexamer for n-BuLi). Immediately after mixing phenyl ketone 114 and s-BuLi in cyclohexane solvent, a new band was observed due to the reversible formation of prelithiation complex 115, which reacts irreversibly to form enolate 116 (Scheme 1.39). Kinetic analysis indicated that in these hydrocarbon solvent conditions, both the aggregated and monomeric alkyllithium species are involved in the lithiation reaction and the relative importance of each depended on the ketone substrate used in the reaction.
Scheme 1.39. *In situ* IR stopped flow monitoring of the s-BuLi lithiation of ketone 114

In 1997, Collum *et al.* used *in situ* IR spectroscopy (ReactIR™) to investigate the LDA-mediated deprotonation of ester 117 to elucidate how the coordination of LDA changes during the enolisation reaction.\(^68\) Previous work had shown that LDA exists as a dimeric species 118 over a range of LDA and THF concentrations.\(^69,70\) Upon addition of ester 117 to a solution of LDA/THF in toluene, the ester 117 (\(v_{\text{C=O}} = 1727\ \text{cm}^{-1}\)) absorbance disappeared and an absorbance corresponding to the enolate 119 (\(v_{\text{C=O}} = 1646-1664\ \text{cm}^{-1}\)) formed over the period of the reaction. No prelithiation complex was observed by the ReactIR™ apparatus during the course of the LDA/THF-mediated lithiation. However, when LDA/Et₂O lithiating conditions were used, an absorption due to prelithiation complex 120 (\(v_{\text{C=O}} = 1703\ \text{cm}^{-1}\)) was observed (Scheme 1.40).\(^68\) Further kinetic analysis indicated that disolvated LDA monomers (\(i\text{-Pr}_2\text{NLi(THF)}_2\cdot 117\)) were the reactive lithiating species for the LDA/THF-mediated lithiation of esters such as 117.\(^71\)

Scheme 1.40. ReactIR™ monitored LDA/THF enolisation of ester 117

The first ReactIR™ monitored \(\alpha\)-lithiation reaction of an N-Boc substrate was reported by Beak in 2001.\(^72\) The \(n\text{-BuLi/}(\text{—})\text{-sparteine-mediated lithiation of N-Boc allylamine (E)}\)-121
in toluene at −73 °C was monitored using ReactIR™ equipment to investigate the kinetics and mechanism of the reaction. Upon addition of n-BuLi to a premixed solution of (E)-121 and (−)-sparteine in toluene, an absorbance assigned to (E)-121 ($\nu_{\text{C=O}} = 1695 \text{ cm}^{-1}$) rapidly decreased as the starting material (E)-121 was consumed. Meanwhile, an absorption for the lithiated intermediate 124 ($\nu_{\text{C=O}} = 1640 \text{ cm}^{-1}$) grew in at a slower rate. A third absorbance peak was also observed during the reaction at 1675 cm$^{-1}$, which increased in absorbance on the addition of n-BuLi and decreased in intensity for the duration of the reaction and this was assigned to the $\nu_{\text{C=O}}$ of the prelithiation complex 123 (Scheme 1.41). The presence of a prelithiation complex for the alkyllithium/diamine lithiation of N-Boc pyrrolidine 9 was previously identified by mechanistic work carried out by Beak and Gallagher (see Scheme 1.9).\textsuperscript{32}

\textbf{Scheme 1.41. ReactIR™ monitored n-BuLi/(−)-sparteine lithiation of allylamine (E)-121 ($\nu_{\text{C=O}}$ measured in toluene solvent)}

![Scheme 1.41](image)

More recently, the O’Brien group has monitored the asymmetric lithiation of N-Boc piperidine 10 using s-BuLi/(−)-sparteine and s-BuLi/(+)-sparteine surrogate 17 by ReactIR™.\textsuperscript{31} N-Boc piperidine 10 and (−)-sparteine were combined in MTBE at −70 °C and a peak at 1696 cm$^{-1}$ was observed and assigned to N-Boc piperidine 10. Upon addition of s-BuLi, two more peaks were observed at 1675 cm$^{-1}$ and 1644 cm$^{-1}$ and assigned to prelithiation complex 125 and lithiated intermediate 126 respectively. After a 6 h lithiation, a ~45:45:10 mixture of starting reagent 10, prelithiation complex 125 and lithiated intermediate 126 was obtained (Scheme 1.42). This mirrored the ~8% yield of trapped product (S)-12 previously reported by Beak \textit{et al.} (see Scheme 1.10).\textsuperscript{34} On the other hand, the ReactIR™ monitored s-BuLi/(+) -sparteine surrogate 17 lithiation of N-Boc piperidine 10 provided a much faster lithiation (< 6 h) which was consistent with the high yields of trapped adducts obtained (see Scheme 1.12).
Coldham and O’Brien have also used ReactIR™ monitoring to find optimal reaction conditions for the lithiations of 2-substituted N-Boc heterocycles such as 2-phenyl pyrrolidine 127 and 2-phenyl piperidine 129. For 2-phenyl pyrrolidine 127, the lithiation was initially attempted with n-BuLi/THF at –78 °C. ReactIR™ analysis showed that the initial lithiation was fast with the pyrrolidine 127 (νC=O = 1696 cm⁻¹) absorbance decreasing concurrently with a new absorbance arising due to the formation of quaternary lithiated intermediate 128 (νC=O = 1644 cm⁻¹). However, after two minutes the reaction stalled at ~40% lithiation. No further lithiation takes place due to the extremely slow interconversion of rotamers 127a and 127b at –78 °C and the fact that n-BuLi/THF is not reactive enough to lithiate rotamer 127a. When the lithiation was repeated at 0 °C, interconversion of the rotamers 127a and 127b did occur and complete lithiation was achieved in 2 minutes (Scheme 1.43).

Similarly, the n-BuLi/THF lithiation of 2-phenyl N-Boc piperidine 129 was also monitored at –78 °C. In this case, complete formation of lithiated intermediate 130 was achieved within 2 minutes (Scheme 1.44). Evidently, the rotamer interconversion for 2-phenyl piperidine 129
was much faster at $-78 \, ^\circ C$ than that of 2-phenyl pyrrolidine 127. VT-NMR spectroscopic studies confirmed this finding, indicating a substantial difference in the energy barriers for rotamer interconversion of 2-phenyl pyrrolidine 127 and piperidine 129 ($\sim 64.5$ and $\sim 50.0$ kJ mol$^{-1}$ respectively).

**Scheme 1.44. ReactIR$^\text{TM}$ monitored \textit{n-BuLi}/THF lithiation of 2-phenyl N-Boc piperidine 129 ($\nu_{C=O}$ measured in THF solvent)**

Coldham has also used ReactIR$^\text{TM}$ to find optimal reaction conditions for the lithiation of N-Boc tetrahydroisoquinoline 131.$^74$ A range of solvents was investigated including Et$_2$O, THF and toluene and two different alkylithiums were trialled (\textit{n-BuLi} and \textit{s-BuLi}). The reactions were also attempted with or without TMEDA. It was found that the lithiation temperature was key. At $-78 \, ^\circ C$, incomplete lithiation was observed due to the slow interconversion of rotamers. However, at $-50 \, ^\circ C$, rotamer interconversion was fast enough for complete lithiation of 131 to occur. Coldham found that the optimal lithiating conditions required \textit{n-BuLi}/THF at $-50 \, ^\circ C$ for $< 5$ min. The choice of alkylithium is also important as the use of \textit{n-BuLi} ensured the regioselectivity $\alpha$ to nitrogen and the phenyl ring. Using these optimal conditions and trapping with Me$_3$SiCl, the desired 2-substituted tetrahydroisoquinoline 132 was obtained in 74% yield (Scheme 1.45).

**Scheme 1.45. Lithiation-trapping of tetrahydroisoquinoline 131 using optimised conditions ($\nu_{C=O}$ measured in THF solvent)**

More recently, Coldham has reported the lithiation-trapping of 2-phenyl azepane 133 and used ReactIR$^\text{TM}$ monitoring to find optimal conditions for the $\alpha$-lithiation reaction.$^75$ As observed with other 2-phenyl N-Boc heterocycles, the rotamer interconversion resulted in incomplete lithiation at low temperature ($-78 \, ^\circ C$) (see Schemes 1.43 and 1.45). When the
lithiation was conducted at −5 °C, complete lithiation was observed within 3 min. These optimised conditions allowed the efficient synthesis of 2,2-dilsutituted azepanes, such as 134-136 in good yield (Scheme 1.46).

**Scheme 1.46. Lithiation-trapping of 2-phenyl N-Boc azepane 133**

The examples presented show that ReactIR™ is a powerful tool that can provide mechanistic information and can allow determination of optimised reaction conditions for lithiation reactions. Additionally, ReactIR™ can help to diagnose problematic lithiations where little or no lithiation is observed, for example where slow rotamer conversion prohibits lithiation. ReactIR™ is a particularly valuable method for monitoring organolithium reactions as the *in situ* nature of the technique means that the water sensitivity of the organolithium reagents and the low temperatures (−78 °C) that are typically required do not pose a problem. For these reasons, the ReactIR™ monitoring of α-lithiation reactions of substrates has now become widespread. Some other substrates whose α-lithiations reactions have been monitored by ReactIR™ include N-Boc piperazines 137,50,52 N-Boc dimethylamine 138,76 ester 13977 and urea 14078 (Figure 1.4).

**Figure 1.4. Substrates whose α-lithiation reactions were monitored with ReactIR™**
1.3.2. *In situ* ReactIR™ spectroscopic studies of the trapping reactions of lithiated intermediates

Currently, there have only been a handful of examples where the trapping reaction of a lithiated intermediate has been monitored using *in situ* ReactIR™. The first of these was reported by Yamamoto in 2008, where ReactIR™ was used to elucidate the mechanism of the oxidative decarboxylation of bicyclic carboxylates.\(^7\) Phenyl ester 141 (\(\nu_{C=O} = 1763\) cm\(^{-1}\)) was treated with LDA at \(-78^\circ\)C which rapidly formed the lithium enolate 142 (\(\nu_{C=O} = 1702\) cm\(^{-1}\)). Upon the addition of PhNO, the rapid trapping (< 1 min) of enolate 142 was observed and a new absorption corresponding to the spirocyclic intermediate 144 (\(\nu_{C=O} = 1763\) cm\(^{-1}\)) was detected (which occurs via 143). When the reaction was warmed to \(-20^\circ\)C, absorbance for intermediate 144 decayed as the fragmentation of 144 occurred. Two additional absorptions appeared and increased in intensity as this fragmentation occurred. These two new absorbances were assigned to the phenyl imine isomers 145 (\(\nu_{C=N} = 1695, 1679\) cm\(^{-1}\)) that are formed during the fragmentation (Scheme 1.47).

**Scheme 1.47. ReactIR™ monitored lithiation-trapping of phenyl ester 141 and *in situ* rearrangement to form imine 145 (\(\nu_{C=O}\) measured in THF solvent)**

A combined *in situ* IR and online NMR spectroscopic study of the lithiation and trapping reaction of benzimidazole 146 has been reported by a process development group at Pfizer.\(^8\) The reaction involved the LDA/THF-mediated lithiation of benzimidazole 146 followed by nucleophilic addition of the generated organolithium into pyridinium triflate salt 148. The product, dihydropyridone 150, is of interest as it is a precursor to an active pharmaceutical ingredient (API) 151, reported previously by Pfizer.\(^9\) Unfortunately, the desired product
dihydropyridone 150 was only isolated in 50-60% yield with 30-40% of starting material 146 recovered (Scheme 1.48). Therefore, it was decided to monitor the reaction progress using ReactIR™ and NMR spectroscopy to attempt to find the cause of the disappointing yields.

Scheme 1.48. ReactIR™ and NMR monitored LDA/THF lithiation of benzimidazole 146 and nucleophilic addition into pyridinium triflate 148

The ReactIR™ monitoring of the lithiation of benzimidazole 146 indicated that complete lithiation had occurred. This lithiation was performed at a range of temperatures between −40 to −10 °C and complete conversion occurred at each temperature. This indicated that lithiation of 146 was not the reason for the poor yield of 150. Next, the stability of lithiated intermediate 147 was investigated. Lithiated intermediate 147 was incubated at temperatures between −40 and −10 °C for 5.5 h and only small amounts of degradation were observed, indicating that intermediate 147 was stable at these temperatures. Finally, the nucleophilic addition of 147 into pyridinium triflate 148 was monitored by ReactIR™ and online NMR spectroscopy. After addition of triflate 148, an absorption for the desired enol ether product 149 appeared along with the reappearance of starting material 146. This indicated that triflate 148 could act as a proton source allowing the quenching of intermediate 147, thus giving a mixture of the desired product 150 and starting material 146. Further kinetic studies indicated similar reaction rates for formation of trapped product 149 and quenching of
intermediate 147. It was concluded that these similar rates of reaction would make it difficult for higher yields of the desired product 150 to be achieved.

The O’Brien group used in situ IR spectroscopy to monitor a one-pot lithiation, transmetallation and Negishi coupling of N-Boc pyrrolidine 9, allowing the generation of α-arylated products such as (R)-127. To synthesise α-arylated pyrrolidine (R)-127, N-Boc pyrrolidine 9 was lithiated with s-BuLi/(−)-sparteine, underwent transmetallation with ZnCl₂ and then was subjected to Negishi coupling with bromobenzene. This afforded α-arylated product (R)-127 in a good 82% yield with excellent 96:4 er (Scheme 1.49).

Scheme 1.49. ReactIR™ monitored s-BuLi/(−)-sparteine lithiation, transmetallation and Negishi coupling of N-Boc pyrrolidine 9 (νC=O measured in MTBE solvent)

The ReactIR™ monitoring indicated that the s-BuLi/(−)-sparteine lithiation of N-Boc pyrrolidine 9 required 1 h for complete lithiation at −78 °C. During the lithiation, absorptions were observed for N-Boc pyrrolidine 9 (νC=O = 1697 cm⁻¹), the prelithiation, complex (νC=O = 1675 cm⁻¹) and lithiated intermediate (S)-23 (νC=O = 1644 cm⁻¹). After lithiation was complete, the addition of ZnCl₂ led to little change in the IR spectra but when the reaction was warmed to −20 °C a new peak (νC=O = 1653 cm⁻¹) was observed and assigned to an organozinc species (RZnCl, R₂Zn or R₃ZnLi). When the Negishi coupling reagents were added, another new signal was observed and assigned to arylated pyrrolidine (R)-127 (νC=O = 1702 cm⁻¹).

Aggarwal et al. have used ReactIR™ to monitor the enantioretentive lithiation-trapping reactions of enantioenriched benzoate (R)-152. Lithiation of benzoate (R)-152 with s-BuLi/TMEDA formed configurationally stable lithiated intermediate (R)-153. When intermediate (R)-153 was trapped with ClCO₂Me, trapped adduct (R)-154 was obtained with good stereoretention (96:4 er). However, when the lithiation-trapping was repeated with Me₃SiCl, stereoretention was poor with (R)-155 obtained in only 60:40 er (Scheme 1.50).
It was suggested the poor stereoretention observed for Me₃SiCl-trapped adduct (R)-155 may result from a slow trapping reaction which allowed time for the erosion of stereochemistry of lithiated intermediate (R)-153 to occur via configurational instability. To validate this hypothesis, the lithiation of (R)-152 and trapping reactions with Me₃SiCl and ClCO₂Me were monitored by ReactIR™. The ReactIR™ indicated that s-BuLi/TMEDA lithiation of (R)-152 (ν<sub>C=O</sub> = 1680 cm<sup>-1</sup>) was rapid with complete formation of lithiated intermediate (R)-153 (ν<sub>C=O</sub> = 1585 cm<sup>-1</sup>) requiring only 5 min. Upon addition of ClCO₂Me to lithiated intermediate (R)-153, a fast trapping reaction was observed and complete trapping occurred within 5 min. However, when the reaction was repeated and Me₃SiCl was added to intermediate (R)-153, a slow trapping reaction was observed and after 1 h, only 50% of (R)-153 had been trapped. This evidence suggests that the slow rate of trapping with Me₃SiCl may indeed be responsible for the poor stereoretention observed for (R)-155.

Fandrick et al. have also used ReactIR™ to monitor the enantioretentive α-lithiation and boronate trapping of carbamate 156. The subsequent rearrangement of boronate 159 was also observed by ReactIR™. 84 When LDA was added to carbamate 156 (ν<sub>C=O</sub> = 1700 cm<sup>-1</sup>) at −78 °C, a new peak appeared due to the formation of the LDA-carbamate prelithiation complex 157 (ν<sub>C=O</sub> = 1667 cm<sup>-1</sup>). No lithiated intermediate 158 was observed and this was desired as the lithiated intermediate 158 was known to be configurationally unstable and would result in poor stereoretention. It was planned that the boronate electrophile could be added to the prelithiation complex 157 and then on warming up lithiation and trapping would occur in rapid succession, not allowing time for the erosion of lithiated intermediate 158 to occur. When the boronic ester was added, no change was observed by ReactIR™. The reaction was then warmed to −40 °C, where rapid formation of boronate complex 159 (ν<sub>C=O</sub> = 1650 cm<sup>-1</sup>)
occurred and no signal for the lithiated intermediate was observed. After further warming to
–25 °C, the boronate complex 159 peak decreased and rearrangement product 160 was
observed by HPLC in 99:1 er and 80% conversion (Scheme 1.51).

**Scheme 1.51. ReactIR™ monitored cryogenic lithiation and boronate rearrangement of carbamate 156 (νC=O measured in MTBE solvent)**

Using ReactIR™ to monitor the trapping reactions of α-lithiated intermediates does not only provide information on the time required for trapping to occur. The examples presented, show that mechanistic features of the trapping reactions and subsequent rearrangements can also be probed. In addition, the monitoring of the trapping can diagnose unexpected results such as poor enantioselectivity or quenching of the lithiated intermediate and provide evidence to suggest how they occur.
1.4 Computational Studies of the α-Lithiation Reactions of N-Boc Heterocycles

The asymmetric α-lithiation reaction of N-Boc pyrrolidine 9 has been subjected to several computational investigations to investigate the source of the enantioselectivity. Wiberg and Bailey investigated the enantioselectivity of the i-PrLi/(-)-sparteine α-deprotonation of N-Boc pyrrolidine 9 with DFT modelling.\textsuperscript{85,86} Experimental work by Beak and Kerrick found that the lithiation of N-Boc pyrrolidine 9 with i-PrLi/(-)-sparteine provided high levels of enantioselectivity by favourable deprotonation of the pro-S α-proton (96:4 er).\textsuperscript{28} Prelithiation complexes and transition states were optimised for both the pro-R and pro-S i-PrLi/(-)-sparteine α-deprotonation of N-Boc pyrrolidine 9 using the B3P86 DFT functional within a 6-31G(d) basis set. The difference in enthalpy and free energy between the lower energy pro-S and higher energy pro-R transition states were 4.5 kcal mol\textsuperscript{-1} (ΔΔH\textsuperscript{†}) and 3.2 kcal mol\textsuperscript{-1} (ΔΔG\textsuperscript{†}) respectively. The significant energy differences between the transition states indicated that pro-S deprotonation is significantly favoured, which was consistent with the high er obtained by experiment (Scheme 1.52).\textsuperscript{3}

Scheme 1.52. pro-S and pro-R pathways for the s-BuLi/(-)-sparteine lithiation of N-Boc pyrrolidine 9

\[ \Delta \Delta \Delta E^\ddagger (\text{pro-R} - \text{pro-S}) = 4.5 \text{ kcal mol}\textsuperscript{-1} \]
\[ \Delta \Delta \Delta G^\ddagger = 3.2 \text{ kcal mol}\textsuperscript{-1} \]

Wiberg and Bailey concluded that steric effects were responsible for the significant energy differences between the pro-R and pro-S α-deprotonation pathways. This conclusion was
reached by examination of the distances between atoms of the \( i\)-PrLi/(–)-sparteine and \( N\)-Boc pyrrolidine 9 moieties in the prelithiation complexes and transition states for the formation of both enantiomers. In the prelithiation complexes and transition states for pro-\( R \) \( \alpha \)-deprotonation, the distances between these moieties were smaller than those for pro-\( S \), resulting in a higher energy system for pro-\( R \) \( \alpha \)-deprotonation.

Computational modelling has also been used to model the enantioselectivity of the \( \alpha \)-lithiation of \( N\)-Boc pyrrolidine 9 with other chiral diamines. For example, the \( \alpha \)-lithiation of \( N\)-Boc pyrrolidine 9 using chiral diamine (\( S,S \))-161, which offers no enantioselectivity has also been modelled computationally.\(^\text{86,87}\) When \( N\)-Boc pyrrolidine 9 was subjected to lithiation with \( s\)-BuLi/(\( S,S \))-161 and trapping with Me\(_3\)SiCl, racemic 2-silyl \( N\)-Boc pyrrolidine \( \text{rac-11} \) was formed in 90% conversion (by GC) (Scheme 1.53).\(^\text{88}\)

**Scheme 1.53. Lithiation-trapping of pyrrolidine 9 using chiral diamine (\( S,S \))-161**

Computational modelling was conducted to investigate whether the modelling could reproduce the lack of enantioselectivity that was observed experimentally. Prelithiation complexes and transition states for the \( i\)-PrLi/(\( S,S \))-161-mediated pro-\( S \) and pro-\( R \) deprotonations of \( N\)-Boc pyrrolidine 9 were modelled and energies were calculated for each. The difference in enthalpy and free-energy between pro-\( S \) and pro-\( R \) transition states was also less significant (\( \Delta \Delta H^\ddagger = 1.1 \text{ kcal mol}^{-1} \) and \( \Delta \Delta G^\ddagger = 1.2 \text{ kcal mol}^{-1} \)) compared to the ~3 kcal mol\(^{-1} \) difference with (–)-sparteine (see Scheme 1.52). These energy differences indicated a much smaller preference for pro-\( S \) lithiation, which was reflected in the experimental result where \( \text{rac-11} \) was obtained.

Kozlowski \textit{et al.} used a combined experimental and computational approach to investigate the selectivity of the most simple chiral portion of (–)-sparteine, fragment (–)-162. Diamine ligand (–)-162 was synthesised and employed in the \( s\)-BuLi/(–)-162 lithiation of \( N\)-Boc pyrrolidine 9. After trapping with Me\(_3\)SiCl, 2-silyl \( N\)-Boc pyrrolidine (\( R \))-11 was formed in 45% yield and 67:33 er (Scheme 1.54). Surprisingly, the removal of the ‘A’ ring from (–)-sparteine reversed the enantioselectivity of the deprotonation forming (\( R \))-11. This result
indicated that the ‘A’ ring is essential for enantioselectivity whereas the ‘D’ ring has little effect, as discovered by the O’Brien group with (+)-sparteine surrogate (+)-17.

**Scheme 1.54.** $s$-BuLi/($-$)-162 lithiation and Me$_3$SiCl trapping of N-Boc pyrrolidine 9

When the $i$-PrLi/($-$)-162 lithiation of N-Boc pyrrolidine 9 was modelled using DFT, the modelling was able to account for the lower selectivity observed with diamine ($-$)-162. However, the modelling was not able to rationalise the reversal in the enantioselectivity that was observed experimentally.

Another combined computational and experimental study was carried out by O’Brien, Wiberg and Bailey to probe the enantioselectivity afforded by (+)-sparteine surrogate 17. DFT calculations which modelled the $i$-PrLi/(+) -17 lithiation of N-Boc pyrrolidine 9 were able to emulate the enantioselectivity observed experimentally. The energies calculated provided significant energy differences between and pro-$S$ and pro-$R$ $\alpha$-deprotonation with $\Delta \Delta H^\ddagger = 3.5$ and $\Delta \Delta G^\ddagger = 2.8$ kcal mol$^{-1}$. These energies indicated a clear preference for pro-$R$ deprotonation which provided good agreement with the 94:6 er that was obtained experimentally with $i$-PrLi/(+) -17 lithiation of pyrrolidine 9.

Wiberg and Bailey have also used DFT modelling to investigate the enantioselectivity afforded by the $i$-PrLi/(−)-sparteine lithiation of N-Boc piperidine 10. The study found that the lowest energy pro-$S$ and pro-$R$ deprotonation pathways were similar in energy with only small differences in energy of the transition states ($\Delta \Delta H^\ddagger = 0.41$ and $\Delta \Delta G^\ddagger = 0.08$ kcal mol$^{-1}$). Wiberg and Bailey claimed that the small energy differences between the pro-$S$ and pro-$R$ deprotonation pathways explained the reduced 87:13 er observed experimentally. However, with the energy differences being this small, in the margins of calculation error, it would be expected that very little or no enantioselectivity would be observed at all. The activation energies calculated for the $i$-PrLi/(−)-sparteine lithiation of N-Boc piperidine 10
were significantly higher than those calculated for the \(i\text{-PrLi}/(-)\text{-sparteine}\) lithiation of \(N\)-Boc pyrrolidine \(9\). This reflected the slower rate of lithiation of \(N\)-Boc piperidine \(10\) versus \(N\)-Boc pyrrolidine \(9\) observed experimentally.

Wiberg and Deng later reattempted the modelling of the \(i\text{-PrLi}/(-)\text{-sparteine}\) lithiations of both \(N\)-Boc pyrrolidine \(9\) and \(N\)-Boc piperidine \(10\) using QM/QM modelling.\(^90\) QM/QM modelling was carried out using the ONIOM method developed by Morokuma \textit{et al.},\(^91\) which allows the system to be separated into parts which can be treated with different levels of theory. This methodology can be particularly useful for large systems where only a small portion of the total system is chemically active. This chemically important part of the system can be calculated using a more accurate, computationally expensive method and the rest can be calculated using a less expensive method, without adversely affecting the quality of the results. This method is particularly useful for modelling enzymes and proteins where the active site can be modelled at a high level theory and the surrounding systems can be modelled with lower levels of theory or molecular mechanics.\(^92\) Wiberg and Deng attempted many different partitions for the lithiation of both \(N\)-Boc pyrrolidine \(9\) and \(N\)-Boc piperidine \(10\). These included treating the entire \((-)\text{-sparteine}\) ring with a lower level of theory and treating other half of the pyrrolidine and piperidine rings at lower levels of theory. Unfortunately, each of the QM/QM partitioning schemes that were attempted were unable to sufficiently describe the system and provided calculated energies that significantly differed to those calculated when the entire system was modelled using a high level of theory. They did, however, find that treatment of the other half of the piperidine or pyrrolidine ring at a lower level of theory did not adversely affect the results, suggesting that the totality of the heterocycle ring was not crucial for QM/QM calculations.

In summary, the enantioselectivity of the lithiation of \(N\)-Boc pyrrolidine \(9\) and \(N\)-Boc piperidine \(10\) can, to some extent, be rationalised with computational DFT modelling. In many cases, the calculated differences in energy between the transition states of enantiomeric \(\alpha\)-deprotonation provides a good description of the enantioselectivity that was observed experimentally. These results suggest that DFT modelling may provide a sufficient description of the system to allow reactivity differences that arise with different \(N\)-Boc heterocycles and ligands to be modelled.
1.5 Project Outline

This project aims to study two of the key factors in the α-lithiation-trapping reactions of \( N \)-Boc heterocycles: the rate/kinetics and, where relevant, the diastereoselectivity. Both topics will be investigated using a combination of experimental (synthesis and \textit{in-situ} IR spectroscopy) and computational DFT modelling. Combining experimental and computational techniques could potentially allow rates of reaction and the diastereoselectivity (if applicable) for unknown lithiation reactions to be modelled and predicted computationally. The combination of these techniques may also help to rationalise and/or quantify the chemical behaviour that is observed experimentally.

Chapter 2 of this thesis uses \textit{in situ} IR spectroscopy to study the rates of lithiation when different \( N \)-Boc heterocycle substrates and different ligands are employed in the lithiation reaction (Scheme 1.55). We have found that both the structure of the \( N \)-Boc heterocycle and ligand employed in the lithiation can have a dramatic effect on the reactivity observed. This collated reactivity data can then help to identify reactivity trends which can be used to rationalise why the rate of lithiation is fast or slow for particular substrates or ligands.

\textbf{Scheme 1.55. Quantification of the rate of lithiation using \textit{in situ} IR spectroscopy}

\[ \text{N-Boc} \xrightarrow{\text{s-BuLi/ligand, \(-78^\circ C\)}} \text{Li} \text{t-BuO} \]

In Chapter 3, the α-lithiation reactions that were conducted in Chapter 2 are modelled computationally using DFT. This was conducted to determine whether a theoretical treatment of the α-lithiation reaction can account for the reactivity differences that were observed by experiment. If the DFT modelling can reproduce these reactivity differences then there is a potential that the computational modelling could be used to predict the reactivity of unknown \( N \)-Boc heterocycles or ligands.

The rates of the trapping reactions between the α-lithiated intermediates and electrophiles are studied using \textit{in situ} IR spectroscopy in Chapter 4 (Scheme 1.56). This investigation explores the trapping reactions of a variety of different lithiated intermediates with a range of different electrophiles. Our results show that the rate of trapping can differ by several magnitudes when different combinations of lithiated intermediate and electrophile are used.
A knowledge of the rate of trapping of organolithiums is important for synthetic chemists so that products can be obtained in high yield and er/dr.

**Scheme 1.56. Quantification of the rate of trapping using *in situ* IR spectroscopy**

Finally, in Chapter 5, all the techniques utilised in the previous chapters are applied to investigate the diastereoselective lithiation-trapping of 3,4-disubstituted N-Boc pyrrolidine 96 (Scheme 1.57). The diastereoselectivity of the lithiation of 96 can be altered by the ligand employed in the lithiation and the identity of the electrophile used in the subsequent trapping reaction. The effect of the ligand on diastereoselectivity is investigated using synthetic experiments and DFT modelling. The effect that the electrophile has on diastereoselectivity has been determined with synthetic experiments and *in situ* IR spectroscopic analysis has elucidated how the choice of electrophile affects the dr of the products observed.

**Scheme 1.57. General lithiation-trapping reaction for N-Boc pyrrolidine 96**
Chapter 2: *In situ* IR Spectroscopic Monitoring of the α-Lithiation Reaction of N-Boc Heterocycles

The *in situ* IR spectroscopic monitoring of the α-lithiation reaction provides useful information to synthetic chemists on how long such reactions require to reach completion (Scheme 2.1). If the electrophile was added too early, only partial lithiation would have occurred which would result in a decreased yield of the desired product and makes separation of the product and starting material necessary. Addition of the electrophile when large amounts of unreacted alkylolithium remain can pose a problem by forming by-products that further complicate the separation. α-Lithiation reactions are routinely conducted at −78 °C and it is important that the reaction is not allowed to warm before the electrophile is added as the lithiated intermediates could become unstable at higher temperature.

**Scheme 2.1. General scheme for the α-lithiation of a N-Boc heterocycle**

\[
\begin{align*}
\text{N} & \quad \text{Boc} \\
\xrightarrow{\text{solvent, } -78 \degree C \text{, time ?}} \\
& \quad \text{t-BuO} \\
\end{align*}
\]

*In situ* IR spectroscopic monitoring of the reaction should enable optimised lithiation conditions to be obtained quickly without having to carry out many repeat reactions using a process of trial and error. It is also advantageous to have the probe in the reaction flask due to the low reaction temperatures required and the water sensitivity of both the reagents and intermediates. Many alternative methods to monitor reaction progress require aliquots of the reaction mixture to be taken from the reaction and then analysed. This method could be problematic as it is possible to quench the reaction/aliquot by exposure to air/water, the temperature of the aliquot needs to be maintained so that erroneous results are not obtained and concentration effects may occur due to the removal of portions of the reaction mixture.

On a large or industrial scale, maintaining low reaction temperatures, such as −78 °C, may not pose a problem. However, it is important that the reaction is only conducted for the length of time required for complete conversion to occur, to ensure that the process is efficient. Maintaining these low temperatures for longer than is required will significantly decrease both the energy and cost efficiency of a reaction.

Previous work in the O’Brien group, both published and unpublished, has focussed on using *in situ* IR spectroscopy (ReactIR™) to determine the reaction time for the s-BuLi/diamine...
lithiation of a range of structurally different $N$-Boc heterocycles.$^{31,50,52,53,73,93,94}$ This has included using several diamines, including TMEDA, ($-$)-sparteine and the ($+$)-sparteine surrogate $^{17}$. Traditionally, these lithiation reactions have been allowed between 3-6 h for completion at $–78 \, ^\circ\mathrm{C}$ but there is little synthetic evidence that these lengthy reaction times are needed for the majority of the heterocycle substrates.

This chapter presents work that builds on this previous in-group research. This work expands the range of $N$-Boc heterocycles whose lithiation reactions have been studied by ReactIR$^\text{TM}$. There is a deeper focus on constructing a reactivity series for the different substrates and attempts to rationalise the differences in reactivity of the substrates are provided. Research in this chapter also applies kinetic modelling to the lithiation reaction. This allowed $k_{\text{obs}}$ values to be extracted from the ReactIR$^\text{TM}$ data to enable more accurate comparisons of reactivity for the different substrates.

### 2.1 Reactivity Series for the s-BuLi/TMEDA Lithiation of $N$-Boc Heterocycles

The ReactIR$^\text{TM}$ monitoring of the s-BuLi/TMEDA lithiation reactions of a host of different $N$-Boc heterocycles has already been carried out in the O’Brien group.$^{53,94}$ Many of these lithiations were repeated in this investigation for two reasons. First, for the lithiation reactions which took $> 1$ h, the monitoring was ended prematurely in previous work due to worries that the lithiated intermediate may not be stable over longer reaction times using the ReactIR$^\text{TM}$ set-up. During this new investigation of reactivity, it was found that most lithiated intermediates were stable using the ReactIR$^\text{TM}$ apparatus for many hours. Second, some of the previous lithiations were carried out by adding the s-BuLi and $N$-Boc heterocycle first, forming a presumably solvent-ligated prelithiation complex to which the diamine ligand was then added to initiate lithiation. However, this order of addition can provide unreliable kinetic information, as work in this study indicated that the lithiation can still occur with just s-BuLi/Et$_2$O, albeit at a slower rate. The addition of s-BuLi to a mixture of the substrate and diamine provides more accurate and reliable data, as the reaction begins directly after the addition of the s-BuLi. The reliability and accuracy of the kinetic data is particularly important as we are attempting to compare reactivities of substrates.
The first substrate monitored using ReactIR™ in this reactivity study was N-Boc pyrrolidine 9, one of the first N-Boc heterocycles whose lithiation was reported by Beak in 1989. The s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9 using Beak’s conditions: –78 °C in Et₂O, was monitored using in situ IR spectroscopy (Scheme 2.2). Our standard conditions for lithiation used 1.3 eq. of s-BuLi/TMEDA in 14 mL of Et₂O solvent. The only modification to Beak’s conditions was that the concentration of the reaction mixture was halved, as there was concern that higher concentrations of the s-BuLi reagent could damage the ReactIR™ probe.

For N-Boc pyrrolidine 9, the carbonyl stretching frequency (ν_{C=O}) of the Boc group can be used as a spectroscopic handle. Carbonyl groups provide a particularly useful spectroscopic handle due to their strong IR absorbance signals which allow easy identification and monitoring of the carbonyl species in the reaction. In addition, there were no other absorbances in the 1800-1600 cm⁻¹ region of the IR spectrum for this chemistry which made tracking changes to these signals easier. Monitoring of the lithiation using C-H stretching and bending frequencies was not possible for two reasons. First, the ReactIR™ apparatus used can only monitor IR frequencies in the ranges of 2500-2250 cm⁻¹ and 2000-650 cm⁻¹, this meant that most C-H stretching frequencies were out of this observable window. Second, the diamine ligand and s-BuLi (which is in cyclohexane solvent) were added after the solvent background was recorded, this meant that many C-H stretching/bending frequencies were observed upon addition at the reaction setup. These overlapping frequencies meant that finding a correlation between reaction progress and any changes in ν_{C-H} absorbance intensity was not possible.

During the lithiation of N-Boc pyrrolidine 9, three different IR signals are observed for the Boc carbonyl: the uncomplexed starting material N-Boc pyrrolidine 9 (ν_{C=O} = 1701 cm⁻¹), the prelithiation complex 163 (ν_{C=O} = 1678 cm⁻¹) and the lithiated intermediate 164 (ν_{C=O} = 1647 cm⁻¹) (Scheme 2.2.a). These three signals appear at different wavenumbers as the Boc carbonyl has a different coordinating environment in each of these species. The ν_{C=O} for the carbamate decreases in the three species 9, 163 and 164. This can be attributed to the increasing coordination of the electropositive Li centre to the carbonyl bond during the reaction which weakens the bond and therefore shifts the ν_{C=O} to lower wavenumbers.
Scheme 2.2. The ReactIR™ monitored s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9 with 3D and 2D ReactIR™ traces.

Recording the absorption of the three νC=O signals during the reaction allows the changes in concentration of the three species to be observed over the course of the lithiation (Scheme 2.2.b). Importantly, the νC=O signal for N-Boc pyrrolidine 9 shows consumption of the starting material and the νC=O signal of lithiated intermediate 164 tracks the formation of the product.
The ν\textsubscript{C=O} absorbance of prelithiation complex 163, a reaction intermediate, indicates that a pre-equilibria process occurs during the reaction, where the prelithiation complex 163 is formed rapidly at the start of the reaction. The rapid formation of 163 arises from the fast equilibrium reaction between the N-Boc pyrrolidine 9 starting material and prelithiation complex 163. This fast equilibrium is evident in the ReactIR\textsuperscript{TM} monitored lithiation reaction, as consumption of prelithiation complex 163 and the starting material 9 mirror each other during the reaction once the equilibrium has been established. This is because as prelithiation complex 163 is consumed by the slow rate determining deprotonation step, the rapidly occurring equilibrium reaction restores the original ratio of species 9 and 163. Previous mechanistic work conducted by Beak provided evidence for this fast equilibrium between the substrate and alkyl lithium/diamine, followed by a slow rate determining deprotonation for the i-PrLi/(−)-sparteine lithiation of N-Boc pyrrolidine 9 (see Scheme 1.9).\textsuperscript{32}

By visual inspection of Scheme 2.2.b, the s-BuLi/TMEDA lithiation N-Boc pyrrolidine 9 requires 4 min for complete lithiation, at which point concentrations of starting material 9 and lithiated intermediate 164 no longer change. This 4 min reaction time is a stark contrast to the 3.5 h lithiation time initially used by Beak and highlights how useful ReactIR\textsuperscript{TM} can be for the optimisation of reaction conditions.\textsuperscript{2}

To further probe the rate of the initial equilibrium reaction between the N-Boc pyrrolidine 9 starting material and prelithiation complex 163, the lithiation reaction was repeated using the rapid-collect mode on the ReactIR\textsuperscript{TM} apparatus (Scheme 2.3). This allowed the collection of IR absorbance data for each second rather than at the 15, 30 or 60 second intervals used for normal ReactIR\textsuperscript{TM} experiments. This method did have two constraints. First, fewer scans at each interval resulted in a low signal/noise ratio which provided a reaction trace with a significant amount of noise. Second, due to the processing power required to process the volume of data per second, the results were not given in real time and the trace was only viewable after the experiment. This was not an issue for the lithiation of N-Boc pyrrolidine 9 as it was a repeat reaction and timings for the addition of reagents were known. The rapid-collect ReactIR\textsuperscript{TM} trace indicated that prelithiation complex formation was extremely rapid, occurring in < 1s. This offered further evidence that a rapid equilibrium reaction exists between the starting material 9 and prelithiation complex 163 and that the rate determining step is the deprotonation/lithiation of the prelithiation complex 163.
Scheme 2.3. Rapid-collect ReactIR™ monitored s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9

\[
\begin{align*}
\text{N-Boc} & \quad \text{s-BuLi/TMEDA} \quad \text{Et}_2\text{O}, \quad -78 \degree \text{C} \quad \text{fast < 1s} \\
9 & \quad \overset{\text{163}}{\text{N}}_{\text{Bu}} \quad \text{Me}_2 \quad \text{Me}_2 \quad \text{N} \quad \text{Li} \\
\text{N} & \quad \overset{\text{164}}{\text{Bu}} \quad \text{Me}_2 \quad \text{N} \quad \text{Me}_2 \\
\nu_{\text{C}=\text{O}} & = 1700 \text{ cm}^{-1} \\
\nu_{\text{C}=\text{O}} & = 1678 \text{ cm}^{-1} \\
\nu_{\text{C}=\text{O}} & = 1648 \text{ cm}^{-1}
\end{align*}
\]

The ReactIR™ monitored lithiation of N-Boc piperidine 10, another substrate whose lithiation was reported in Beak’s 1989 publication,\textsuperscript{2} indicated that a significantly longer time was required for complete lithiation to occur. Using s-BuLi/TMEDA in Et\textsubscript{2}O at -78 °C the lithiation of N-Boc piperidine 10 required 6 h to reach completion (Scheme 2.4). This dramatic difference in reactivity highlights the significant effect that the structure of the N-Boc heterocycle has on the lithiation reaction. These large reactivity differences between substrates are a key reason why monitoring the lithiation of substrates is so important and explains why the monitoring of α-lithiation reactions by ReactIR™ is becoming more popular.
Analogous to the lithiation of \( N \)-Boc pyrrolidine 9, the carbamate ν\( \text{C}=\text{O} \) of the \( N \)-Boc heterocycle shifts to lower wavenumbers during the lithiation reaction as the degree of coordination to the Li atom is increased in species 10, 165 and 166. A prelithiation complex intermediate was also observed for \( N \)-Boc piperidine, 165 (ν\( \text{C}=\text{O} \) = 1674 cm\(^{-1} \)) and it displayed the same pre-equilibrium kinetics which were more easily identified over the longer reaction time.

The same ReactIR\(^\text{TM}\) monitoring procedure carried out for the lithiations of \( N \)-Boc pyrrolidine 9 and \( N \)-Boc piperidine 10 was then employed to investigate the reactivity of 12 additional \( N \)-Boc heterocycle substrates (Figure 2.1). These substrates were selected as they provided a diverse selection of heterocycles with differing ring sizes, heteroatoms in the ring and substituents. It was envisaged that a wide spectrum of reactivity would be observed when lithiating with \( s \)-BuLi/TMEDA. Additionally, it was anticipated that the differing structural aspects of the \( N \)-Boc heterocycles may provide some trends between certain features of a substrate and the lithiation reactivity.
Many substrates were selected as there was already precedent for their lithiation either in the literature \( (9, 10, 32, 34, 39, 47, 48, 57, 58, 66, 84, 96) \) or in-group \( (167, 169) \). All of the heterocycles except bicyclic pyrrolidine \( 84 \) and 4-amino \( N \)-Boc piperidine \( 168 \) were prepared using simple one- or two-step procedures available either in-group \( (53, 94) \) or from the literature \( (39, 63, 97, 98) \). The synthesis and \( s \)-BuLi/TMEDA \( \alpha \)-lithiation of bicyclic pyrrolidine \( 84 \) was previously reported by researchers at AstraZeneca as part of a synthetic route for the synthesis of a GlyT1 inhibitor for the treatment of schizophrenia \( \) (see Scheme 1.30). \( 63 \) Unfortunately, no kinetic data or reaction times for the lithiation were reported so it was decided to explore the lithiation with ReactIR™ monitoring. Synthesis of bicyclic pyrrolidine \( 84 \) was achieved using the literature synthetic route involving the Boc protection of amino-cyclohexanol \( 170 \) followed by mesylation of the resulting \( N \)-Boc alcohol \( 171 \) and subsequent cyclisation of mesylate \( 172 \) with KOt-Bu. \( 99 \) Bicyclic pyrrolidine \( 84 \) was afforded in multi-gram quantities and a moderate 46% yield over three steps \( \) (Scheme 2.5).
4-Amino N-Boc piperidine 168 was selected to probe how the reactivity of a 4-substituted N-Boc piperidine would be affected with a heteroatom in the 4-position that was not oxygen. There was no precedent for the α-lithiation of 168, although the synthesis of 4-amino N-Boc piperidine 168 was reported in the literature.\textsuperscript{100} This synthetic route involved the reductive amination of N-Boc 4-piperidone 173 with dimethylamine using H\textsubscript{2} and Pd/C at elevated temperature and pressure. However, a synthetic procedure more amenable to a research laboratory which had been used to prepare similar amine compounds\textsuperscript{101} was employed to synthesise 4-amino N-Boc piperidine 168. Reductive amination of N-Boc 4-piperidone 173 with dimethylamine hydrochloride and NaBH\textsubscript{4} in the presence of Ti(Oi-Pr)\textsubscript{4} provided the desired 4-amino N-Boc piperidine 168 in moderate 40% yield (Scheme 2.6).

**Scheme 2.6. Synthesis of 4-amino N-Boc piperidine 168**

For the s-BuLi/TMEDA α-lithiations of all N-Boc heterocycles, identical reaction conditions were used and all lithiations were conducted at –78 °C to ensure trends in reactivity could be drawn from the results. A wide range of reactivities were displayed by the 14 substrates studied (Table 2.1). Many substrates, such as N-Boc morpholine 169, 4-O-trisyl N-Boc piperidine 167 and \(N'\)-Me and \(N'\)-Bn piperazines 58 and 57 exhibited fast lithiation reactions with < 4 min lithiation times. Conversely, others such as 4-amino piperidine 168 and N-Boc piperidine 10 required several hours to reach completion.
Table 2.1. Reactivity series for the s-BuLi/TMEDA lithiation at –78 °C of N-Boc heterocycles

\[
\begin{array}{cccccc}
\text{N-Boc} & \text{Cl} & \text{OTrisyl} & \text{N-Boc} & \text{N-Boc} & \text{N-Boc} \\
169 & 48 & 167 & 58 & 9 & 96
\end{array}
\]

\( t_{\text{lith}} / \text{min} \) 
\(< 1^a\) | \( 2^a, b\) | \( 2^a, b, c\) | 4 | 4 | 4

\[
\begin{array}{cccccc}
\text{Bn} & \text{Boc} & \text{N-Boc} & \text{OTIPS} & \text{Ph} & \text{N-Boc} \\
57 & 84 & 66 & 39 & 32 & 34
\end{array}
\]

\( t_{\text{lith}} / \text{min} \) 
4 | 15 | 22 | 45 | 90 | 100

\( t_{\text{lith}} / \text{min} \) 
120 | 360

\(^a\) 2.6 eq. of s-BuLi and diamine were used. \(^b\) results from previous in-group work.\(^c\) Trisyl = 2,4,6-tri-\(i\)-propylbenzenesulfonyl

\( N \)-Boc morpholine 169 was the fastest heterocycle to lithiate and underwent rapid lithiation with s-BuLi/TMEDA with complete lithiation requiring < 1 min. 2.6 eq. of both the alkyllithium and diamine were used as the initial lithiation forms lithiated intermediate 174 which subsequently ring opens and is followed by vinylic lithiation to from di-lithiated intermediate 175 (Scheme 2.7.a). This mechanism is proposed as previous unpublished work within the group described the successful trapping of di-lithiated species 175 (formed by \( s \)-BuLi/(\(–\))sparteine lithiation of 169) with benzophenone to give trapped adduct 176 in 40% yield (Scheme 2.7.b).\(^53\) The lithiation and similar ring opening of a bicyclic \( N \)-Boc morpholine was also reported by Lautens (see Scheme 1.26).\(^59\)
Scheme 2.7. α-Lithiation and ring opening of N-Boc morpholine 169

The ReactIR™ monitoring of the lithiation reactions of both 4-chloro N-Boc piperidine 48 and 4-O-trisyl piperidine 167 indicated that lithiation was rapid, reaching completion within 2 min. Both lithiation reactions were carried out with 2.6 eq. of s-BuLi/TMEDA, due to the formation of a bicyclic intermediate 49 which then undergoes a second lithiation (believed to be rapid due to the acidifying effect of the cyclopropyl group) forming lithiated bicycle 52 (Scheme 2.8). It is presumed that it is lithiated bicycle 52 which is observed by ReactIR™. Previous work has successfully trapped bicyclic intermediate 52, generated by the lithiation of 4-chloro N-Boc piperidine 48 (see Scheme 1.19).^42,44

Scheme 2.8. Lithiation of 4-chloro and 4-O-trisyl piperidines 48 and 167

Lithiation times of 4 min were observed for N-Boc pyrrolidines 9 and 96 which was a surprising result for two quite different pyrrolidine substrates. It was expected that the additional steric bulk from the cyclohexyl ring fused to the pyrrolidine would hinder and retard the rate of lithiation of pyrrolidine 96. However, the identical reactivities of both 9 and 96 suggest that the steric bulk is too far away from the reaction centre to have a significant effect on the kinetics of the lithiation.
When the lithiation of bicyclic pyrrolidine 84 was monitored using ReactIR™ it was initially expected that the lithiation of 84 would be extremely slow as the deprotonation occurs at a sterically complex tertiary bridgehead carbon. However, it was discovered that only 15 min were required for complete lithiation of bicyclic pyrrolidine 84 to occur. This faster than expected lithiation may result from the rigid geometry imposed by the bridgehead making the deprotonation of the tertiary α-proton more favourable than in a non-bicyclic tertiary pyrrolidine such as 2-methyl pyrrolidine 14 (Figure 2.2).

![Figure 2.2. Steric environment of the α-proton in bicyclic pyrrolidine 84 and 2-methyl pyrrolidine 14](image)

It is also evident that the ring-size has a pronounced effect on the lithiation reactivity with a striking 6 h reaction time difference observed between the N-Boc pyrrolidine 9 and N-Boc piperidine 10 lithiations. It is possible that the difference in reactivity arises from the conformational differences of the five- and six-membered rings. However, ring-size is not the only factor that can determine reactivity. Other six-membered heterocycles including N-Boc morpholine 169, piperazines 57, 58 and 66 and 4-substituted N-Boc piperidines such as 39 all have significantly faster lithiation reactions than N-Boc piperidine 10.

\[ N'\text{-Bn and } N'\text{-Me } N\text{-Boc piperazines, 57 and 58, both exhibited short 4 min lithiation times whereas lithiation of } N'\text{-t-Bu piperazine 66 was more sluggish, requiring 22 min to reach completion. The lower reactivity of } N'\text{-t-Bu piperazine 66 compared to } N'\text{-Bn and } N'\text{-Me piperazines 57 and 58 is difficult to rationalise and, at present, we do not have an explanation for the differences in reactivity. It is unlikely that steric bulk attached to the distal nitrogen would directly hinder the lithiation as the substituent is far removed from the reaction centre.}

All three of the piperazines studied have significantly faster lithiation reactions than N-Boc piperidine 10. Presumably, the increased lability of the α-proton must arise from the nitrogen atom present in in the heterocycle ring. We suggest that back donation can occur from the C–H σ bond of the α-proton into the lower lying C–N σ* orbital (Figure 2.3.a). This orbital overlap would weaken the C-H bond and make the α-proton more kinetically acidic.\[53\] The
facile lithiation of N-Boc morpholine 169 (1 min lithiation time) may also be the result of the same orbital overlap effect (Figure 2.3.b).

![Figure 2.3. Proposed orbital overlap for N-Boc piperazines (a) and N-Boc morpholine 169 (b) increasing the α-proton acidity](image)

The identity of the substituent on the C-4 position of N-Boc piperidines also has a substantial effect on reactivity and this is evident when comparing the respective 2 min and 6 h lithiation times of 4-chloro N-Boc piperidine 48 and unsubstituted N-Boc piperidine 10. We propose that a different type of orbital overlap could occur in the 4-substituted piperidines which would facilitate the lithiation by increasing the α-proton acidity. Specifically, back donation from the C–H σ orbital of the α-proton to the C–X (where X = Cl, N, O) σ* orbital (Figure 2.4). The conformation of the six-membered piperidine ring enables the overlap of the orbitals on the C-2 and C-4 carbons, analogous to the explanation of the $^3J_W$-coupling that can occur between protons in $^1$H NMR spectroscopy.

![Figure 2.4. Proposed orbital overlap for the 4-substituted N-Boc piperidines](image)

The various substituents (X) on the C-4 position will have differing electronic properties which may affect the extent of orbital overlap and back-donation that occurs. This would account for the wide range of reactivities observed with the different 4-substituted N-Boc pyrrolidines. For example, both the 4-chloro- and 4-O-trisyl substituted piperidines 48 and 167 have 2 min lithiation times, presumably due to the electron-withdrawing nature of the substituents. 4-OTIPS N-Boc piperidine 39 has an intermediate reactivity, requiring 40 min for complete lithiation to occur. Alkoxy groups are known to have a smaller electron withdrawing (–I) effect than chloro groups, this difference in inductive effect may explain why 4-OTIPS piperidine 39 exhibits a lower level of reactivity than that of 4-chloro piperidine 48. 4-Ph piperidine 32, ketal 34 and 4-amino N-Boc piperidine 168 are slower still, requiring 1.5-2 h for complete lithiation of the substrates to occur. However, all three
lithiations still only require less than a third of the time needed for the lithiation of unsubstituted piperidine 10, indicating a significant activating effect is still present. Both 4-Ph piperidine 32 and 4-amino piperidine 168 have groups on the C-4 position of the piperidine ring with weak electron withdrawing effects, meaning that these substituents will offer a more modest activating effect for the lithiation reaction. An explanation of the lower reactivity observed with ketal 34 is more complex. This could arise due to the geometry of the ketal promoting poorer overlap between the C4 and C2 orbitals, resulting in a lesser degree of back donation between orbitals and therefore a poorer activating effect on the piperidine α-proton. Alternately, it is possible that the oxygen atoms of the ketal substituent may chelate the s-BuLi/TMEDA lithiating complex leading to retardation of the lithiation reaction.

In summary, a diverse selection of N-Boc heterocycles have exhibited a wide spectrum of reactivities for their respective s-BuLi/TMEDA lithiation reactions. The use of ReactIR™ can not only allow optimal conditions for each of the substrates to be determined but also allows construction of a reactivity series for the substrates. Comparisons between the experimental reactivity data and the structural differences of the substrates has allowed hypotheses to be made to rationalise the reactivity trends we observe. Furthermore, the experimentally obtained reactivity series obtained will allow comparison with the computationally predicted reactivity series for the same substrates, as described in Chapter 3 of this thesis.
2.2 Reactivity Series for the Lithiation of \textit{N}-Boc Heterocycle Substrates with Different Diamine Ligands

Five of the 14 substrates included in the \textit{s-BuLi}/TMEDA reactivity series had rapid lithiation reactions which were complete within 2 min. As the ReactIR\textsuperscript{TM} equipment only gave absorbance readings for each signal per minute (on the older ReactIR\textsuperscript{TM} iC10 apparatus used during this part of the investigation), this meant that the lithiation time was only determined to the nearest minute. This provides a significant amount of error in the lithiation times determined for rapidly reacting substrates. It was hoped that the use of a different diamine would slow the rate of the lithiation reactions so that more precise lithiation times could be obtained, thus allowing the construction of a reactivity series for the more reactive substrates.

First of all, a reactivity order was constructed using \textit{s-BuLi}/(\textendash )-sparteine to lithiate the \textit{N}-Boc heterocycles that had a rapid lithiation reaction with \textit{s-BuLi}/TMEDA. Previous in-group data was pooled for the \textit{s-BuLi}/(\textendash )-sparteine lithiations of seven heterocycle substrates; lithiation of \textit{N}-Boc heterocycles with \textit{s-BuLi}/(\textendash )-sparteine has been studied extensively in the group previously.\textsuperscript{53} It was initially expected that the reactivity order of the seven \textit{N}-Boc heterocycles with \textit{s-BuLi}/(\textendash )-sparteine would be identical to that with \textit{s-BuLi}/TMEDA but with longer lithiation times due to the more bulky (\textendash )-sparteine ligand. All of the lithiations were slower but it was also noted that some substrates were placed in different positions in the reactivity series using \textit{s-BuLi}/(\textendash )-sparteine lithiating conditions. We propose that the difference in reactivity order observed for the substrates may derive from complications due to the asymmetric lithiation that occurs with \textit{s-BuLi}/(\textendash )-sparteine; these asymmetric effects will be discussed in detail later in this chapter.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.5.png}
\caption{Synthesis of achiral diamine ligands and construction of a diamine reactivity series}
\end{figure}

As the use of \textit{s-BuLi}/(\textendash )-sparteine appeared to provide outlying results for substrate reactivity, our aim was to find an achiral diamine that could be used to elucidate the differences in reactivity for the most reactive \textit{N}-Boc heterocycles. Additionally, it was also of interest to investigate how the structure of the diamine affected the rate of lithiation. To this end, four diamine ligands were trialled: TMCDA \textit{trans-161}, di-pyrrolidino ethane (DPE) \textit{177}, tetra-isopropyl ethane \textit{178} and TMPDA \textit{179} (Figure 2.5). These diamines were selected for two reasons. First, they were either commerically available (TMPDA \textit{179}) or had
relatively short synthetic sequences (trans-161, 177 and 178). Second, we hoped that the differing levels of flexibility of the diamines and the different amounts of steric bulk around the amine groups would provide a broad range of lithiation times when used with s-BuLi.

TMCDA *trans*-161 was synthesised by Eschweiler-Clarke methylation of *trans*-cyclohexane diamine 180 by refluxing in excess formaldehyde and formic acid following a literature procedure (Scheme 2.9).\(^\text{105}\) The diamine was purified by formation and subsequent recrystallisation of the bis-HCl salt. Treatment with NaOH liberated the free diamine TMCDA *trans*-161 in 42% overall yield.

**Scheme 2.9. Synthesis of the ligand TMCDA *trans*-161**

The tetra-isopropyl TMEDA analogue 178 was synthesised by LiAlH\(_4\) reduction of bisamide 181 which was formed using oxalyl chloride and di-isopropylamine as described in the literature (Scheme 2.10).\(^\text{106}\) This furnished tetra-isopropyl diamine 178 in 69% yield over both steps.

**Scheme 2.10. Synthesis of tert-isopropyl diamine 178**

TMEDA analogue di-pyrrolidino-ethane 117 (DPE) was synthesised by a double nucleophilic displacement reaction between 1,2-dichloroethane and pyrrolidine in the
presence of $\text{K}_2\text{CO}_3$ (Scheme 2.11). Subsequent fractional distillation gave the desired diamine DPE 177 in 65% yield.

**Scheme 2.11. Synthesis of TMEDA analogue DPE 177**

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N}
\end{align*}
\]

The $s$-BuLi/diamine lithiation of $N$-Boc pyrrolidine 9 at $-78 \, ^\circ\text{C}$ was selected to investigate the reactivity of the different $s$-BuLi/diamine lithiating complexes. A control lithiation reaction of $N$-Boc pyrrolidine 9 was also conducted with identical conditions but no diamine to ensure that the diamines employed were participating in the lithiation reaction. The Et$_2$O solvent used for the lithiation reactions is a coordinating solvent and is known to offer a mild enhancement in the reactivity of $s$-BuLi. Therefore, slow $s$-BuLi/Et$_2$O lithiation of pyrrolidine 9 is still likely to occur if the diamine does not coordinate to the $s$-BuLi. A range of different $s$-BuLi/diamine lithiating complex reactivities were observed for the lithiation of $N$-Boc pyrrolidine 9; lithiation times ranged from minutes to several hours (Table 2.2). The lithiation time for the ‘diamine-free’ $s$-BuLi/THF lithiation of $N$-Boc pyrrolidine 9 is also included in Table 2.2 and provides insight into how a monodentate ligand affects the rate of lithiation. For all the lithiation reactions in Table 2.2 except that with $s$-BuLi/THF, an electrophile (PhCHO) was added to trap the lithiated intermediate and the crude product was analysed by $^1$H NMR spectroscopy to ensure complete lithiation had occurred.
Table 2.2. ReactIR™ obtained lithiation times (t_{lith}) for s-BuLi/ligand lithiation of N-Boc pyrrolidine 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine</th>
<th>t_{lith}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMEDA</td>
<td>4 min</td>
</tr>
<tr>
<td>2</td>
<td>TMCDA  \textit{trans}-161</td>
<td>4 min</td>
</tr>
<tr>
<td>3</td>
<td>(-)-sparteine</td>
<td>45 min</td>
</tr>
<tr>
<td>4</td>
<td>177</td>
<td>46 min</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>5 h\textsuperscript{a}</td>
</tr>
<tr>
<td>6</td>
<td>178</td>
<td>9 h</td>
</tr>
<tr>
<td>7</td>
<td>179</td>
<td>12 h</td>
</tr>
<tr>
<td>8</td>
<td>No diamine</td>
<td>12 h</td>
</tr>
</tbody>
</table>

\textsuperscript{a} PhCHO trapping was not carried out for the s-BuLi/THF lithiation of N-Boc pyrrolidine 9

The lithiating complexes with the tetra-methyl substituted diamines s-BuLi/TMEDA and s-BuLi/TMCDA \textit{trans}-161 provided identical reactivities for the lithiation of N-Boc pyrrolidine 9 (Table 2.2, entries 1 and 2). This indicated that the additional rigidity offered by the cyclohexane ring has no effect on the reactivity of the s-BuLi/TMCDA \textit{anti}-161 lithiating complex. The steric environments of the amine groups in TMEDA and TMCDA \textit{anti}-161 are very similar which may explain why the reactivities of these two diamines are so similar. This result mirrors previous work carried out by the O’Brien group, where a reactivity series for the s-BuLi/diamine-mediated lithiation of N-Boc pyrrolidine 9 was
constructed using competition experiments. The study found that s-BuLi/TMEDA or s-BuLi/TMCDA _anti-_161 were the most reactive lithiating reagents, and were significantly more reactive than s-BuLi/(−)-sparteine.

The s-BuLi/DPE 177 lithiating complex provided a moderate reactivity with _N_-Boc pyrrolidine 9, with lithiation requiring 46 min to complete (Table 2.2, entry 4). This result was initially a surprise, as it was expected that the 5-membered pyrrolidine rings on the ligand would constrain the steric bulk around the two amine groups resulting in a facile lithiation with a similar reactivity to that of s-BuLi/TMEDA. However, the slower rate of lithiation of _N_-Boc pyrrolidine 9 with s-BuLi/DPE 177 suggests that the pyrrolidinyl rings have an increased steric bulk which retards the lithiation. The s-BuLi/DPE 177 lithiating complex appears to have a similar reactivity to that of s-BuLi/(−)-sparteine which required 45 min for complete lithiation of _N_-Boc pyrrolidine 9 (Table 2.2, entry 3).

The s-BuLi/THF lithiation of _N_-Boc pyrrolidine 9 offered an even slower rate of lithiation, with the ReactIR™ monitoring indicating that complete lithiation required 5 h (Scheme 2.12.a and Table 2.2 entry 5). Unlike the s-BuLi/diamine lithiation reactions of _N_-Boc pyrrolidine 9, no prelithiation complex was observed during the lithiation reaction (Scheme 2.X.b). This absence of a prelithiation complex ν_C=O has been observed for the ReactIR™ monitored s-BuLi/THF lithiation reactions of other heterocycle substrates.50,53,94 Another difference between the s-BuLi/diamine and s-BuLi/THF lithiations of _N_-Boc pyrrolidine 9 was that two IR signals were detected at 1663 cm⁻¹ and 1646 cm⁻¹ for the lithiated intermediate formed by s-BuLi/THF. It is believed that they are both due to the ν_C=O of the carbamate group in lithiated intermediate 182 and that the two signals may indicate that the lithiated intermediate is present in two different aggregation states.
The slow rate of lithiation observed for the s-BuLi/THF lithiation of $N$-Boc pyrrolidine 9 likely results from the steric bulk of the ligand as proposed with the diamine ligands. It is conceivable that the monodentate THF ligand means that two molecules of THF ligate the alkyllithium. These two molecules of THF will have a sizeable steric bulk and an additional entropic factor of having two molecules of ligand rather than one may lead to a hindered high energy transition state 183 for the lithiation. However, this rationalisation of reactivity is uncertain as the aggregation states of the alkylolithium and intermediates is currently unknown for lithiation reactions with s-BuLi/THF.

Lithiation of $N$-Boc pyrrolidine 9 with s-BuLi/tetra-isopropyl TMEDA analogue 178 was a significantly slower reaction, with the ReactIR™ monitoring indicating that complete lithiation was only achieved after 9 h at $-78 \, ^\circ C$ (Table 2.2, entry 6). The slow rate of lithiation observed is likely due to the large amount of steric bulk around the coordinating nitrogen atoms of the ligand. This could retard the lithiation due to the sterically bulky s-BuLi/178 complex formed which performs the lithiation, resulting in a more sterically hindered higher energy transition state. In addition, the increased steric bulk around the two coordinating amine groups in diamine 178 afforded by the four $i$-Pr groups, could result in poor coordination between the diamine and s-BuLi. A lesser degree of coordination between
alkyllithium and diamine will likely mean that the less reactive s-BuLi/Et₂O species (entry 8, Table 2.2) is also present in significant quantities which may reduce the overall rate of lithiation.

The slowest lithiations of N-Boc pyrrolidine 9 were observed when s-BuLi/TMPDA 179 or s-BuLi/Et₂O lithiating conditions were employed, with both lithiating complexes requiring 12 h for complete lithiation of N-Boc pyrrolidine 9 (Table 2.2, entries 7 and 8). As both lithiating complexes required the same lithiation time for N-Boc pyrrolidine 9, this suggested that either s-BuLi/TMPDA and s-BuLi/Et₂O have the same reactivities or more likely that the TMPDA ligand 179 does not coordinate to s-BuLi and so it is the s-BuLi/Et₂O reagent that conducts the lithiation. If the slow lithiation reaction is indeed caused by a lack of coordination of TMPDA 179 and s-BuLi, it is possible that the additional methylene group in the linker between the two amines may be responsible. The longer linker means that the coordinating amine groups are further apart, which may disrupt the coordination of TMPDA 179 to the s-BuLi.

2.2.2 Investigating the N-Boc heterocycle reactivity series obtained with s-BuLi/DPE 177 and comparison with s-BuLi/(−)-sparteine and s-BuLi/TMEDA reactivity series

As the s-BuLi/DPE 177 lithiating complex offered a moderate reactivity with N-Boc pyrrolidine 9 similar to that of s-BuLi/(−)-sparteine, the construction of a reactivity series of the more reactive substrates with s-BuLi/DPE 177 lithiating conditions was attempted. Five of the most reactive substrates that were investigated using both s-BuLi/TMEDA and s-BuLi/(−)-sparteine lithiating conditions were lithiated using s-BuLi/DPE 177. The lithiation times for these five substrates with s-BuLi/DPE 177 and the seven substrates studied using s-BuLi/(−)-sparteine are presented in Table 2.3, along with the corresponding s-BuLi/TMEDA lithiation times. The order of the substrates in the reactivity series obtained with both s-BuLi/DPE 177 and s-BuLi/TMEDA lithiating conditions were identical. However, there were significant differences in the reactivity order of the substrates obtained with s-BuLi/(−)-sparteine, which suggested that N'-Me and N'-Bn piperazines 58 and 57 were less reactive than N-Boc pyrrolidine 9. This contradicted the reactivity series obtained with both s-BuLi/TMEDA and s-BuLi/DPE 177 lithiating conditions.
Table 2.3. $s$-BuLi/diamine reactivity series for rapidly lithiating $N$-Boc heterocycles

![Reactivity series diagram](image)

<table>
<thead>
<tr>
<th>DPE 177</th>
<th>(-)-sparteine</th>
<th>TMEDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{lith}}$ / min</td>
<td>$t_{\text{lith}}$ / min</td>
<td>$t_{\text{lith}}$ / min</td>
</tr>
<tr>
<td>0.25$^a$</td>
<td>1$^a$</td>
<td>1$^a$</td>
</tr>
<tr>
<td>1$^a$</td>
<td>10$^a$</td>
<td>2$^a$</td>
</tr>
<tr>
<td>30$^a$</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>46</td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td>--</td>
<td>&gt;300</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$ 2.6 eq. of $s$-BuLi and diamine were used (see Scheme 2.8).

All three of the $s$-BuLi/diamine combinations indicated that $N$-Boc morpholine 169 was the most reactive substrate. Both $s$-BuLi/TMEDA and $s$-BuLi/(-)-sparteine required only 1 min for complete lithiation of morpholine 169 to occur and with $s$-BuLi/DPE 177 the newer ReactIR$^{\text{TM}}$ apparatus (which takes reading every 15 s) provided a lithiation time of 15 s for 169. This provides further evidence that the presence of the oxygen atom in the six-membered ring has a significant activating effect on the $\alpha$-deprotonation.

4-$O$-trisyl and 4-chloro piperidines 167 and 48 were placed in the same positions in the substrate reactivity series by each of the three $s$-BuLi/diamine combinations. The slower lithiation rates offered with $s$-BuLi/DPE 177 and $s$-BuLi/(-)-sparteine allowed the elucidation of a reactivity difference between the two substituted piperidines, which indicated that 4-$O$-trisyl piperidine 167 was more reactive than 4-chloro piperidine 48. However, the lithiation times obtained with $s$-BuLi/(-)-sparteine and $s$-BuLi/DPE 177 for each of the substituted piperidines 167 and 48 differed significantly. This was a surprise as both the $s$-BuLi/(-)-sparteine and $s$-BuLi/DPE 177 lithiating complexes showed similar reactivity for the lithiation of $N$-Boc pyrrolidine 9. This was particularly evident for 4-chloro $N$-Boc piperidine.
which required only 5 min for complete lithiation with s-BuLi/DPE 177 but presented a significantly slower 30 min lithiation with s-BuLi/(−)-sparteine.

We postulate that slow rotamer interconversion may be the reason for the slow rate of lithiation observed with enantiopure ligands such as (−)-sparteine; rotamers do not pose a problem when an achiral ligand such as DPE 177 is utilised. When s-BuLi and a chiral diamine such as (−)-sparteine are used to lithiate a 4-substituted N-Boc piperidine, only one rotamer has an energetically favoured, matched situation for the asymmetric deprotonation.

For rotamer 184, the kinetically favoured pro-S deprotonation will dominate (Figure 2.6). However, for rotamer 185, pro-S deprotonation is disfavoured as the proton H_{S2} is in an axial position on the piperidine ring. In this case, the Complex Induced Proximity Effect (CIPE) cannot occur since the α-proton is not in the same plane as the coordinating Boc carbonyl group.

![Diagram](image)

**Figure 2.6. Interconversion of rotamers for a 4-substituted N-Boc piperidine**

It is also unfavourable for the piperidine in rotamer 185 to ring-flip so that the kinetically favoured α-proton H_{S2} is in an equatorial position, as the substituent (X) at the 4-position would be placed in an energetically disfavoured axial position. If rotamer interconversion can occur at −78 °C, rotamer 185 will interconvert to rotamer 184, where pro-S deprotonation is the primary reaction path, providing the lithiated intermediate in an enriched er.

Conversely, very slow or non-occurring rotamer interconversion leads to either <50% conversion as only one rotamer (184) would be lithiated or a >50% conversion, where both the pro-S and disfavoured higher energy pro-R (H_{R2}) deprotonation occur giving the product in an eroded er. In the case of >50 % conversion the rate of lithiation may be slowed due to the higher energy pro-R (H_{R2}) deprotonation occurring and/or dependency on the rate of rotamer interconversion. This means that constructing a reactivity series using an enantioselective ligand such as (−)-sparteine will provide unreliable reactivity data as there is also a dependency on the rate of rotamer interconversion for each substrate.
When the lithiation of 4-chloro piperidine 48 with s-BuLi/(−)-sparteine at −78 °C was carried out previously the enantioselectivity of the reaction was found to be poor, with an almost racemic product formed in 94% yield. This provided strong evidence that the rotamer conversion may indeed be slow and that the disfavoured deprotonation of H_{R2} does occur. Inspection of the ReactIR™ trace for the s-BuLi/(−)-sparteine lithiation of 4-chloro N-Boc piperidine 48 suggests that the reaction may have two different regions where the rates of reaction differ (Scheme 2.13). The initial fast lithiation and subsequent slow lithiation can be observed most clearly by monitoring the consumption of the prelithiation complex 186. However, visual inspection of the ReactIR™ does not provide conclusive evidence. If the two regions of differing lithiation rates are present for the s-BuLi/(−)-sparteine lithiation of 4-chloro piperidine 48, this would suggest a slow rate of rotamer interconversion for 48 at −78 °C. If rotamer interconversion is slow, one rotamer would undergo a fast pro-S deprotonation as is evident at the start of the reaction and concurrently the other rotamer would undergo a slower, energetically unfavourable, pro-R deprotonation only evident later in the reaction.

**Scheme 2.13. ReactIR™ monitored s-BuLi/(−)-sparteine lithiation of 4-chloro N-Boc piperidine 48**

![Scheme 2.13](image-url)
The use of \textit{s-BuLi/\text{--}-sparteine} also provided some unexpected results for the rate of lithiations of \textit{N’-Me} and \textit{N’-Bn} piperazines, \textbf{58} and \textbf{57}. Lithiation with \textit{s-BuLi/TMEDA} suggests that both piperazines have similar reactivity to \textit{N-Boc} pyrrolidine \textbf{9} with each of the three substrates requiring 4 min for complete lithiation. When the lithiation of \textit{N’-Me} piperazine \textbf{58} was carried out with \textit{s-BuLi/DPE} \textbf{177}, a 30 min lithiation time was observed which indicated that piperazine \textbf{58} is more reactive than \textit{N-Boc} pyrrolidine \textbf{9}, which required 46 min for complete lithiation with \textit{s-BuLi/DPE} \textbf{177}. In contrast, the 60 and 90 min \textit{s-BuLi/\text{--}-sparteine} lithiation times of \textit{N’-Bn} and \textit{N’-Me} piperazines \textbf{57} and \textbf{58} suggested that both substrates had similar or lower reactivity than \textit{N-Boc} pyrrolidine \textbf{9}.

At present, we have no conclusive evidence for why the rates of lithiation of both \textit{N’-Bn} and \textit{N’-Me} piperazines \textbf{57} and \textbf{58} are significantly slower with \textit{s-BuLi/\text{--}-sparteine}. However, the issue of slow rotamer interconversion, discussed previously to explain the anomalous reactivities of the \textit{4-substiutet} piperidines \textbf{48} and \textbf{167} with \textit{s-BuLi/\text{--}-sparteine}, may provide a rationale for the slower rates of lithiation observed for piperazines \textbf{57} and \textbf{58}. This explanation differs slightly for the piperazines, as the distal nitrogen can invert and then a subsequent ring-flip would always allow the pro-\textit{S} proton to be placed in an equatorial position allowing pro-\textit{S} deprotonation in each rotamer (Figure 2.7). However, if the nitrogen inversion or ring-flip occurs slowly at \textit{\textdegree}78 °C, this would mean that only one rotamer can undergo the energetically favoured pro-\textit{S} deprotonation. Therefore, if \textit{>50\%} conversion occurs, the rate of lithiation will be retarded as higher energy pro-\textit{R} deprotonation may occur and/or the rate of lithiation becomes dependent on rotamer interconversion or the \textit{N}-inversion and ring flip. Low temperature (\textit{\textdegree}60 °C) \textit{1H} NMR spectroscopic studies have indicated that both conformers of \textit{N-N’-dimethyl} piperazine were visible on the NMR timescale and that \textit{N-N’-dimethyl} piperazine has a significantly higher ring flip-inversion energy barrier than both morpholine and \textit{N-methyl} piperidine.\textsuperscript{110,111} Therefore, it is possible that for \textit{N-Boc} piperazines such as \textbf{57} and \textbf{58}, the rate of \textit{N-inversion/ring-flipping} may be slow at \textit{\textdegree}78 °C.
The s-BuLi/(−)-sparteine lithiation of N'-t-Bu piperazine 66 was the slowest of the seven substrates, with lithiation still ongoing after a 300 min reaction time. This matched the s-BuLi/TMEDA reactivity series, where N'-t-Bu piperazine 66 is also the least reactive of the seven substrates. However, it is difficult to ascertain whether there is any additional retardation of the s-BuLi/(−)-sparteine lithiation reaction of N'-t-Bu piperazine 66, as observed with piperazines 57 and 58, because the reaction was not allowed to go to completion.

In summary, a wide spectrum of reactivity was observed when the lithiation of N-Boc pyrrolidine 9 was carried out with several different s-BuLi/ligand lithiating complexes. This shows that the identity of the ligand can have a considerable influence on the rate of the lithiation reaction. The reactivity series constructed with the less reactive s-BuLi/DPE 177 lithiating complex provided a strong agreement with the reactivity series constructed with s-BuLi/TMEDA and allowed the subtler reactivity differences of the fast lithiating substrates to be elucidated. The reactivity series constructed using s-BuLi/DPE 177 will be valuable when the experimental and computationally predicted reactivities of the reactive substrates are compared in Chapter 3 of this thesis. Comparison of the s-BuLi/DPE 177 and s-BuLi/(−)-sparteine reactivity trends has indicated that s-BuLi/(−)-sparteine provides conflicting information about the reactivities of 4-substituted piperidines and piperazines. These anomalous results obtained with s-BuLi/(−)-sparteine may arise due to the retardation of the lithiation caused by slow rotamer interconversion. Therefore, lithiation times obtained using s-BuLi and a chiral ligand may not provide a reliable measure of the reactivity of substrates due to the possible rotamer interconversion complication.
2.3 Quantitative Kinetic Analysis of the s-BuLi/TMEDA Reactivity Series

Whilst conducting the substrate reactivity investigations described so far, it became apparent that determining the lithiation of time of a N-Boc heterocycle by visual inspection of the ReactIR™ trace can be unreliable and is not a robust method to quantify reactivity. The unreliability in the lithiation times arises as the visual inspection of ReactIR™ traces requires the user to select an end-point for the reaction. The user determines when both \( \nu_{C=O} \) signals for starting material and lithiated intermediate plateau and no further change is observed which can be difficult to pinpoint with precision. This determination can be made even more difficult if the ReactIR™ data is particularly noisy, especially towards the end of a reaction where the signal/noise ratio will be small. This selection of the end-point of a lithiation reaction is a significant source of error in the determined lithiation times for both slow (> 2 h) or fast reactions (< 5 min). As an example, for a fast lithiation reaction (i.e. \( N'\)-Me piperazine 58 where \( t_{lith} = 4 \) min), an imprecise end-point provides a significant margin of error (Scheme 2.14).

Scheme 2.14. ReactIR™ monitored s-BuLi/TMEDA lithiation of \( N'\)-Me \( N\)-Boc piperazine 58 showing the difficulty in establishing a reaction end-point

This problem is also compounded by the sampling interval, which at the fastest scanning
speed (on the newer ReactIR™ 15 apparatus) only records one data point per 15 s interval. In this case, an end-point can only be selected after each 15 s interval for the reaction which incurs a significant amount of error for a fast lithiation reaction.

For a slow lithiation reaction, determination of the reaction end-point can be problematic as it can be very difficult to locate the point in time at which both the consumption of starting material and formation of lithiated intermediate plateau. For instance, the lithiation of 4-amino N-Boc piperidine 168 requires 2 h to reach completion and close to the end of the reaction, the gradients of the consumption traces for both N-Boc piperidine 168 ($\nu_{C=O} = 1700$ cm$^{-1}$) and lithiated intermediate cis-188 ($\nu_{C=O} = 1644$ cm$^{-1}$) become very shallow (Scheme 2.15). These shallow gradients make accurately pinpointing the end of the reaction prone to significant amounts of error.

Scheme 2.15. ReactIR™ monitored s-BuLi/TMEDA lithiation of 4-amino N-Boc piperidine 168 showing the difficulty in establishing a reaction end-point

Initially, an attempt to mathematically locate at what point time both signals plateau was undertaken to remove the source of human error that arises from the visual inspection. The reaction end-point was located by measuring the distance between the starting material trace and the lithiated intermediate trace. At the point in time where this distance becomes
constant, the two traces will have stopped diverging and the reaction is deemed to be complete (Figure 2.8). A cut-off parameter was included so that once the change in this distance was below a certain value, an end-point would be identified. This parameter was included as the noise in the ReactIR™ readings meant that both traces would never have perfectly parallel lines.

Figure 2.8. An attempt to mathematically find the end-point for the lithiation reaction of 4-amino N-Boc piperidine 168

Unfortunately, this method was not able to find an end-point for lithiation reactions due to the ReactIR™ instrument noise present in the data. The noise resulted in false positives, where both lines ceased to diverge but then continued to diverge after more readings as the reaction progressed. This problem prompted us to find an alternative method to measure reaction rate without needing to accurately determine the end-point of the reaction. Hence, we turned to a kinetic investigation of the reaction which uses much more of the collected absorbance data rather just the start and end-point.

As discussed previously, the lithiation reactions for all the N-Boc heterocycles investigated proceeded via a multi-step reaction involving three different species: un-complexed substrate 189, prelithiation complex 190 and the lithiated intermediate 191. This involves two consecutive reactions where, initially, the un-complexed starting material 189 rapidly converts into the prelithiation complex 190 via an equilibrium reaction, with forward and backward rate constants, \( k_1 \) and \( k_1^{-1} \). Then, pre-lithiation complex 190 undergoes the slow rate determining deprotonation, with rate constant \( k_2 \), to form the lithiated intermediate product 191 (Scheme 2.16).
Scheme 2.16. A general reaction scheme for the s-BuLi/TMEDA lithiation of N-Boc heterocycles showing the different reaction steps occurring

As the deprotonation of the prelithiation complex \((k_2)\) is unimolecular, a first order relationship is expected between the reaction rate and concentration of the prelithiation complex. Unfortunately, for many of the lithiation reactions studied, the equilibrium between un-complexed starting material \(189\) and prelithiation complex \(190\) lies toward the un-complexed reagents. This means that the IR signal for the prelithiation complex is small and this results in a smaller signal/noise ratio which makes kinetic analysis using the prelithiation complex more difficult. Additionally, for many lithiation reactions there is overlap of the \(\nu_{C=O}\) signals of the prelithiation complex and lithiated intermediate; this also can provide erroneous and unreliable results when consumption of prelithiation complex is analysed. The overlap between prelithiation complex and lithiated intermediate \(\nu_{C=O}\) signals can be observed in the 3D ReactIR\textsuperscript{TM} trace for N-Boc pyrrolidine 9 in Scheme 2.2.a. The measurement of \(k_{obs}\) for the lithiation using consumption of prelithiation complex and the unreliability of these results is discussed later in this Chapter. It was therefore decided to attempt to obtain \(k_{obs}\) by measuring the consumption of N-Boc heterocycle and applying the pre-equilibrium approximation. As there is a rapid equilibrium reaction that forms between prelithiation complex 190 and the N-Boc heterocycle and s-BuLi/TMEDA, the pre-equilibrium approximation can be applied for this reaction giving a rate equation for the reaction (Equation 2.1).

\[
\frac{-d[N-Boc\ heterocycle]}{dt} = k_2K[N-Boc\ heterocycle][s-BuLi/TMEDA] \quad \text{(Equation 2.1)}
\]

This provides a rate equation where the rate of lithiation is dependent on rate constant \(k_2\), the equilibrium constant between \(189\) and \(190\), \(K\), and the concentrations of the N-Boc heterocycle and s-BuLi/TMEDA reagents. The ReactIR\textsuperscript{TM} traces collected for the s-BuLi/TMEDA lithiations of all N-Boc heterocycle substrates in this study indicated that once the equilibrium is established, both the starting material \(189\) and prelithiation complex \(190\) are consumed at the same rate throughout the lithiation. These identical rates of consumption
for 189 and 190 are observed since, when the prelithiation complex is consumed, the equilibrium will rapidly convert the un-complexed starting material 189 into prelithiation complex 190 to maintain the equilibrium. In addition, no dependency on \([s\text{-}BuLi/TMEDA]\) is observed at any point in the reaction, as first order kinetics are observed for all of the lithiation reactions investigated in this thesis (except for \(N\text{-}t\text{-}Bu\ N\text{-}Boc\) piperazine 66 which appears to display kinetics consistent with two consecutive first order reactions – see section 6.4). This suggests that either 1.3 eq. of \(s\text{-}BuLi/TMEDA\) is a sufficient excess to maintain pseudo-first order conditions or that the pre-equilibrium is responsible for the zero-order kinetics observed with respect to \(s\text{-}BuLi/TMEDA\). Previous kinetic studies by Beak have provided evidence that the \(i\text{-}PrLi/(–)\)-sparteine lithiation of \(N\text{-}Boc\) pyrrolidine 9 has a zero order dependency on the concentration of the alkylolithium/ligand but this study was conducted using larger excesses of alkylolithium (> 10 eq.).\(^{32}\) Therefore, we propose that dependency on \([s\text{-}BuLi/TMEDA]\) can be removed from the pre-equilibrium rate equation for the purpose of obtaining a \(k_{\text{obs}}\) for the lithiation reaction (Equation 2.2).

\[
- \frac{d[N\text{-}Boc\ heterocycle]}{dt} = k_{\text{obs}}[N\text{-}Boc\ heterocycle] \quad \text{(Equation 2.2)}
\]

By using the integrated form of Equation 2.2, a first order kinetic plot can be constructed that allows calculation of \(k_{\text{obs}}\) for lithiation reaction. Plotting the natural logarithm of the absorbance of the un-complexed starting material 189 vs time should provide a linear graph where the gradient is equal to \(−k_{\text{obs}}\). This kinetic analysis was first applied to the lithiation of \(N\text{-}Boc\) pyrrolidine 9 with \(s\text{-}BuLi/TMEDA\) at \(-78 °C\), for which visual inspection had indicated 4 min were required for complete lithiation to occur (Scheme 2.17).

**Scheme 2.17. \(s\text{-}BuLi/TMEDA\) lithiation of \(N\text{-}Boc\) pyrrolidine 9**

The ReactIR\textsuperscript{TM} absorbance data for the consumption of \(N\text{-}Boc\) pyrrolidine 9 (Figure 2.9.a) was used to construct a first order plot for the lithiation of \(N\text{-}Boc\) pyrrolidine 9 (Figure 2.9.b). The ReactIR\textsuperscript{TM} reading at \(t = 0\) s, where addition of \(s\text{-}BuLi\) occurs was not included in the analysis as the period between 0-15 s included the establishment of the equilibrium between
uncomplexed pyrrolidine 9 and prelithiation complex 163. The pre-equilibrium approximation cannot be applied before the equilibrium is established and if these data were included, it would provide an erroneous result. The final 5% conversion for the reaction is discounted as at these low concentrations of N-Boc pyrrolidine 9, the ReactIR™ signal/noise ratio becomes very small, resulting in erroneous data. All of the points excluded from the analysis are highlighted in red in Figure 2.9.a.

Figure 2.9. (a) ReactIR™ data for the consumption of N-Boc pyrrolidine 9 and (b) the resulting first-order kinetic plot for the lithiation of N-Boc pyrrolidine 9. Absorbance is relative to the selected end-point (t = 240 s) of the reaction where absorbance has been normalised to zero

The first order kinetic plot provided a clear linear correlation (R² = 0.991), suggesting that the deprotonation of prelithiation complex 163 occurs via a first order reaction and that the pre-equilibrium approximation can be applied for the lithiation of N-Boc pyrrolidine 9. An observed first order rate constant, kobs = (2.70 ± 0.12) ×10⁻² s⁻¹ was obtained for the s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9. A detailed procedure for the kinetic analysis and the calculation of errors for the lithiation reactions presented is detailed in section 6.2 of this thesis.

A problem that is still encountered when conducting the first order kinetic analysis arises from the fact that an end-point for the reaction is still required. This end-point is required to correct for a non-zero baseline on the ReactIR™ equipment due to the baseline shift that occurs during the lithiation. This gives a similar problem to that posed by the visual inspection method where determination of the end-point is difficult due to the low signal/noise ratio at the end of a reaction on the ReactIR™.
For the kinetic analysis of the s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9 the end-point was selected as 240 s by visual inspection of the raw data, which provided \( k_{\text{obs}} = (2.70 \pm 0.12) \times 10^{-2} \text{ s}^{-1} \) for the lithiation reaction. However, by visual inspection, an end-point of 165 s could also be valid for the reaction if the decreasing absorbance of the last points are due to instrument noise. If the same kinetic analysis is conducted where the reaction is deemed to end at 165 s the value of \( k_{\text{obs}} \) is changed significantly (a 20% difference), with \( k_{\text{obs}} = (3.23 \pm 0.12) \times 10^{-2} \text{ s}^{-1} \) (Figure 2.10). This indicates that inaccurate end-point determination still has a significant effect on the kinetic results for the lithiation of each of the substrates.

![Figure 2.10. (a) ReactIR™ data for the consumption of N-Boc pyrrolidine 9 using a different end-point and (b) the resulting first-order kinetic plot for the lithiation of N-Boc pyrrolidine 9. Absorbance relative to selected reaction endpoint (t = 165 s)](image)

To eliminate this source of error, it was decided to improve upon this kinetic analysis by use of non-linear regression to fit the consumption curve for the N-Boc heterocycle substrate. By fitting a curve to the raw data, this eliminates the need to determine an end-point and so removes this source of error. This curve fitting method also has other advantages including the fact that the lithiation does not have to be complete for extraction of a rate constant so very slow reactions and/or data for incomplete reaction can still be used. Additionally, noisy ReactIR™ data poses less of a problem as the curve can be fit through all the points to average out the noise.

As the lithiation reactions of the N-Boc heterocycles appear to be first order with respect to the substrate, an exponential decay curve can be fitted once the equilibrium has been established after \( t = 0 \) (Equation 2.3). Using a curve fitting algorithm enables the \( k_{\text{obs}} \) for the
lithiation to be determined along with the curve constants A and c which are not required for this analysis.

\[ \text{absorbance of substrate} = Ae^{-k_{\text{obs}}t} + c \]  \hspace{1cm} \text{(Equation 2.3)}

For the lithiation of N-Boc pyrrolidine 9, the curve fitting of the consumption of 9 provided a rate constant \( k_{\text{obs}} = (3.34 \pm 0.15) \times 10^{-2} \text{ s}^{-1} \) (Figure 2.11). The \( k_{\text{obs}} \) obtained by the curve fitting matched more closely the \( k_{\text{obs}} \) from the linear plots when the end-point of the lithiation was deemed to be 165s. This suggests that the changes in the absorbance observed after 165s for the lithiation of N-Boc pyrrolidine 9 likely arise from the instrument rather than the reaction.

For the lithiation of N-Boc pyrrolidine 9 with \( \text{s-BuLi/TMEDA} \), \( t_{1/2} = (20.7 \pm 0.9) \text{ s} \).

A lithiation time can also be predicted for N-Boc pyrrolidine 9 using the \( t_{1/2} \) value as it requires 7 half-lives for 99% conversion to occur. The \( t_{1/2} \) for the \( \text{s-BuLi/TMEDA} \) lithiation

\[ t_{1/2} = \frac{\ln 2}{k_{\text{obs}}} \]  \hspace{1cm} \text{(Equation 2.4)}

**Figure 2.11. Non-linear curve fitting for the s-BuLi/TMEDA lithiation of N-Boc pyrrolidine 9 to obtain \( k_{\text{obs}} \)**

As the \( \text{s-BuLi/TMEDA} \) of lithiation N-Boc pyrrolidine 9 appears displays first order kinetics, the reaction half-life (\( t_{1/2} \)) can be calculated using \( k_{\text{obs}} \) and Equation 2.4. The \( t_{1/2} \) for lithiation provides a more easily comprehendible measure of the rate of reaction than \( k_{\text{obs}} \) and this makes comparison between the reactivities of the different N-Boc heterocycles easier.
of \(N\)-Boc pyrrolidine 9 suggests that 99\% conversion to lithiated intermediate 164 requires 3 min which differs to the 4 min lithiation time measured by visual inspection. For this fast lithiation reaction, the difference between 3 and 4 min is a considerable margin of error. In this case, visual inspection of the ReactIR\textsuperscript{TM} trace overpredicts the lithiation time required for \(N\)-Boc pyrrolidine 9. As discussed previously, when using visual inspection it is easy to overpredict lithiation time as it is hard to accurately locate where both the starting material and lithiation ReactIR\textsuperscript{TM} traces have ceased diverging.

The \(s\)-BuLi/TMEDA lithiation of 4-amino \(N\)-Boc piperidine 168 at \(-78^\circ\)C was subjected to the same kinetic analysis (Scheme 2.18). The non-linear regression provided a first-order decay curve with a very good fit to the ReactIR\textsuperscript{TM} data indicating that the lithiation of piperidine 168 obeys first order kinetics with respect to the \(N\)-Boc heterocycle where \(k_{\text{obs}} = (6.64 \pm 0.16) \times 10^{-4}\) s\(^{-1}\) and \(t_{1/2} = (1040 \pm 20)\) s (Figure 2.12).

Scheme 2.18. \(s\)-BuLi/TMEDA lithiation of 4-amino \(N\)-Boc piperidine 168

$$k_{\text{obs}} = (6.64 \pm 0.15) \times 10^{-4}\text{ s}^{-1}$$

$$R^2 = 0.989$$

Figure 2.12. Non-linear curve fitting for the \(s\)-BuLi/TMEDA lithiation of 4-amino \(N\)-Boc piperidine 168 to obtain \(k_{\text{obs}}\)
By comparing the $t_{1/2}$s of both $N$-Boc pyrrolidine 9 ($t_{1/2} = 20.7 \pm 0.9$ s) and 4-amino $N$-Boc piperidine 168 ($t_{1/2} = 1040 \pm 20$ s), it is evident that piperidine 168 is a much less reactive substrate. The $t_{1/2}$s show that $N$-Boc pyrrolidine 9 is ~50 times more reactive than amino piperidine 168. The time required for 99% conversion for 4-amino $N$-Boc piperidine 168 was also calculated using $t_{1/2}$ which provided a 121 min lithiation time, which is remarkably close to the 120 min lithiation time measured determined by visual inspection.

Finally, the $s$-BuLi/TMEDA lithiations of an additional eight $N$-Boc heterocycles whose reactivities had already quantified using visual inspection were analysed using the kinetic analysis procedure developed. The $s$-BuLi/TMEDA lithiation reactions of each of these eight substrates all displayed first order kinetics with respect to the substrate (see section 6.4 for the kinetics plots for all substrates). Substrates with fast $s$-BuLi/TMEDA lithiations ($< 3$ min) such as $N$-Boc morpholine 169 were not included as these fast reactions would give too few data points for regression analysis and provide results with large margins of error. The kinetically obtained $k_{obs}$, $t_{1/2}$, the lithiation time calculated using $t_{1/2}$ ($t_{\text{lith-half}}$) and the lithiation time obtained by visual inspection ($t_{\text{lith-visual}}$) are presented for each of the eight additional substrates plus $N$-Boc pyrrolidine 9 and piperidine 10 are presented in Table 2.4.
Table 2.4. Half-lives for the s-BuLi/TMEDA lithiations of a selection of 10 N-Boc heterocycle substrates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$k_{obs}$ / s$^{-1}$</th>
<th>$t_{1/2}$ / s</th>
<th>$t_{lith}$-half / min</th>
<th>$t_{lith}$-visual / min</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>$3.79 \times 10^{-2}$</td>
<td>18.3 ± 0.9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>58</td>
<td>$3.72 \times 10^{-2}$</td>
<td>18.7 ± 1.8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>66</td>
<td>$3.34 \times 10^{-2}$</td>
<td>20.7 ± 0.9</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>84</td>
<td>$8.16 \times 10^{-3}$</td>
<td>84.9 ± 4.4</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>66</td>
<td>$6.56 \times 10^{-3}$</td>
<td>105 ± 3</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>39</td>
<td>$2.16 \times 10^{-3}$</td>
<td>320 ± 8</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>34</td>
<td>$1.11 \times 10^{-3}$</td>
<td>624 ± 22</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>32</td>
<td>$1.08 \times 10^{-3}$</td>
<td>642 ± 5</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>168</td>
<td>$6.64 \times 10^{-4}$</td>
<td>1040 ± 20</td>
<td>121</td>
<td>120</td>
</tr>
<tr>
<td>10</td>
<td>$2.17 \times 10^{-4}$</td>
<td>3190 ± 30</td>
<td>372</td>
<td>360$^d$</td>
</tr>
</tbody>
</table>

*a* $k_{obs}$ measured by non-linear regression analysis of N-Boc heterocycle consumption (except 66 which has been modelled as two consecutive first order processes – see experimental)

*b* $t_{1/2}$ calculated using $k_{obs}$

*c* $t_{lith}$-half calculated using $t_{1/2} \times 7$ (as $7 t_{1/2}$s = 99% conversion)

*d* lithiation of N-Boc piperidine 10 may not be complete (see below for discussion)

The rates of lithiation measured using the consumption of the N-Boc heterocycle provided an almost identical reactivity order for all of the heterocycle substrates that was obtained previously using visual inspection. The only difference in the reactivity trend was observed with ketal 34 and 4-phenyl piperidine 32, which the kinetic analysis suggested have almost identical reactivities, whereas visual inspection indicated that ketal 34 was less reactive with a 10 min slower lithiation reaction. The kinetic analysis also allowed some of the subtle differences in reactivity between the fast lithiating heterocycles piperazines 57 and 58 and N-Boc pyrrolidine 9 to be elucidated. Visual inspection indicated that all three substrates
required 4 min for complete lithiation with s-BuLi/TMEDA so no reactivity differences for these substrates could be extracted. However, the kinetic analysis suggests that \( N'\)--Bn piperazine 57 is slightly more reactive than \( N\)-Boc pyrrolidine 9. Unfortunately, where \( N'\)--Me piperazine 58 fits in this reactivity trend could not be further elucidated due to the large margin of error in the \( t_{1/2} \) determined for the lithiation of 58.

It is important to note, however, that these small differences between the lithiation \( t_{1/2} \)s for substrates 9, 57 and 58 may not be of sufficient accuracy to construct a reactivity order for these three substrates with complete certainty. This is first due to the significant amounts of standard error that are provided by the curve-fitting and secondly due to temperature variations that have not been accounted for in this kinetic treatment. These temperature variations occur at the start of the reaction due to addition of the \( s\)-BuLi which is kept at 5 °C (cooling the \( s\)-BuLi further causes the cyclohexane solvent to freeze). It is also likely that the lithiation will be exothermic which may also cause the reaction temperature to increase.

When the temperature of the \( s\)-BuLi/TMEDA lithiation of \( N\)-Boc pyrrolidine 9 was monitored using a thermocouple, an 8°C increase in reaction temperature was observed after the addition of \( s\)-BuLi, after 1 min the reaction temperature had returned to −78 °C.

Achieving complete conversion of \( N\)-Boc piperidine 10 to the trapped products proved to be problematic using \( s\)-BuLi/TMEDA, with starting material still present after the lithiation and trapping reactions. \( \text{Me}_3\text{SiCl} \) was used to trap lithiated piperidine 166 after the ReactIR™ monitoring and this suggested that the \( s\)-BuLi/TMEDA lithiation was complete after 6 h. The \( \text{Me}_3\text{SiCl} \) trapping reaction was allowed 12 h for complete trapping to occur and the ReactIR™ monitoring indicated trapping was complete within 8 h (the ReactIR™ monitoring of trapping reactions is discussed in detail in Chapter 4). The reaction was attempted twice and, after each work-up, \(^1\text{H} \) NMR spectroscopic analysis indicated that a 90:10 ratio of the \( \text{Me}_3\text{SiCl} \)-trapped product 12 and unreacted substrate 10 was present (Scheme 2.19).

**Scheme 2.19. \( s\)-BuLi/TMEDA lithiation and \( \text{Me}_3\text{SiCl} \) trapping of \( N\)-Boc piperidine 10**

\[
\begin{align*}
\text{N} & \quad \text{Boc} \\
\text{10} & \quad \text{Et}_2\text{O}, -78 \degree \text{C}, 6 \text{ h} \\
\text{166} & \quad \text{Li} \\
\text{Me}_3\text{SiCl} & \quad -78 \degree \text{C}, 8 \text{ h} \\
\text{N} & \quad \text{Boc} \\
\text{12} & \quad 90:10 (12:10)
\end{align*}
\]
The ample time allowed for the trapping reaction of lithiated intermediate 166 and the complete trapping observed by ReactIR™ indicated that the lithiation reaction of 10 was likely responsible for the incomplete conversion observed in the final products. There are two possible causes for the incomplete conversion during the lithiation. The first is that the lithiation reaction is incomplete when the electrophile is added, so unreacted piperidine 10 starting material remains. Otherwise, the recovered 10 may result from instability of lithiated intermediate 166 during the 6 h lithiation which decomposes back to the starting material; this decomposition could involve deprotonation of the Et₂O solvent by the reactive lithiated intermediate 166. Further analysis of the non-linear regression kinetic analysis applied to the consumption of piperidine 10 indicated that the reaction may not be complete after 6 h (Figure 2.13). The kinetic analysis of the s-BuLi/TMEDA lithiation of N-Boc piperidine 10 suggested that it was not complete after 6 h and that 99% conversion required a lithiation time of 6.25 h.

![Figure 2.13. Non-linear regression to obtain $k_{obs}$ for the s-BuLi/TMEDA lithiation of N-Boc piperidine 10 with extrapolated curve of best fit to determine lithiation end-point](image)

This again highlights the difficulty in determining an end-point for such a slow reaction by visual inspection of the ReactIR™ data. However, the curve of best fit for the s-BuLi/TMEDA lithiation of piperidine 10 indicated that 98% conversion is expected at 6 h but only 90% conversion was observed in the final crude product. This suggested that the instability of the lithiated intermediate may be a problem with the long 6 h lithiation of N-Boc piperidine 10.
An attempt to measure the $t_{1/2}$S for the lithiation of the 10 N-Boc heterocycles by non-linear regression analysis of the consumption of the prelithiation complex ($t_{1/2}$-prelith) was also carried out. For comparative purposes, the $t_{1/2}$S calculated by consumption of prelithiation complex, $t_{1/2}$-prelith and the $t_{1/2}$ calculated by consumption of the N-Boc heterocycle, $t_{1/2}$-substrate are presented in Table 2.5. The $t_{1/2}$S obtained by non-linear regression of the consumption of the prelithiation complexes ($t_{1/2}$-prelith) did differ somewhat from the $t_{1/2}$S obtained by non-linear regression of the N-Boc heterocycle consumption ($t_{1/2}$-substrate).

Table 2.5. Half-lives determined by consumption of N-Boc heterocycle and prelithiation complex consumption for the s-BuLi/TMEDA lithiations of a selection of 10 N-Boc heterocycle substrates

<table>
<thead>
<tr>
<th>Compound</th>
<th>$t_{1/2}$-prelith / s</th>
<th>$t_{1/2}$-sub / s</th>
<th>$t_{1/2}$-prelith / min</th>
<th>$t_{1/2}$-sub / min</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>15.2 ± 1.6</td>
<td>9.3 ± 6.6</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>58</td>
<td>9.3 ± 6.6</td>
<td>17.8 ± 0.5</td>
<td>1</td>
<td>66 ± 3</td>
</tr>
<tr>
<td>9</td>
<td>17.8 ± 0.5</td>
<td>101 ± 4</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>84</td>
<td>101 ± 4</td>
<td>65.5 ± 3.7</td>
<td>12</td>
<td>65.5 ± 3.7</td>
</tr>
<tr>
<td>66</td>
<td>65.5 ± 3.7</td>
<td>10 ± 4</td>
<td>2</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>39</td>
<td>18.3 ± 0.9</td>
<td>18.7 ± 1.8</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>34</td>
<td>20.7 ± 0.9</td>
<td>84.9 ± 4.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>32</td>
<td>84.9 ± 4.4</td>
<td>105 ± 3</td>
<td>10</td>
<td>105 ± 3</td>
</tr>
<tr>
<td>168</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
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</tr>
<tr>
<td>4</td>
<td>4</td>
<td>15</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>320 ± 8</td>
<td>642 ± 5</td>
<td>1040 ± 20</td>
<td>3190 ± 30</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>73</td>
<td>121</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>282 ± 10</td>
<td>310 ± 19</td>
<td>806 ± 24</td>
<td>2850 ± 30</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>36</td>
<td>94</td>
<td>333</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>120</td>
<td>360c</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>75</td>
<td>121</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>282 ± 10</td>
<td>310 ± 19</td>
<td>806 ± 24</td>
<td>2850 ± 30</td>
<td></td>
</tr>
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<td>45</td>
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<td>120</td>
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<td></td>
</tr>
<tr>
<td>OTIPS</td>
<td>624 ± 22</td>
<td>1040 ± 20</td>
<td>3190 ± 30</td>
<td></td>
</tr>
<tr>
<td>N-Boc</td>
<td>75</td>
<td>121</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>N-Boc</td>
<td>121</td>
<td>372</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>282 ± 10</td>
<td>310 ± 19</td>
<td>806 ± 24</td>
<td>2850 ± 30</td>
</tr>
<tr>
<td>N-Boc</td>
<td>94</td>
<td>333</td>
<td>333</td>
<td></td>
</tr>
<tr>
<td>N-Boc</td>
<td>120</td>
<td>360c</td>
<td>360c</td>
<td></td>
</tr>
</tbody>
</table>

* $t_{1/2}$ measured by non-linear regression analysis of N-Boc heterocycle consumption
* $t_{1/2}$ measured by non-linear regression analysis of prelithiation complex consumption
* Lithiation of N-Boc piperidine 10 may not be complete
* Lithiation of 66 modelled as two consecutive first order processes (see experimental)
For most of the substrates, an identical reactivity order was obtained using the $t_{1/2}$ values calculated by both analysis of substrate consumption and prelithiation complex consumption. However, there were a few outlying results that did not follow the trends observed by both visual inspection and kinetic analysis of the $N$-Boc heterocycle consumption. For example, the reactivity order of bicyclic pyrrolidine 84 and $N'$-t-Bu piperazine 66 is swapped when $t_{1/2}$ are measured using the consumption of prelithiation complex. In addition, the $t_{1/2}$ measured for the lithiation of 4-ketal piperidine 34 using prelithiation complex consumption ($t_{1/2}$-prelith = 310 ± 19 s) is nearly half that measured when $t_{1/2}$ is measured by the consumption of the substrate ($t_{1/2$-substrate} = 624 ± 22 s). As mentioned previously, these unreliable results provided by the measurement of prelithiation complex consumption likely arise due to the overlap of signals for prelithiation complex and lithiated intermediate. This overlap will affect the gradient of the prelithiation complex signal during the reaction and provide unreliable data for regression analysis. Also, the smaller intensity of the $\nu_{C=O}$ signal of the prelithiation complex results in unreliable rate data as the signal/noise ratio is much smaller than that of the uncomplexed $N$-Boc heterocycle $\nu_{C=O}$ signal. For these reasons, we believe that the $t_{1/2}$ values calculated from the consumption of $N$-Boc heterocycle provide the most reliable reactivity order; hence it is these $t_{1/2}$ values that have been used when correlating the results with the DFT reactivity study described in Chapter 3.

Next, the s-BuLi/DPE 177 lithiation reactions of $N$-Boc heterocycles presented in Table 2.6, were also subjected to the same kinetic analysis procedure. Unfortunately, the s-BuLi/DPE 177 lithiations of $N$-Boc morpholine 169 and 4-chloro and 4-$O$-trisyl piperidines 48 and 167 were too rapid for sufficient ReactIR™ data to be collected for kinetic analysis. Even though the s-BuLi/DPE 177 lithiation of 4-chloro piperidine 48 was 5 min, ReactIR data was only collected every minute (due to the older iC10 apparatus that was used) so too few points were recorded for a reliable kinetic analysis. Therefore, non-linear regression analysis was only carried out for the s-BuLi/DPE 177 lithiations of $N$-Boc pyrrolidine 9 and $N'$-Me $N$-Boc piperazine 58. Close fitting, first order decay curves were obtained for the s-BuLi/DPE 177 lithiations of both substrates (Figure 2.14), confirming that the reaction is first order with respect to the $N$-Boc heterocycle.
The $t_{1/2}$s, for each of the s-BuLi/DPE 177 lithiation reactions, calculated using the extracted from the kinetic analysis, are presented in Table 2.6 along with the lithiation time calculated using $t_{1/2}$ ($t_{\text{lith-half}}$) and the lithiation time obtained by visual inspection ($t_{\text{lith-visual}}$).

**Table 2.6. Half-lives for the s-BuLi/DPE 177 lithiations of N'-Me N-Boc piperazine 58 and N-Boc pyrrolidine 9**

<table>
<thead>
<tr>
<th></th>
<th>58</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ / s</td>
<td>282 ± 4 s</td>
<td>680 ± 12 s</td>
</tr>
<tr>
<td>$t_{\text{lith-half}}$ / min</td>
<td>33</td>
<td>80</td>
</tr>
<tr>
<td>$t_{\text{lith-visual}}$ / min</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

The $t_{1/2}$s obtained for the s-BuLi/DPE 177 lithiation of N-Boc pyrrolidine 9 and N'-Me N-Boc piperazine 58, indicated that piperazine 58 is over two times faster to lithiate than N-Boc pyrrolidine 9 with $t_{1/2}$ of 282 s and 680 s respectively. This two-fold increase in reactivity is not observed for these two substrates with s-BuLi/TMEDA, which provided very similar $t_{1/2}$s of 18.7 and 20.7 s for heterocycles 58 and 9 respectively. It is uncertain whether the rapid reaction rates make comparisons of $t_{1/2}$ unreliable for rapid lithiations or whether subtle reactivity difference are present with the s-BuLi/DPE 177 and s-BuLi/TMEDA lithiating complexes. The 33 min lithiation time estimated using $t_{1/2}$ for the lithiation of N'-Me N-Boc piperazine 58 closely matched the 30 min lithiation time measured.
by visual inspection. However, the estimated 80 min $s$-BuLi/DPE 177 lithiation time for $N$-Boc pyrrolidine 9 differed significantly to the 46 min lithiation time obtained using visual inspection. This again highlights how unreliable measuring the rate of lithiation of substrates can be using visual inspection.

In summary, the kinetic analysis provides a more reliable and precise method to determine the reactivity of the lithiation reactions of different $N$-Boc heterocycle substrates. As discussed, the lithiation reactions of the $N$-Boc heterocycle substrates can be modelled as first order reactions which allows an observed rate constant ($k_{obs}$) to be obtained by fitting an exponential decay curve ReactIR™ absorbance of the uncomplexed substrate. The $s$-BuLi/TMEDA reactivity series of the 10 substrates studied using the kinetic analysis was in good agreement with the reactivity series obtained by visual inspection and only measurement of the reactivity of ketal 34 provided a differing result. The kinetic analysis was particularly useful to elucidate reactivity trends for $N$-Boc heterocycle substrates with fast lithiation reactions. For example, the kinetically obtained $t_{1/2}$s were able to identify that $N'$-Bn piperazine 57 is more reactive than $N$-Boc pyrrolidine 9 using $s$-BuLi/TMEDA lithiating conditions.
2.4 Conclusions and Future Work

In this chapter, \textit{in situ} ReactIR\textsuperscript{TM} monitoring has provided a reactivity series for 14 $N$-Boc heterocycle substrates with differing ring sizes, heteroatoms in the ring and substituents on the rings. Both $s$-BuLi/TMEDA and $s$-BuLi/DPE lithiating conditions provided the same reactivity series for the $N$-Boc heterocycles studied, with the $s$-BuLi/DPE conditions being particularly useful to elucidate the reactivity of fast reacting substrates such as $N'$-Bn piperazine 57 and $N$-Boc pyrrolidine 9. Furthermore, a more reliable and precise method to determine the reactivity of the substrates with $s$-BuLi/TMEDA was developed which involved kinetic analysis of the lithiation reaction. This kinetic analysis has also aided in elucidating some of the reactivity trends between the fast lithiating substrates. The more precise measure of reactivity afforded by the kinetic analysis will be beneficial when the experimental reactivities and computationally predicted reactivities for substrates are compared in Chapter 3. By combining the reactivity data for the $s$-BuLi/TMEDA and $s$-BuLi/DPE 177 conditions and the kinetic analysis results, a reactivity series for the 14 $N$-Boc heterocycle substrates studied can be constructed (Figure 2.15).

![Figure 2.15. Final reactivity series of the 14 $N$-Boc heterocycle substrates studied in this thesis using $s$-BuLi/TMEDA and $s$-BuLi/DPE 177 lithiating conditions](image)

The use of $s$-BuLi/(-)-sparteine provided some significant differences in the reactivity series of the fast lithiating substrates compared to those obtained with both $s$-BuLi/TMEDA and $s$-BuLi/DPE. It was rationalised that the outlying reactivities displayed by 4-chloro piperidine 48 and $4-O$-trisyl piperidine 167 with $s$-BuLi/(-)-sparteine, could be due to the combination...
of the enantioselective lithiation and slow rotamer interconversion at −78 °C. A combination of slow rotamer interconversion and a slow rate of N-inversion/ring flipping may also be the reason that N'-Me and N'-Bn piperazines 58 and 57 also displayed lower than expected reactivities with s-BuLi/(−)-sparteine. This effect could be probed further by investigating whether the rotamer interconversion does occur at −78 °C for the 4-substituted piperidines and piperazines using VT-NMR. However, the rates of rotamer interconversion obtained may not be applicable as the N-Boc heterocycle/s-BuLi/(−)-sparteine prelithiation complex could have a different barrier for rotation of the carbamate to the uncomplexed substrate. Another possible experiment that could confirm whether the enantiopure nature of ligand is responsible for the outlying reactivity of substrates would be to conduct the lithiations with (±)-sparteine. If the s-BuLi/(±)-sparteine reactions were faster, giving similar results to those obtained with s-BuLi/DPE 177, this would indicate the enantioselectivity of the lithiation may be responsible for the retardation of the lithiation.

The more detailed mathematical kinetic analysis of the lithiation reactions of N-Boc heterocycles presented in section 2.4 was developed in the latter stages of this study, this meant that further investigation and elucidation of the reaction kinetics was not possible. Our current kinetic model for the lithiation reaction assumes that the lithiation is first order with respect to the uncomplexed N-Boc heterocycle; the consumption of the substrate does appear to exhibit a first order decay suggesting that this is the case. However, further experiments could be conducted to conclusively confirm whether the lithiation reaction does indeed show zero order kinetics with respect to the concentration of s-BuLi/diamine. Repeating the lithiations of N-Boc heterocycles with varying concentrations of s-BuLi/diamine would provide clear evidence whether there is zero order response to the concentration of s-BuLi/diamine used. Additionally, the aggregation state of the alkylthium and any aggregation state changes during the lithiation reaction has not been investigated. At present, it is assumed that all alkylthium species are in a monomeric form due to the stoichiometric amounts of diamine ligand added but it possible that these alkylthium species exist as aggregates in the reaction. A better understanding of the alkylthium aggregates, using methods such as Li NMR, may provide a more accurate kinetic model for these lithiation reactions.

Further development of the kinetic analysis methodology used in this investigation may also be able to provide more reliable and accurate values of \( k_{\text{obs}} \) for particularly fast or slow
lithiating N-Boc heterocycles. For fast lithiating substrates such as N-Boc morpholine 169, it may be possible to use the rapid-collect feature on the newer ReactIR™ apparatus which allows a reading to be taken every second. This was used in this project to investigate the fast equilibrium between the un-complexed heterocycle substrate and prelithiation complex (see Scheme 2.3). Due to the more significant noise present in the rapid-collect ReactIR™ trace it was not used to monitor the fast lithiation reactions as determining an end-point would be difficult by visual inspection. However, with the recently developed kinetic analysis method, a curve could be fit to these data which would be less affected by the more significant amount of noise present. Similarly, kinetic analysis using curve fitting may enable $k_{\text{obs}}$ and $t_{1/2}$ values to be obtained for slow lithiation reactions as the curve fitting does not require the reactions to reach completion. This would be particularly useful as maintaining a temperature of −78 °C for over 10 h is problematic when monitoring slow lithiation reactions by ReactIR™. An interesting substrate to study would be the 7-membered nitrogen heterocycle, N-Boc azepane 192 (Figure 2.16), which in-group data suggests is even less reactive than N-Boc piperidine 10. The s-BuLi/TMEDA lithiation of azepane 192 at −50 °C required 2 h for complete lithiation whereas piperidine 10 only required 35 min at −50 °C. This indicates that azepane 192 is significantly less reactive than piperidine 10 likely due to the conformational flexibility of the large 7-membered heterocycle.

![Figure 2.16. N-Boc azepane 192](image_url)
Chapter 3: Computational DFT Modelling of the α-Lithiation of N-Boc Heterocycles

The DFT modelling of the α-lithiation of N-Boc heterocycles has previously been reported by Wiberg and Bailey,\textsuperscript{34,85,89} as discussed in section 1.4. However, these previous investigations were primarily focused upon reproducing the enantioselectivity observed when a chiral diamine such as (−)-sparteine, was employed in the lithiation. The computational study reported in this Chapter focuses on exploring the differences in reactivity observed when different diamines and substrates are used in the lithiation reaction.

Previous literature precedent and the kinetic analysis of the α-lithiation reaction presented in Chapter 2 indicate that deprotonation in the prelithiation complex is the rate determining step.\textsuperscript{32,72} Therefore, in order to calculate the activation free energy barrier (\(\Delta G^\ddagger\)) for these α-lithiation reactions, it is this step that needs to be modelled. This requires the ground state prelithiation complex 193 and transition state for the deprotonation 194 for the α-lithiation of the N-Boc heterocycle to be constructed and optimised (Figure 3.1).

\[ \text{N-Boc} + \text{s-BuLi/TMEDA} \rightarrow \text{prelithiation complex 193} \]

\[ \begin{align*}
\text{trans} & \quad \text{transition state 194} \\
\text{lithiated} & \quad \text{intermediate}
\end{align*} \]

\[ \Delta G^\ddagger \]

Figure 3.1. Partial reaction coordinate diagram for the RLi/diamine α-lithiation reaction of N-Boc heterocycles
3.1 Computational DFT Modelling of the $\alpha$-Lithiation Reactions of $N$-Boc Pyrrolidine and $N$-Boc Piperidine

First, the $\alpha$-lithiation reactions of both $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10 were modelled and this required the optimisation of prelithiation complexes and transition states for each of the substrates. The enantioselective $\alpha$-lithiation reactions of $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10 with $i$-PrLi/($-$)-sparteine have been modelled previously by Wiberg and Bailey (see section 1.4). 34,85,86 Their computational study also optimised prelithiation complexes and deprotonation transition states for the $i$-PrLi/($-$)-sparteine lithiation of 9 and 10. Wiberg and Bailey’s work provided useful information about the expected geometries of the prelithiation complex and transition states for the lithiation which assisted the construction of initial geometries for our computational study.

For the modelling of the $\alpha$-lithiation reactions of $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10, $i$-PrLi was used as the alkyllithium and di-methyl bispidine 195 as the diamine (Scheme 3.1). As with Wiberg and Bailey’s method, $i$-PrLi was chosen as a model of $s$-BuLi as $i$-PrLi lacks a stereogenic centre. The absence of the stereocentre simplifies the calculations by removing the complication caused by diastereomeric prelithiation complexes and transition states. Di-methyl bispidine 195 was selected as it has a simple and rigid structure making optimisation faster and easier. It was expected that a flexible diamine such as TMEDA would provide a shallow potential energy surface making the location of minima more complex and time consuming. However, later in our computational study it was found that TMEDA could be modelled as the diamine ligand without adding significant computational expense to the optimisation process with DFT modelling. The DFT modelling of the $\alpha$-lithiation of $N$-Boc heterocycles with TMEDA and other diamines will be discussed later in this chapter.
Scheme 3.1. Reaction conditions used to model the α-lithiation reactions of N-Boc pyrrolidine 9 and N-Boc piperidine 10

All calculations were conducted in the gas phase and the enthalpies ($H$) and free energies ($G$) calculated by frequency analysis were corrected to $-78 \, ^\circ C$, as this is the temperature at which the lithiation reactions were conducted experimentally. These conditions were used as the standard for all of the modelling carried out in this computational reactivity study. Solvent corrections were not applied to the calculations but are discussed briefly in section 3.2.4. DFT scaling factors were not required as the calculated energies were only used relative to one another. i.e. only the trends between the experimentally determined rate of reaction ($k_{\text{obs}}$) and the calculated activation energies for the lithiation of the substrates ($\Delta G^\ddagger$) were compared. Scaling factors are only required when absolute activation energies comparable to experimentally determined activation energies are needed. All geometry optimisation and frequency analysis calculations were carried out using GAUSSIAN 09.

For the α-lithiation reactions of N-Boc pyrrolidine 9 and N-Boc piperidine 10, prelithiation complexes and transition states were optimised using two different computational methods: the *ab-initio* post-Hartree-Fock MP2 method and DFT. When the optimisations of geometries was carried out using DFT, two different hybrid functionals were used, B3LYP$^{113-115}$ and Truhlar’s M06 Minnesota functional.$^{116}$ B3LYP is a well-established DFT functional that is commonly used for the modelling of organic systems.$^{117}$ The M06 functional is a more recently developed DFT functional which has been shown to better describe dispersion interactions,$^{118}$ the inaccurate description of dispersion interactions is a common pitfall when chemical systems are modelled using DFT.$^{119}$ The DFT modelling was conducted with two functionals to allow any outliers that may have resulted from the fitting of functional to be identified. Additionally, it was envisaged that the M06 DFT functional may provide a better description of the system as it more accurately accounts for dispersion interactions.
Both the DFT and MP2 optimisation methods were used within a moderately sized Pople 6-31G(d) basis set. This size of basis set was selected to provide sufficiently flexible description of orbitals without making the computational expense of the calculations prohibitively large. The systems modelled in this study are relatively large (~80 atoms) which prohibits larger basis sets being used for optimisation as the additional basis functions on each atom would increase the complexity and time required for the calculation. For both DFT functionals, a larger than default, pruned (99,950) integral grid was used (GAUSSIAN 09 keyword Int=UltraFine).

Both the MP2 and DFT modelling with B3LYP and M06 functionals provided nearly identical optimised geometries for both the prelithiation complex and transition state for the $\alpha$-lithiation of $N$-Boc pyrrolidine 9. The geometries optimised for $N$-Boc pyrrolidine 10 using B3LYP/6-31G(d) are shown in Figure 3.2.

![Figure 3.2. B3LYP/6-31G(d) geometries for the prelithiation complex (a) and transition state (b) of the $N$-Boc pyrrolidine 9 deprotonation (C and H atoms of the di-methyl bispidine ligand 195 are hidden for clarity)](image)

To confirm that the saddle point located for the $\alpha$-lithiation of $N$-Boc pyrrolidine 9 was the correct transition state, corresponding to the deprotonation of the nitrogen $\alpha$-proton, an Intrinsic Reaction Coordinate (IRC) calculation was also conducted. The IRC calculation followed the reaction coordinate in both a forward (towards the lithiated intermediate product 196) and reverse (towards the prelithiation complex) direction from the transition
This calculation was conducted at a B3LYP/6-31G(d) level of theory using the optimised transition state geometry obtained when the lithiation of N-Boc pyrrolidine 9 was modelled. As expected, the reaction coordinate converged toward prelithiation complex in the reverse direction and the forward direction converged toward the lithiated intermediate 196 (Figure 3.3). This confirmed that the correct transition state for the α-lithiation of N-Boc pyrrolidine 9 had been located.

![Reaction Coordinate and Geometries](image)

**Figure 3.3.** B3LYP/6-31G(d) calculated reaction coordinate for the i-PrLi/di-methyl bispidine 195 lithiation of N-Boc pyrrolidine 9 (a) and an output geometry from the forward path showing formation of the lithiated intermediate 196 and i-propane (b)

Once prelithiation complex and transitions state geometries had been optimised for the α-lithiation reaction of N-Boc pyrrolidine 9, the activation free energy for the lithiation (ΔG‡) was calculated using both the MP2 and DFT methods (Table 3.1). The calculated ΔG‡ values were corrected to −78 °C to replicate the temperature at which the lithiation reactions are carried out experimentally. The magnitudes of the ΔG‡ values obtained were appropriate for a reaction that occurs at −78 °C. The ΔG‡ values obtained for the reaction from the DFT functionals and MP2 were similar, suggesting that DFT does provide a sufficient description for the interactions occurring in the reaction and a more thorough MP2 treatment may not be required for this system.
Table 3.1. Activation free energies ($\Delta G^\ddagger$) calculated for the lithiation of N-Boc pyrrolidine 9

<table>
<thead>
<tr>
<th>Method</th>
<th>$\Delta G^\ddagger$ / kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP/6-31G(d)</td>
<td>13.77</td>
</tr>
<tr>
<td>M06/6-31G(d)</td>
<td>13.63</td>
</tr>
<tr>
<td>MP2/6-31G(d)</td>
<td>13.87</td>
</tr>
</tbody>
</table>

Next, the $i$-PrLi/di-methyl bispidine 195 lithiation of the corresponding 6-membered heterocycle, N-Boc piperidine 10, was modelled with the same MP2 and DFT methods that were used to model the lithiation of N-Boc pyrrolidine 9. Optimisation of prelithiation complexes and transition states for the lithiation of N-Boc piperidine 10 was more complex, as two possible reaction pathways were found. These reaction pathways differed by the location of the $i$-PrLi during the reaction. In one of the reaction pathways the $i$-PrLi straddles the piperidine ring adjacent to the $\alpha$-proton that is deprotonated - this is denoted as ‘top’ deprotonation (Figure 3.4.a). The other reaction path places the $i$-PrLi reagent to the side of the piperidine ring again adjacent to the $\alpha$-proton that is deprotonated - this is denoted as ‘side-on’ deprotonation’ (Figure 3.4.b).

Figure 3.4. Prelithiation complexes for the ‘top’ deprotonation (a) and ‘side-on’ deprotonation (b) of N-Boc piperidine 10 (C and H atoms of the di-methyl bispidine ligand 195 are hidden for clarity)
Geometries for the prelithiation complex and transition state for the ‘side-on’ and ‘top’ deprotonation of N-Boc piperidine 10 were optimised using MP2 and the B3LYP and M06 DFT functionals. All three methods provided very similar optimised geometries for both faces of attack from the \( i \)-PrLi. In all of the calculations, the experimentally observed equatorial lithiation was lowest in energy. The B3LYP/6-31G(d) optimised geometries of the prelithiation complex and transition state for the ‘side-on’ and ‘top’ deprotonation of N-Boc piperidine 10 are presented in Figures 3.5 and 3.6. For the transition states located for both the ‘side-on’ and ‘top’ deprotonation pathways, IRC calculations were carried out to ensure that the saddle point corresponded to the lithiation, as described previously for N-Boc pyrrolidine 9. These IRC calculations confirmed that the saddle points located did indeed correspond to the transition state for the \( \alpha \)-lithiation of N-Boc piperidine 10 (reaction coordinate diagrams are included in the experimental data in section 6.5).

![Figure 3.5](image1.png)

Figure 3.5. B3LYP/6-31G(d) optimised geometries for the prelithiation complex (a) and transition state (b) for the ‘side-on’ deprotonation of N-Boc piperidine 10 (C and H atoms of the di-methyl bispdine ligand 195 are hidden for clarity)
Figure 3.6. B3LYP/6-31G(d) optimised geometries for the prelithiation complex (a) and transition state (b) for the ‘top’ deprotonation of N-Boc piperidine 10 (C and H atoms of the di-methyl bispidine ligand 195 are hidden for clarity)

Activation free energies ($\Delta G^\ddagger$) were also calculated for both the ‘side-on’ and ‘top’ deprotonation of N-Boc piperidine 10 with the three computational methods (Table 3.2). Interestingly, the calculated $\Delta G^\ddagger$ values indicated that the MP2 and the M06 DFT methods favoured the ‘top’ attack of $i$-PrLi whereas the B3LYP DFT functional favoured the ‘side-on’ attack.

Table 3.2. Activation free energies ($\Delta G^\ddagger$) calculated for the $i$-PrLi/di-methyl bispidine 195 lithiation of N-Boc piperidine 10

<table>
<thead>
<tr>
<th>Method</th>
<th>Face of Attack</th>
<th>$\Delta G^\ddagger$ /kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP/6-31G(d)</td>
<td>Side-on</td>
<td>16.11</td>
</tr>
<tr>
<td></td>
<td>Top</td>
<td>16.39</td>
</tr>
<tr>
<td>M06/6-31G(d)</td>
<td>Side-on</td>
<td>15.34</td>
</tr>
<tr>
<td></td>
<td>Top</td>
<td><strong>14.85</strong></td>
</tr>
<tr>
<td>MP2/6-31G(d)</td>
<td>Side-on</td>
<td>15.58</td>
</tr>
<tr>
<td></td>
<td>Top</td>
<td><strong>15.33</strong></td>
</tr>
</tbody>
</table>

Comparison of the activation energies calculated for both N-Boc pyrrolidine 9 and N-Boc piperidine 10 with all methods indicated a significant difference in the energy barriers for
the lithiation of the two substrates. For example, using B3LYP/6-31G(d) the lithiation of \( N\)-Boc pyrrolidine 9 showed \( \Delta G^\ddagger = 13.77 \) kcal mol\(^{-1}\) whereas for \( N\)-Boc piperidine 10 it was found that \( \Delta G^\ddagger = 16.11 \) kcal mol\(^{-1}\). This significant 2.34 kcal mol\(^{-1}\) \( \Delta \Delta G^\ddagger \) suggests that \( N\)-Boc pyrrolidine 9 should be substantially more reactive than \( N\)-Boc piperidine 10 at –78 °C. This is supported by the experimental ReactIR\textsuperscript{TM} determined reactivity series, where \( N\)-Boc pyrrolidine 9 (\( t_{1/2} = 20.7 \pm 0.9 \) s) was significantly more reactive than \( N\)-Boc piperidine 10 (\( t_{1/2} = 3190 \pm 30 \) s).

We postulate that the significant difference in the free energies of activation for the lithiation of \( N\)-Boc pyrrolidine 9 and \( N\)-Boc piperidine 10 result from differences in steric interactions due to the differing conformations of the 5- and 6-membered rings. Inspection of the non-bonding distances between \( i\)-PrLi, di-methyl bispidine 195 and the \( N\)-Boc heterocycle (9 or 10) in the B3LYP optimised transition states did offer some differences in non-bonding distances between the protons on the \( N\)-Boc heterocycle and \( i\)-PrLi. For the ‘side-on’ lithiation of \( N\)-Boc piperidine 10, there was a smaller non-bonding distance between the \( i\)-PrLi protons and the axial \( \alpha\)-proton on the \( N\)-Boc piperidine 10 which is not deprotonated (2.438 Å) (Figure 3.7). It is possible that steric repulsion between the axial \( \alpha\)-proton and the \( i\)-PrLi could raise the energy for deprotonation of \( N\)-Boc piperidine 10. For the ‘top’ lithiation of \( N\)-Boc piperidine 10 the distance between the axial \( \alpha\)-proton and the \( i\)-PrLi protons are larger (3.099 and 3.412 Å) so this steric effect is likely not to be responsible for the higher energy required for lithiation. However, there are smaller distances between the \( \beta\)-protons of the carbamate and the protons of \( i\)-PrLi in the ‘top’ lithiation transition state of \( N\)-Boc piperidine (2.470 and 2.346 Å) than those in the transition state for lithiation of \( N\)-Boc pyrrolidine 9 (2.658 and 2.349 Å). The closer proximity of the \( i\)-PrLi to these \( \beta\)-protons for the ‘top’ lithiation of \( N\)-Boc piperidine 10 may be responsible for the larger calculated energy barrier of the ‘top’ lithiation compared to that of \( N\)-Boc pyrrolidine 9.
Figure 3.7. Non-bonding distances between \( i \)-PrLi and \( N \)-Boc heterocycle for the ‘side-on’ lithiation of \( N \)-Boc piperidine 10 (a), ‘top’ lithiation of \( N \)-Boc piperidine 10 (b) and lithiation of \( N \)-Boc pyrrolidine 9 (c) (C and H atoms of the di-methyl bispidine ligand 195 are hidden for clarity)

The results in Table 3.2 also indicate that the modelling of the lithiation of \( N \)-Boc piperidine 10 with MP2 and DFT provided \( \Delta G^\ddagger \) values for the lithiation with a larger variance to those calculated for \( N \)-Boc pyrrolidine 9. For the \( \alpha \)-lithiation of \( N \)-Boc pyrrolidine 9, the three computational methods used provided \( \Delta G^\ddagger \) values for the reaction that varied by ~0.1-0.2 kcal mol\(^{-1}\). However, for the lithiation of \( N \)-Boc piperidine 10 these calculated \( \Delta G^\ddagger \) varied more significantly by ~0.5-1.3 kcal mol\(^{-1}\). The difference between the \( \Delta G^\ddagger \) values calculated
by MP2 and B3LYP was 0.78 kcal mol$^{-1}$ and between MP2 and M06 was 0.48 kcal mol$^{-1}$. Clearly, the activation energies calculated with both DFT functionals deviate from the energy calculated using MP2 and this may suggest that dispersion interactions are more significant for the deprotonation of $N$-Boc piperidine 10 than $N$-Boc pyrrolidine 9, since MP2 should describe dispersion interactions better than DFT.

However, optimisation of the prelithiation complex and transition states for the lithiation of $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10 at the MP2 level of theory proved difficult. These MP2 calculations are more computationally expensive due to inclusion of electron correlation effects by perturbation of the HF Hamiltonian. HF and DFT calculations scale to $N^4$ (where $N$ is number of basis functions) whereas MP2 calculations scale to $N^5$ due to the addition of correlation corrections. The calculations also proved difficult due to the flat potential energy surfaces of both the prelithiation complex and transition state and required analytical calculation of the second derivatives of energy (Hessian matrix) for each iteration of the geometry optimisation (using the Opt=CalcAll keyword in GAUSSIAN 09). Calculation of the second derivatives of energy during every step of the optimisation made the calculation extremely computationally expensive. The MP2 optimisation of the prelithiation complex and transition state for the $\alpha$-lithiation of $N$-Boc pyrrolidine 9 required nearly one month of calculation time on an 8-core CPU. For comparison, the same optimisation using the B3LYP or M06 DFT functional required only two days using 2 CPU cores. Therefore, optimisation using the MP2 method was used only for $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10 due to the large computational expense involved and is not used in any of the modelling discussed further in this Chapter.
3.2 Use of DFT to Explore the $\alpha$-Lithiation for a Range of $N$-Boc Heterocycles

3.2.1 Modelling the $\alpha$-lithiation of $N$-Boc heterocycles to probe reactivity

With the modelling of the $i$-PrLi/di-methyl bispidine 195 $\alpha$-lithiations of both $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10 complete, we next focussed on modelling the $\alpha$-lithiation reactions of a wider range of $N$-Boc heterocycles. To this end, the $i$-PrLi/di-methyl bispidine 195 lithiation reactions of the 14 substrates included in the experimental $s$-BuLi/TMEDA reactivity study in section 2.1 were modelled with DFT. The structures of these 14 $N$-Boc heterocycles are shown in Figure 3.8.

$\alpha$-Lithiation reactions of each $N$-Boc heterocycle were modelled using the B3LYP and M06 DFT functionals used previously. It was envisaged that DFT modelling might be able to reproduce the reactivity differences observed experimentally with the different $N$-Boc heterocycles, as it had done for the $\alpha$-lithiations of $N$-Boc pyrrolidine 9 and $N$-Boc piperidine 10. This would provide useful information about whether the structural features of the substrates were responsible for the differences in the rates of lithiation observed.

The B3LYP optimised geometries of the transition states for the $\alpha$-lithiation of the 12 additional $N$-Boc heterocycles are presented in Figure 3.9. For the lithiation of 4-$O$-trisyl $N$-Boc piperidine 167, the lithiation of a similar $N$-Boc heterocycle 4-$O$-mesyl piperidine 197 was modelled instead, to reduce the computational complexity of the calculation. Both ‘side-
on’ and ‘top’ faces of attack for the \textit{i}-Pr\textit{Li}/di-methyl bispidine 195 were modelled for all of the six-membered heterocycles, which included \textit{N}-Boc piperidine 10 (discussed earlier), \textit{N}-Boc morpholine 169, 4-substituted piperidines 32, 34, 39, 48, 168, 197 and piperazines 57, 58 and 66. Only the optimised geometry for the lowest energy type of deprotonation is included in Figure 3.9.

Figure 3.9. \(\alpha\)-Lithiation transition state geometries for the 12 additional \textit{N}-Boc heterocycles (excluding \textit{N}-Boc pyrrolidine 9 and \textit{N}-Boc piperidine 10 – see Figure 3.8), the preferred type of deprotonation for 6-membered rings ‘side-on’ or ‘top’ is noted next to the compound number.
\[ \alpha \text{-lithiation of } N\text{-Boc pyrrolidine } 96 \text{ can occur either } \text{cis} \text{ or } \text{trans} \text{ to the cyclohexyl ring, lithiation } \text{trans} \text{ to the ring is lower energy and is used for this reactivity study (computational modelling of the } \text{cis/trans} \text{ selectivity of } N\text{-Boc pyrrolidine } 96 \text{ lithiation is described in Chapter 5).} \]

\[ \text{b to simplify modelling, } 4\text{-O-trisyl } N\text{-Boc piperidine } 167 \text{ was modelled as } 4\text{-O-mesyl piperidine } 197. \]

In general, when the lithiation reactions of the 6-membered heterocycles were modelled with the B3LYP DFT functional, the ‘side-on’ deprotonation was favoured. Only for \(N^\prime\text{-t-Bu piperazine} \text{ 66 and } N\text{-Boc morpholine } 169\) was the ‘top’ deprotonation lowest in energy. In contrast, when the \(\alpha\)-lithiations of these same 6-membered heterocycles were optimised using the M06 DFT functional, there was no clear preference for either of the \(i\text{-PrLi}\) orientations. The lowest energy pathways for \(\alpha\)-deprotonation of the 6-membered heterocycles with both the B3LYP and M06 DFT calculations are summarised in Table 3.3.
Table 3.3. Lowest energy $i$-PrLi orientation for the $\alpha$-lithiation of 6-membered $N$-Boc heterocycles with B3LYP and M06 DFT functionals

<table>
<thead>
<tr>
<th></th>
<th>B3LYP</th>
<th>M06</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>‘side-on’</td>
<td>‘side-on’</td>
</tr>
</tbody>
</table>

|        | ‘top’ | ‘side-on’ | ‘side-on’ | ‘top’ | ‘top’ |

Free energies of activation ($\Delta G^\ddagger$) were calculated for the $\alpha$-lithiations of each of the 14 $N$-Boc heterocycles in Figure 3.8 with the B3LYP and M06 DFT functionals. These are presented in the experimentally determined order of reactivity in Table 3.4. All of the calculated $\Delta G^\ddagger$ values were corrected to a temperature of $–78$ °C, the temperature at which the lithiations were carried out experimentally. The experimentally determined half-lives ($t_{1/2}$) for the lithiation reactions of all 14 substrates are shown along with the computationally calculated $\Delta G^\ddagger$, to allow comparison between the theoretical and experimentally determined reactivities for the substrates. For the substrates 169, 48, 167/197 and 96 for which kinetic analysis was conducted in Chapter 2, the reaction half-lives were estimated using $t_{1/2} = t_{\text{lith}}/7$ (as 7 $t_{1/2S} = 99\%$ conversion). The $\Delta G^\ddagger$ values presented in Table 3.4 for each of the 6-membered heterocycles are taken from the whichever lithiation (‘side-on’ or ‘top’) has the lowest $\Delta G^\ddagger$ value (see Table 3.3).
Table 3.4. *N*-Boc heterocycle experimentally obtained reactivities \( (t_{1/2}) \) and B3LYP/M06 calculated activation free energies

<table>
<thead>
<tr>
<th>Compound</th>
<th>DFT</th>
<th>Experimental</th>
<th>B3LYP</th>
<th>M06</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuO\text{N}-Boc</td>
<td>( \Delta G^\ddagger ) (B3LYP)\textsuperscript{a}</td>
<td>( \Delta G^\ddagger ) (M06)\textsuperscript{a}</td>
<td>( \Delta G^\ddagger ) (B3LYP)\textsuperscript{a}</td>
<td>( \Delta G^\ddagger ) (M06)\textsuperscript{a}</td>
</tr>
<tr>
<td>169</td>
<td>16.79</td>
<td>11.97</td>
<td>12.61</td>
<td>11.79</td>
</tr>
<tr>
<td>48</td>
<td>11.67</td>
<td>12.36</td>
<td>12.68</td>
<td>11.67</td>
</tr>
<tr>
<td>167/197</td>
<td>12.96\textsuperscript{c}</td>
<td>14.38 \textsuperscript{c}</td>
<td>13.11\textsuperscript{c}</td>
<td>14.59</td>
</tr>
<tr>
<td>58</td>
<td>13.85</td>
<td>13.85</td>
<td>14.59</td>
<td>14.43</td>
</tr>
<tr>
<td>57</td>
<td>13.48</td>
<td>13.48</td>
<td>14.43</td>
<td>14.43</td>
</tr>
<tr>
<td>( t_{1/2} )</td>
<td></td>
<td></td>
<td>( t_{1/2} )</td>
<td></td>
</tr>
<tr>
<td>(s)</td>
<td></td>
<td></td>
<td>(s)</td>
<td></td>
</tr>
<tr>
<td>( \Delta G^\ddagger ) (B3LYP)\textsuperscript{a}</td>
<td></td>
<td></td>
<td>( \Delta G^\ddagger ) (M06)\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>169</td>
<td>16.79</td>
<td>11.97</td>
<td>12.61</td>
<td>11.79</td>
</tr>
<tr>
<td>48</td>
<td>11.67</td>
<td>12.36</td>
<td>12.68</td>
<td>11.67</td>
</tr>
<tr>
<td>167/197</td>
<td>12.96\textsuperscript{c}</td>
<td>14.38 \textsuperscript{c}</td>
<td>13.11\textsuperscript{c}</td>
<td>14.59</td>
</tr>
<tr>
<td>58</td>
<td>13.85</td>
<td>13.85</td>
<td>14.59</td>
<td>14.43</td>
</tr>
<tr>
<td>57</td>
<td>13.48</td>
<td>13.48</td>
<td>14.43</td>
<td>14.43</td>
</tr>
</tbody>
</table>

\textsuperscript{a} DFT calculated activation free energies reported in kcal mol\textsuperscript{-1}

\textsuperscript{b} kinetic data not available; \( t_{1/2} \) estimated using lithiation time \( (t_{1/2} = t_{lith}/7) \)

\textsuperscript{c} DFT results for 4-\textit{O}-trisyl piperidine 167 (R = 2,4,6-(\textit{i}-Pr)\textsubscript{3}C\textsubscript{6}H\textsubscript{2}) were obtained by modelling the lithiation of 4-methanesulfonyl \( N \)-Boc piperidine 197 (R = Me)
By inspection of the experimental $t_{1/2}$s and theoretical $\Delta G^\ddagger$ values in Table 3.4, a correlation between theory and experiment is observed for the lithiation of the $N$-Boc heterocycles. As expected, this general trend indicated that for most substrates the calculated energy barrier of the lithiation $\Delta G^\ddagger$ increases as the substrates become less reactive with larger experimental $t_{1/2}$s observed.

Many of the reactivity trends observed experimentally that were attributed to key structural features of the $N$-Boc heterocycles were reproducible with the DFT modelling. For example, the DFT modelling with B3LYP and M06 functionals indicated that the 5-membered pyrrolidine substrates 9, 96 and 84, were more reactive than $N$-Boc piperidine 10. Additionally, DFT modelling reproduced the activating effects that were observed for the 6-membered $N$-Boc piperidines, when either a heteroatom was included in the ring or when a C-4 substituent was present. For example, DFT modelling with B3LYP and M06 functionals indicated that morpholine 169 and piperazines 58, 57 and 66 are more reactive than $N$-Boc piperidine 10. For the 4-substituted piperidines, the DFT modelling could predict the magnitude of the activating effect for many of the C-4 substituents. For example, the 4-chloro and 4-$O$-trisyl piperidines 48 and 167/197 were found to be much more reactive than 4-amino piperidine 168 using the DFT modelling with B3YLP and M06 functionals.

At this present time, no further computational evidence for these activating effects or another rationale for the large differences in reactivity observed in the substrates can be suggested. The dihedral angle between the $\alpha$-proton that is deprotonated and the carbonyl of the carbamate was measured in the prelithiation complexes of the 14 substrates, to establish if there was any relationship between this angle and the rate of lithiation. It could be envisaged that different dihedral angles may affect the coordination of the alkyllithium during the lithiation and affect how facile the reaction is. No trend between this dihedral angle and the rate of lithiation was observed for the $N$-Boc heterocycles studied. This same analysis was conducted by Gross and Beak for the lithiation of cyclic carbamates using competition experiments and they also noted that no correlation between the dihedral angle and rate of lithiation was observed.  

Both DFT functionals did produce outlying results for a few of the $N$-Boc heterocycles, where the reactivity order did not match that observed experimentally. For example, the B3LYP functional suggested that $N'$-Bn and $N'$-Me piperazines 57 and 58 are less reactive than observed by experiment. The calculated $\Delta G^\ddagger$ values for both of these piperazines
suggest that they were less reactive than N-Boc pyrrolidine 9 but the experimental \( t_{1/2} \) values suggest that they are either more reactive or have similar reactivity to that of N-Boc pyrrolidine 9. Also, the M06 DFT functional suggested that N'-t-Bu piperazine 66 should be one of the least reactive N-Boc heterocycles, with a similar reactivity to N-Boc piperidine 10. However, experiment indicated the s-BuLi/TMEDA lithiation of N'-t-Bu piperazine 66 is ~30 times faster than that of N-Boc piperidine 10.

Another outlier arose when the lithiation of 4-OTIPS piperidine 39 was modelled with DFT. Calculation of the \( \Delta G^\dagger \) for the \( \text{i-PrLi/di-methyl bispidine lithiation} \) 195 of 4-OTIPS piperidine 39 with M06 DFT functional suggested this substrate is extremely reactive, with a similar reactivity predicted to that of 4-\( \text{O-trisyl} \) piperidine 167/197. However, the experimental study found that 4-OTIPS piperidine 39 is in fact ~20 times less reactive than 4-\( \text{O-trisyl} \) piperidine 167/197 with s-BuLi/TMEDA. Modelling with the B3LYP DFT functional also suggested that the 4-OTIPS piperidine 39 was more reactive than observed experimentally but by a much smaller margin, suggesting a reactivity between that of 3,4-disubstituted N-Boc pyrrolidine 9 and bicyclic pyrrolidine 84.

The differing trends and outliers observed with each of the DFT functionals highlight an important point; different computational methods may not provide the same results. When using computational modelling to help understand chemical reactivity it is important to consider the level of theory and for DFT, the functional that is used. This is one of the primary reasons why two different DFT functionals were used for the computational modelling in this study.

With so many different N-Boc heterocycles and such a large quantity of reactivity data, it was difficult to judge precisely the quality of the trend between theory and experiment. Therefore, a method that allowed the linear correlation of these two sets of data was required, as this would enable the correlation between the experimental and theoretical results to be analysed quantitatively. This was achieved using the Eyring equation which relates both the rate constant \( k \) and activation energy for a reaction \( (\Delta G^\dagger) \) at a temperature \( T \) (Equation 3.1).

\[
k = \frac{k_B T}{h} e^{-\frac{\Delta G^\dagger}{RT}}
\]  
(Equation 3.1)

Using a linear form of this equation allowed linear regression of the experimentally obtained \( k_{\text{obs}} \) values for the N-Boc heterocycle substrates and the computationally predicted \( \Delta G^\dagger \)s (Equation 3.2). In this linear form of the Eyring equation, the experimentally obtained
In ($k_{obs}$) data can be plotted against the computationally obtained $\Delta G^\dagger$ and the correlation between the two sets of data can be analysed.

$$
ln(k_{obs}) = -\Delta G^\dagger \frac{1}{RT} + \ln\left(\frac{k_B T}{h}\right)
$$

$$
y = mx + c \text{ where: } \ y = ln(k_{obs}), \ m = -\frac{1}{RT} \text{ and } c = \ln\left(\frac{k_B T}{h}\right) \quad (\text{Equation 3.2})
$$

This Eyring regression was first applied to the theoretical and experimental results for the lithiation reactions for all of the 14 $N$-Boc heterocycles included in Table 3.4. The experimentally obtained $ln(k_{obs})$ values were plotted versus the calculated $\Delta G^\dagger$ values obtained with both B3LYP and M06 DFT functionals ($\Delta G^\dagger$ values are in kJ mol$^{-1}$ to allow analysis of the gradient) (Figure 3.10). Error bars are not included for the $ln(k_{obs})$ values as the $k_{obs}$ standard error obtained by the kinetic analysis is too small to observe on the logarithmic scale.

Figure 3.10. Eyring linear regressions for experimentally obtained $k_{obs}$ and calculated $\Delta G^\dagger$ values for the lithiation of the 14 $N$-Boc heterocycle substrates in Table 3.4

The Eyring analysis with the B3LYP calculated $\Delta G^\dagger$ values for the $N$-Boc heterocycles in Table 3.4 provided a promising correlation ($R^2 = 0.716$) between theory and experiment. On the other hand, the $\Delta G^\dagger$ values calculated with the M06 DFT functional provided only a moderate correlation with experiment ($R^2 = 0.510$). The Eyring analysis for each DFT
functionals indicated that the three substrates with rapid lithiation \(169, 48\) and \(167/197\) with estimated \(t_{1/2}\)'s, deviated from the trend line. This was particularly evident for \(\Delta G^\ddagger\) values calculated with B3LYP which are circled in Figure 3.10.a. These outliers are likely due to large amounts of error in the experimental data which are further compounded by the rapid rates of reaction. Therefore, it was decided to remove the substrates for which \(t_{1/2}\) was estimated from the Eyring analysis, including \(169, 48, 167/197\) and cyclohexyl pyrrolidine \(96\) and re-evaluate the trend between theory and experiment for the remaining 10 \(N\)-Boc heterocycles (Figure 3.11).

Upon removal of the \(N\)-Boc heterocycles with estimated \(t_{1/2}\)'s, a considerable difference in the correlations between experiment and theory were observed. The \(\Delta G^\ddagger\) values calculated using the B3LYP DFT functional now provided a good correlation \((R^2 = 0.802)\) with the

\[
y = -0.6044x + 32.435 \quad R^2 = 0.802
\]

\[
y = -0.449x + 20.84 \quad R^2 = 0.342
\]

**Figure 3.11.** Eyring linear regressions for experimentally obtained \(k_{obs}\) and calculated \(\Delta G^\ddagger\) for the lithiation for the 10 \(N\)-Boc heterocycle substrates above
experimental results. However, it was noted that the lithiation reactions of the three fastest substrates of the 10, pyrrolidine 9 and N'-Bn and N'-Me piperazines 57 and 58, all had very similar experimental reactivities but the calculated $\Delta G^\dagger$ values suggested they would have more notable differences in reactivity. This could be due to deficiencies in the modelling or the larger margins of experimental error for these fast lithiating substrates, as discussed in Chapter 2. The $\Delta G^\dagger$ values calculated with M06 DFT functional still provided poor correlation with experiment. The quality of the fit can also be assessed by analysis of the gradient of the line of best fit plotted through the regression of the theoretical and experimental data for the 10 N-Boc heterocycles. For these Eyring linear analyses, the gradient is expected to equal $-1/RT$ as stated in Equation 3.2, where $R$ is the universal gas constant and $T$ is the temperature. In this case, $T$ is equal to 195 K as the experimental reactions are conducted at $-78 \, ^\circ C$ and all the free energies ($\Delta G$) calculated have been corrected to 195 K. Therefore, the gradient of the line of best fit is expected to equal:

$$m = -\frac{1}{RT} = \frac{1}{8.314 \times 10^{-3} \times 195} = -0.617 \, kJ^{-1} \, mol$$

For the Eyring regression using the $\Delta G^\dagger$ values calculated using the B3LYP DFT functional the gradient of the line of best fit was equal to $-0.604 \, kJ \, mol^{-1}$. This is very close to the value expected and therefore provides further evidence of a good fit between experiment and theory. The line of best fit from the Eyring analysis of the M06 calculated results provided a gradient of $-0.449 \, kJ \, mol^{-1}$ which differed significantly to what was expected. The gradient provided by the M06 results as well as the poor correlation between theory and experiment suggests that modelling with the M06 DFT functional does not provide an accurate description of this system.

In summary, DFT modelling of the $\alpha$-lithiation reactions of different N-Boc heterocycles does describe many of the reactivity differences that were observed experimentally. The DFT modelling does not perfectly describe the reactivity of each substrate but does account for most of the large differences in reactivity between substrates that were observed experimentally. The Eyring regression analysis indicates a good overall correlation between the B3LYP calculated $\Delta G^\dagger$ values and experimental reactivity data. This promising correlation between theory and experiment provides an interesting avenue of further investigation which is described in the next section of this Chapter.
3.2.2 Using DFT modelling to predict reactivities of unknown \( N \)-Boc heterocycles

If a good correlation between the DFT modelling results and the experimentally obtained reactivities is observed, it may be possible to use DFT modelling to predict the reactivity of \( N \)-Boc heterocycles for which reactivity is unknown. Even if modelling could only suggest whether the lithiation would be slow (\( > 2 \) h), occur at a moderate rate (5 min to 2 h) or was fast (\( < 5 \) min), this could be of great use to a synthetic chemist. This estimated reactivity would provide information about whether the lithiation is feasible and if so, provide an idea of the reaction of conditions (e.g. reaction temperature) that would be required. This would allow the suitability of the \( \alpha \)-lithiation of a novel substrate to be assessed without any synthetic or kinetic work being done beforehand.

As the \( \Delta G^\ddagger \) values calculated with the B3LYP DFT functional had provided a promising correlation with the experimentally obtained kinetic data, it was decided to use the Eyring regression in Figure 3.11 to attempt to predict the reactivity of \( N \)-Boc heterocycles for which reactivity is unknown. Hence, the \( i \)-PrLi/di-methyl bispidine 195 lithiation reactions of three \( N \)-Boc heterocycles with unknown reactivities \( \text{anti-97, 198 and 192,} \) were modelled using the B3LYP DFT functional. The \( s \)-BuLi/(\( - \))-sparteine lithiation of di-phenyl pyrrolidine \( \text{anti-97} \) had been reported previously but no reactivity data was collected (see Scheme 1.32).\(^4\) The lithiation of 2,5-dimethyl piperidine 198 has not been reported and it was expected that the lithiation would have a high activation energy barrier at \(-78^\circ \)C due to the methyl groups at each of the \( \alpha \)-positions. The lithiation of 7-membered \( N \)-Boc azepane 192 has been reported using higher reaction temperatures (\(-40^\circ \)C) but the rate of lithiation was not studied;\(^40\) preliminary in-group data suggests that \( N \)-Boc azepane 192 is less reactive than \( N \)-Boc piperidine 10.\(^53\) For each of the three \( N \)-Boc heterocycles, \( \Delta G^\ddagger \) was calculated for the respective \( i \)-PrLi/di-methyl bispidine 195 lithiation. Using these calculated \( \Delta G^\ddagger \) values, \( k_{\text{obs}} \) for the \( s \)-BuLi/TMEDA lithiation of each substrate was predicted by interpolation/extrapolation of the Eyring regression obtained with the B3LYP calculated \( \Delta G^\ddagger \) values in Figure 3.11. These estimated \( k_{\text{obs}} \) values have been converted to a predicted \( t_{1/2} \) and predicted lithiation time for each substrate and are presented in Table 3.5.
Table 3.5. B3LYP calculated $\Delta G^\ddagger$ and predicted $t_{1/2}$ (at –78 °C) for N-Boc heterocycles 
*anti*-97, 198 and 192 with unknown reactivities

<table>
<thead>
<tr>
<th></th>
<th>$\Delta G^\ddagger$ / kcal mol$^{-1}$</th>
<th>$\Delta G^\ddagger$ / kJ mol$^{-1}$</th>
<th>Predicted $t_{1/2}$ / s</th>
<th>Predicted $t_{\text{lith}}$a</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-97</td>
<td>11.94</td>
<td>49.96</td>
<td>0.074</td>
<td>0.5 s</td>
</tr>
<tr>
<td>198</td>
<td>16.57</td>
<td>69.33</td>
<td>8920</td>
<td>17 h</td>
</tr>
<tr>
<td>192</td>
<td>16.11</td>
<td>67.40</td>
<td>2790</td>
<td>5.5 h</td>
</tr>
</tbody>
</table>

*a the predicted $t_{\text{lith}}$ was calculated using 7 half-lives for 99% conversion ($t_{\text{lith}} = t_{1/2} \times 7$)

The DFT modelling suggests that di-phenyl pyrrolidine *anti*-97 is very reactive, with a very small $t_{1/2} = 0.074$ s predicted for the lithiation of pyrrolidine *anti*-97 with $s$-BuLi/TMEDA. This small predicted $t_{1/2}$ for the $s$-BuLi/TMEDA of pyrrolidine *anti*-97 would mean only 0.5 s would be required for 99% conversion. The DFT modelling therefore suggests that the phenyl groups on the 3,4-positions of the pyrrolidine ring will have a significant activating effect on the reactivity of this pyrrolidine substrate. As theorised, the DFT modelling predicted a prohibitively high energy barrier for the $s$-BuLi/TMEDA lithiation of 2,5-dimethyl pyrrolidine 198, with a large $t_{1/2} = 8920$ s that translates to a 17 h reaction time for 99% conversion. The DFT modelling predicted that the $s$-BuLi/TMEDA lithiation N-Boc azepane 192 would require 5.5 h with a similar reactivity to that of N-Boc piperidine 10 (azepane 192 predicted $t_{1/2} = 2790$, piperidine 10 $t_{1/2} = 3190$ s). Previous work in the O’Brien group suggests that N-Boc azepane 192 lithiation is slower then N-Boc piperidine 10 so the modelling may not provide a very accurate estimate of lithiation time for this substrate. However, the modelling still predicts that N-Boc azepane 192 will be on the lower end of the reactivity spectrum. For the $s$-BuLi/TMEDA lithiation of both 2,5-dimethyl pyrrolidine 198 and N-Boc azepane 192, the predictive method developed indicates that higher reaction temperatures may be required for complete lithiation to occur. Furthermore, the suggested low reactivity of 2,5-dimethyl pyrrolidine 198 may suggest that the lithiation is unfeasible due to the very high energy barrier for lithiation.
3.2.3 Modelling the \textit{i}-PrLi/TMEDA lithiation of \textit{N}-Boc heterocycles

During this computational investigation, di-methyl bispidine 195 was selected as the diamine ligand used to model the lithiation instead of TMEDA due to its rigidity which was expected to make the location of a minima easier. It was thought that a diamine ligand such as TMEDA would complicate the modelling, as the flexibility of the ligand would provide a shallow potential energy surface, making location of a minima more difficult. However, when modelling the \textit{i}-PrLi/TMEDA lithiation of \textit{N}-Boc pyrrolidine 9 was conducted, the flexibility of TMEDA added little additional computational expense to the calculation.

To investigate whether the use of di-methyl bispidine 195 rather than TMEDA in the modelling affected the correlation observed between the theoretical and experimental results, the lithiation of a selection of \textit{N}-Boc heterocycles were modelled using \textit{i}-PrLi/TMEDA. Six of the \textit{N}-Boc heterocycles modelled previously which spanned a wide range of reactivities were modelled using the B3LYP DFT functional and \textit{i}-PrLi/TMEDA lithiating conditions. The geometries of the optimised prelithiation complexes and transition states of the lithiation with \textit{i}-PrLi/TMEDA did not differ substantially when the diamine used in the model was changed. In addition, the preference for ‘side-on’ or ‘top’ deprotonation by \textit{i}-PrLi/TMEDA for each of the five 6-membered heterocycles was the same observed when \textit{i}-PrLi/di-methyl bispidine 195 was modelled as the lithiating complex.

When the \textit{i}-PrLi/TMEDA calculated $\Delta G^\dagger$ values were compared with the experimentally determined $k_{\text{obs}}$ by Eyring linear regression analysis, a very similar correlation was observed to that obtained when the \textit{i}-PrLi/di-methyl bispidine 195 lithiation was modelled (Figure 3.12). The Eyring regressions for the two different lithiating conditions that were modelled provided linear regressions with very similar gradients and $R^2$ values (0.770 and 0.799). These results suggested that the identity of the diamine used in the modelling may not have any significant effect on trends of reactivity observed for substrates. Therefore, modelling the \textit{i}-PrLi/di-methyl bispidine 195 lithiations of the substrates and making predictions for the \textit{s}-BuLi/TMEDA lithiation should not provide outliers due to the use of a different diamine ligand in the DFT modelling.
3.2.4 Application of solvent corrections to the modelling of the lithiation of N-Boc heterocycles

The effect that the inclusion of solvent effects has on the DFT modelling of the *i*-PrLi/di-methyl bispidine 195 lithiation was also subjected to investigation. Solvent can be modelled either explicitly, where molecules of solvent are included in the geometry that is optimised, or implicitly, where the solvent is treated as a continuum medium which is characterised by its dielectric constant and other electrostatic parameters. For the implicit modelling of solvent, the molecule to be optimised is placed into a cavity inside this medium and electrostatic properties can be calculated on points on the boundary between the cavity and the solvent field. Modelling of the solvent by implicit or explicit methods both have advantages and disadvantages.\textsuperscript{122} For example, explicit solvation is generally more accurate as specific solvent interactions with the molecule modelled are accounted for, whereas the treatment of solvent as an electrostatic field will not reproduce these interactions. On the other hand, the treatment of the solvent as a continuum with only a few parameters is considerably less computationally expensive than the inclusion of solvent molecules to the

$$y = -0.5610x + 26.519$$

$$R^2 = 0.770$$

Figure 3.12. Eyring regression analysis for the *i*-PrLi/di-methyl bispidine 195 and *i*-PrLi/TMEDA modelled lithiation reactions of six N-Boc heterocycles
geometry that is optimised. As the α-lithiation reactions modelled are relatively large systems (~80 atoms), it was opted to model the solvent implicitly so that calculations would not become prohibitively computationally expensive.

The same six N-Boc heterocycles used to investigate the effect of modelling with a different diamine in Section 3.2.2, were used to investigate how solvent corrections affected the modelling. The i-PrLi/di-methyl bispidine 195 lithiations of each of these six N-Boc heterocycles were modelled again using the B3LYP DFT functional with the inclusion of a solvent correction to model the Et₂O solvent used in experiment. This solvent correction was carried out using the Polarisable Continuum Method (PCM) method included in the GAUSSIAN 09 software package.⁵

The inclusion of the solvent correction did not change the geometries of the prelithiation complexes and transition states for the six N-Boc heterocycles and the preference for ‘side-on’ or ‘top’ deprotonation was unchanged by the solvent corrections. However, the solvent corrected calculated $\Delta G^\ddagger$ values for the lithiation of the six substrates provided a reactivity order for the six substrates that significantly differed to the reactivity orders obtained by modelling without solvent corrections and by experiment (Table 3.6). For example, 4-phenyl piperidine 32 which displays a moderate reactivity experimentally is predicted to be the most reactive substrate to lithiate when solvent corrections were included. Additionally, N-Boc pyrrolidine 9 for which experiment suggests is one of the most reactive substrates, is placed between the two least reactive substrates, 4-amino piperidine 168 and N-Boc piperidine 10 in the reactivity series constructed with the solvent corrected DFT calculations.
Table 3.6. Solvent corrected $\Delta G^\ddagger$ values for the $i$-PrLi/di-methyl bispidine 195 lithiations of selected N-Boc heterocycles and experimentally obtained $t_{1/2}$ for the lithiation

<table>
<thead>
<tr>
<th>Compound</th>
<th>$t_{1/2}$ / s</th>
<th>$\Delta G^\ddagger$ (B3LYP) / kcal mol$^{-1}$</th>
<th>Solvent corrected $\Delta G^\ddagger$ (B3LYP) / kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>18.7 ± 1.8</td>
<td>14.59</td>
<td>16.56</td>
</tr>
<tr>
<td>9</td>
<td>20.7 ± 0.9</td>
<td>13.77</td>
<td>17.21</td>
</tr>
<tr>
<td>66</td>
<td>105 ± 3</td>
<td>15.15</td>
<td>16.81</td>
</tr>
<tr>
<td>32</td>
<td>642 ± 5</td>
<td>15.20</td>
<td>16.32</td>
</tr>
<tr>
<td>168</td>
<td>1040 ± 20</td>
<td>15.58</td>
<td>17.14</td>
</tr>
<tr>
<td>10</td>
<td>3190 ± 30</td>
<td>16.11</td>
<td>17.79</td>
</tr>
</tbody>
</table>

The poor correlation of the solvent corrected DFT modelling with experiment became more apparent when Eyring linear regression analysis between the experimental and theoretical results was conducted (Figure 3.13). As mentioned previously, a good correlation between experiment and theory is obtained when calculations are performed in the gas phase. However, a poor correlation ($R^2 = 0.172$) between the solvent corrected B3LYP calculated $\Delta G^\ddagger$ values and the experimentally determined $k_{obs}$ was observed. This poor agreement between theory and experiment suggests that modelling with the B3LYP DFT functional with an implicit solvent correction does not provide an appropriate description of the lithiation reaction. It is possible that modelling solvent implicitly may not be suitable for this reaction where coordination of the solvent and alkyl lithium species may need to be considered. As implicit solvation only models the solvent as a continuum, the coordination of alkyl lithium and solvent is not accounted for. Therefore, for this reaction the explicit modelling of solvent may provide a better description of the solvation during the reaction and provide more accurate reactivity calculations. Unfortunately, explicit solvation is substantially more computationally expensive and hence was not feasible for this study.
In summary, the work presented in this Chapter indicates that the computational DFT modelling can reproduce many of the reactivity differences that were observed experimentally for the N-Boc heterocycles studied. Quantification of the correlation between the modelled $\Delta G^\ddagger$ values and the experimental $k_{obs}$ indicated that a promising correlation between theory and experiment was observed when the B3LYP DFT functional was used. Preliminary work suggests that the identity of the ligand used in the modelling does not affect the reactivity order of substrates provided by the DFT modelling. The addition of solvent corrections to the modelling did not improve the correlation with experiment and provided some outlying predicted reactivities for substrates. We postulate that implicit modelling of solvent may not be appropriate to describe the lithiation reaction, due to the coordination of the solvent and alkylhormide species that is not specifically accounted for in this solvent model.
3.3 Modelling the Effect of the Ligand on the Rate of the α-Lithiation of N-Boc Pyrrolidine

With DFT modelling showing the ability to reproduce many of the reactivity differences of the N-Boc heterocycles observed experimentally, we next turned our attention to attempt to reproduce the differences in the rate of lithiation observed when different ligands were used. In section 2.2, we detailed how the rate of lithiation of N-Boc pyrrolidine 9 can be significantly altered when different ligands were employed in the lithiation reaction. In an attempt to reproduce the experimentally observed differences in reactivity, the i-PrLi/ligand lithiation of N-Boc pyrrolidine 9 was modelled using five of the achiral ligands used in the reactivity study presented in Chapter 2 (Figure 3.14). An attempt to model the lithiation of N-Boc pyrrolidine 9 with i-PrLi/tetra-isopropyl diamine 178 was made but the severe steric bulk of the ligand and overall size of the system meant that the location of minima for the prelithiation complex was not possible. The i-PrLi/di-methyl bispidine 195 lithiation of N-Boc pyrrolidine was included in this comparison, as the calculation had already been performed for the previous DFT modelling of substrate reactivity in section 3.1. This meant that a prediction for the reactivity of the s-BuLi/di-methyl bispidine 195 lithiation complex could be made using the experimental and DFT data collected for the other five ligands.

![Figure 3.14. Ligands used to model the i-PrLi/ligand lithiation of N-Boc pyrrolidine 9](image)

Prelithiation complexes and transition states for the i-PrLi/ligand lithiation reactions of N-Boc pyrrolidine 9 were constructed for each of the six different ligands. The resulting geometries were optimised using the B3LYP and M06 DFT functionals used previously and the activation free energies ($\Delta G^\ddagger$) for each of the different i-PrLi/ligand lithiation reactions were calculated and corrected to $-78$ °C. The DFT calculated $\Delta G^\ddagger$ values for the different i-PrLi/ligand lithiation of N-Boc pyrrolidine 9 and experimentally determined s-BuLi/ligand lithiation times are presented in Table 3.7.
Table 3.7. Calculated $i$-PrLi/ligand lithiation activation free energies ($\Delta G^\ddagger$) and experimental ReactIR$^\text{TM}$ determined $s$-BuLi/ligand lithiation times for $N$-Boc pyrrolidine 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>ReactIR$^\text{TM}$ lithiation time</th>
<th>$\Delta G^\ddagger$ (B3LYP) / kcal mol$^{-1}$</th>
<th>$\Delta G^\ddagger$ (M06) / kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{Me}_2\text{N}\text{NMe}_2$</td>
<td>$t$-BuO</td>
<td>4 min</td>
<td>12.51</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Me}_2\text{N}\text{NMe}_2$</td>
<td>$\text{NMe}_2$</td>
<td>4 min</td>
<td>12.88</td>
</tr>
<tr>
<td>3</td>
<td>DPE 177</td>
<td>$\text{N}\text{N}$</td>
<td>60 min</td>
<td>13.32</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td></td>
<td>5 h</td>
<td>13.78</td>
</tr>
<tr>
<td>5</td>
<td>$\text{Me}_2\text{N}\text{NMe}_2$</td>
<td>TMPDA 179</td>
<td>12 h</td>
<td>12.76</td>
</tr>
<tr>
<td>6</td>
<td>$\text{Me}_2\text{N}\text{NMe}_2$</td>
<td>$\text{Me}$</td>
<td>??</td>
<td>13.77</td>
</tr>
</tbody>
</table>

By comparing the experimental and computational results in Table 3.7, it was noted that the B3LYP DFT functional was able to reproduce the experimental ligand reactivity series for each of the five diamines except TMPDA. However, modelling with the M06 DFT functional provided a substantially different reactivity trend for the lithiating complexes that did not correlate with experiment.

Both B3LYP and M06 DFT functionals predicted that the reactivity of the $i$-PrLi/TMPDA complex would be similar to that of the $i$-PrLi/TMEDA and $i$-PrLi/TMCDA $trans$.
lithiating complexes. In fact, the experimental data indicated that s-BuLi/TMPDA 179 provided one of the slowest lithiation reactions of N-Boc pyrrolidine 9, which required 12 h to complete. As discussed previously in Chapter 2, it was thought that the slow rate of lithiation with s-BuLi/TMPDA 179 may arise from a lack of coordination of the alkyllithium and that it is actually s-BuLi/Et2O lithiation that occurs. The DFT modelling explicitly modelled the TMPDA 179 diamine coordinated to the alkyllithium, so will not account for preferential coordination of the alkyllithium to the solvent rather than diamine. This is the likely reason why the DFT modelling suggests that i-PrLi/TMPDA 179 lithiation is more facile than was observed experimentally with s-BuLi/TMPDA 179.

Even though the B3LYP predicted the correct trend in reactivity for the i-PrLi/DPE 177 and i-PrLi/THF lithiations of N-Boc pyrrolidine 9, the functional provided only a small 0.46 kcal mol\(^{-1}\) difference in activation energy for each reaction. However, the experimental results showed that a significant ~5-fold difference in reactivity resulted with the two different lithiating complexes. This magnitude of reactivity difference should require a more substantial difference in the activation energies for the two different lithiations (~1.5 kcal mol\(^{-1}\)). Conversely, DFT modelling with the M06 functional suggested that i-PrLi/DPE 177 is less reactive than i-PrLi/THF for the lithiation of N-Boc pyrrolidine 9, contradicting the experimental results.

Modelling with the M06 functional also suggested that the i-PrLi/TMEDA and i-PrLi/TMCDA trans-161 lithiations of pyrrolidine 9 have a significant 0.65 kcal mol\(^{-1}\) difference in activation energy. However, the experimental results indicated that s-BuLi/TMEDA and s-BuLi/TMCDA trans-161 have similar reactivities with complete lithiation of N-Boc pyrrolidine 9 requiring 4 min for both of the s-BuLi/diamine complexes.

The B3LYP DFT modelling suggests that the i-PrLi/di-methyl bispidine 195 complex has a similar reactivity to that of i-PrLi/THF, with near identical calculated \(\Delta G^\ddagger\) values of 13.77 kcal mol\(^{-1}\) and 13.88 kcal mol\(^{-1}\) respectively, for the lithiation of N-Boc pyrrolidine 9. Therefore, modelling with B3LYP advocates that the s-BuLi/ di-methyl bispidine 195 lithiation of pyrrolidine 9 will require several hours, with similar reaction time to that of the 5 h s-BuLi/THF lithiation. The M06 DFT functional does not provide a clear trend with the experimental results, so prediction of the reactivity of the s-BuLi/di-methyl bispidine 195 lithiating complex is unreliable. However, the similar \(\Delta G^\ddagger\) values calculated for the i-PrLi/di-methyl bispidine 195 and i-PrLi/TMEDA lithiations of N-Boc pyrrolidine 9 with the M06
DFT functional may suggest that the $s$-BuLi/di-methyl bispidine 195 lithiation of $N$-Boc pyrrolidine 9 would be fast with similar reactivity to the lithiation with $s$-BuLi/TMEDA.

These results provide evidence that computational modelling can reproduce some of the trends in reactivity observed for the different $s$-BuLi/ligand lithiating complexes. Although the B3LYP DFT functional was able to predict the correct reactivity series for four of the five lithiating complexes, the calculated $\Delta G^\dagger$ values did not quantitatively reflect the differences in the rate of reactivity observed experimental. This suggests that at this point in the project, the DFT modelling used provides qualitative rather than quantitative information about the reactivities of the different lithiating complexes. The DFT modelling also does not account for additional factors that can affect the rate of lithiation. For example, how well the ligand binds to the alkyllithium and whether the solvent binding to the alkyllithium is more favourable, which is likely why the lithiation reactions with $s$-BuLi/TPMDA 179 were predicted to be faster than observed. As observed with the computed reactivity trends of the substrates in section 3.2, it is also clearly evident that the DFT functional used can provide very different reactivity series for the different $s$-BuLi/ligand complexes.
3.4 Conclusions and Future Work

In conclusion, this Chapter described the application of DFT modelling to attempt to reproduce and better understand the differences in the reactivities afforded when different 
\(N\)-Boc heterocycles and ligands are used in the \(\alpha\)-lithiation reaction. Work reported in this Chapter has indicated that it is possible to reproduce many of the reactivity differences observed when different substrates are subjected to \(\alpha\)-lithiation. This included the significant reactivity difference between unsubstituted 5- and 6-membered heterocycle rings observed with \(N\)-Boc pyrrolidine 9 and \(N\)-Boc piperidine 10. DFT modelling was also able to reproduce the activating effects observed experimentally with the 6-membered \(N\)-Boc heterocycles, when substituents are added to the C-4 position or additional heteroatoms are included in the heterocycle ring. The DFT modelling has indicated that differences in the rates of lithiation of these substrates must arise due to structural differences between the substrates. Future work further could explore why these reactivity differences in the \(N\)-Boc heterocycles are present. We postulate that conformational and electronic orbital overlap effects may be the reason for these differences in reactivity. More in-depth computational studies may be able to probe whether these effects are the cause of various reactivities observed. For example, computational calculation of \(\alpha\)-proton acidities may provide evidence for the electronic effects that are postulated to facilitate the lithiation reaction.

Linear correlation of the modelled activation free-energies and experimentally obtained \(k_{\text{obs}}\) values indicated that the two DFT functionals used did not provide identical amounts of agreement with experiment. This highlighted the significant impact that using differing levels of theory of DFT functionals can have on the results obtained. In this study, the correlation between theory and experiment suggested that modelling with the M06 functional may not provide an accurate description of the system. This was surprising as it is reported that M06 better describes dispersion interactions, which are likely to be significant in the \(\alpha\)-lithiation reaction, where multiple chemical species are present. In contrast, a good correlation between the B3LYP calculated \(\Delta G^\ddagger\) values and experimental results was obtained. This correlation was then used to predict the reactivities of three additional \(N\)-Boc heterocycles for which little or no reactivity data was available. The use of the computational modelling for a predictive purpose provides an interesting avenue for further investigation and this model could be further developed to provide reliable...
predictions of reactivity for substrates. This in turn would allow optimal reaction conditions to be found \textit{in silico} without the need to conduct the reaction in the laboratory beforehand.

The computational investigation also focussed on investigating the reactivities of alkyllithium/ligand lithiating complexes. The \textit{i-PrLi}/ligand modelled lithiations of \textit{N}-Boc pyrrolidine \textit{9} with the B3LYP DFT functional provided a qualitative agreement with the experimental \textit{s-BuLi}/ligand results, for four of the five \textit{i-PrLi}/ligand lithiating complexes modelled. The DFT modelling suggested the alkyllithium/TMPDA \textit{179} lithiating complex was significantly more reactive than what was observed by experiment. This is likely due to TMPDA \textit{179} having a lower affinity for alkyllithium compared to the Et\textsubscript{2}O solvent; the competing affinities of the ligand and solvent are not accounted for in the DFT modelling conducted. This demonstrates that other processes that occur during the reaction which are not accounted for by the modelling may significantly affect the reactivity observed in experiment.

The computational modelling used for all the studies in this chapter could be developed and investigated further. This could include the investigation of QM/QM or QM/MM modelling, where less significant parts of the molecular geometry can be treated with lower levels of theory (or molecular mechanics) to decrease the computational cost. This would also allow more crucial parts of the molecular geometry to be treated at higher levels of theory which may improve the accuracy and reliability of results without significantly increasing the computational expense. The QM/QM modelling \textit{i-PrLi}/\textit{(-)}-sparteine lithiation of \textit{N}-Boc pyrrolidine \textit{9} and \textit{N}-Boc piperidine \textit{10} have been reported by Wiberg and Deng (see section 1.4).\textsuperscript{90}

Another aspect of modelling that could be explored is the effect of basis set supposition error (BSSE) upon the results of the calculations, which has not been explored in this investigation. The BSSE results from the overlap of the basis functions on atoms that are close to each other and where this overlap does occur, that portion of the molecule has an effectively increased basis set. In the regions of the molecular geometry where this effectively increased basis set occurs, the calculations are improved as the location of electrons are better described due to the larger number of basis functions present. As only small portions of the molecular geometry that is modelled experience these increases in basis set size, this provides a source of error when energy and other properties are calculated for the entire system. BSSE can provide a significant source of error in the calculated energies
of systems especially where intermolecular reactions such as lithiation are modelled.\textsuperscript{124,125} There are many methods that can be used to attempt to correct for the occurrence of the BSSE such as using larger basis sets or by employing a counterpoise (CP) correction. These methods to correct for BSSE were not attempted in this study due to large computational expense of the correction calculations.

Finally, the use of alternative DFT functionals could be investigated. For example, it may be possible to screen a sub-set of the N-Boc heterocycles $\alpha$-lithiation reactions with many different DFT functionals, to find a functional that provides the best description of the lithiation reaction. Alternatively, methods that pair DFT functionals with empirical energy corrections could also be utilised. DFT functionals with combined corrections are particularly useful as effects like dispersion can be better accounted for without the significant increases in computational expense that would result from using a higher level of theory. For example, B3LYP-D3 combines the B3LYP DFT functional with Grimme’s DFT-D3 dispersion correction, allowing the inclusion of dispersion energy corrections throughout the calculation.\textsuperscript{126,127} As previously mentioned in this Chapter, DFT in general does not accurately describe long-range dispersion interactions\textsuperscript{119} and these long-range interactions are likely to play an important role in the intermolecular multi species lithiation reaction. Therefore, inclusion of a dispersion correction should mean that these lithiation reactions can be more accurately modelled using DFT. More recently, Grimme \textit{et al.} have developed a B3LYP-gCP-D3 scheme which includes both a dispersion correction (D3) and a BSSE correction (gCP).\textsuperscript{128} This combination of DFT functional and energy corrections may be particularly beneficial for the modelling of the lithiation chemistry presented in this thesis.
Chapter 4: Investigation of the Rates of Trapping of Lithiated N-Boc Heterocycles with Different Electrophiles

Ensuring a complete and efficient lithiation reaction of an N-Boc heterocycle is only half of the challenge when optimising the lithiation-trapping reaction of a substrate. It is also vital to ensure that complete trapping occurs with reaction conditions which ensure that the desired product is obtained with minimal side reactions (Scheme 4.1).

Scheme 4.1. General scheme for the trapping reaction of a lithiated intermediate

The use of \textit{in situ} IR spectroscopy to monitor the trapping reactions of lithiated intermediates is less common than monitoring the formation of the lithiated intermediates. More recently, however, the ReactIR\textsuperscript{TM} monitoring of the trapping reaction and in some cases the subsequent rearrangements of the trapped adducts is becoming popular (see section 1.3.2). Monitoring the progress of the trapping reaction can in some cases be very useful to ensure that the trapped product can be obtained in a good yield and er/dr. It is well known that lithiated intermediates can become configurationally unstable at higher temperatures and if the trapping is not complete before the reaction is warmed up then this can result in the product being formed in an eroded er.\textsuperscript{31,129,130} Monitoring the rate of trapping can also allow the optimisation of reaction conditions for the trapping, particularly where the trapping may be slow at low temperatures such as −78 °C which are typically used for the preceding lithiation step.

The rate of trapping between a selection of different lithiated N-Boc heterocycles and electrophiles at −78 °C has previously been studied qualitatively in the O’Brien group using reaction times for the trapping.\textsuperscript{53} Some of these trapping reactions were very slow at −78 °C and only small amounts of incomplete trapping were observed; for these reactions, comparison of the trapping rates was not possible. Work in this chapter expands upon this previous work by measuring the rate of the trapping using a quantitative kinetic analysis, similar to that used to measure the rates of α-lithiation reactions in Chapter 2. This will allow quantitative comparisons of trapping rates for different lithiated intermediates and electrophile combinations.
4.1 Use of *in situ* IR Spectroscopy to Study the Rates of Trapping of Lithiated $N$-Boc Heterocycles

In a similar fashion to the monitoring of the $\alpha$-lithiation of $N$-Boc heterocycles, the subsequent trapping reaction of the lithiated intermediate can also be followed using *in situ* IR spectroscopy with the ReactIR™ apparatus. For example, the Me$_3$SiCl trapping of lithiated $N$-Boc pyrrolidine 9, whose ReactIR™ monitored $s$-BuLi/TMEDA lithiation was discussed in section 2.1, required 10 min for complete trapping to occur (Scheme 4.2). During the trapping reaction, two different species are observed: lithiated intermediate 164 ($\nu_{C=O} = 1648$ cm$^{-1}$) and the trapped adduct, 2-silyl pyrrolidine 11 ($\nu_{C=O} = 1693$ cm$^{-1}$). The ReactIR™ monitoring showed the consumption of the lithiated intermediate 164 and formation of the trapped product 2-silyl pyrrolidine 11 during the course of the reaction. After the trapping was complete, Me$_3$SiCl trapped adduct 11 was afforded in 87% isolated yield.

**Scheme 4.2. ReactIR™ monitored Me$_3$SiCl trapping of 2-lithio $N$-Boc pyrrolidine 164**

During the trapping reaction, the $\nu_{C=O}$ of the carbamate in species 164 shifts to a higher frequency during the trapping reaction since the C=O bond becomes stronger during the trapping reaction. This occurs as the species is converted from the 2-lithio pyrrolidine 164,
where the carbamate C=O is strongly coordinated to the lithium, into the trapped adduct \( \text{11} \) which will have little or no coordination between the carbamate C=O and Li.

As discussed in Chapter 2, the visually obtained reaction times from the ReactIR™ monitoring can be inaccurate and unreliable, therefore it was decided to subject the ReactIR™ data to kinetic analysis to quantify the rates of trapping. The trapping reaction of the lithiated intermediates occurs via an S\( \text{N} \)\( \text{2} \) reaction for tetrahedral electrophiles such as Me\(_3\)SiCl, Me\(_2\)SO\(_4\) and MeI and a nucleophilic addition mechanism for sp\(^2\) carbonyl electrophiles such as PhCHO. Both trapping mechanisms are bimolecular and therefore the rate of the trapping reaction is expected to be dependent on both the concentration of electrophile and lithiated intermediate (RLi) (Equation 4.1).

\[
- \frac{d[RLi]}{dt} = k_{trap} [RLi][\text{electrophile}]
\]

(Equation 4.1)

As it is a complex task to obtain a second order rate constant for a reaction, in this case \( k_{trap} \), it was decided to apply a pseudo-first order approximation. This allows a \( k_{obs} \) to be measured which is only dependent on the concentration of the lithiated intermediate (Equation 4.2).

\[
- \frac{d[RLi]}{dt} = k_{obs} [RLi]
\]

(Equation 4.2)

The standard reaction conditions for the trapping of lithiated intermediates use 2.0 eq. of electrophile, which is only a moderate excess. However, it would be beneficial if this amount of excess electrophile could be used to obtain kinetic data for several reasons. First, all the previously collected ReactIR™ kinetic data in the group used a 2.0 eq. excess of electrophile.\(^{53}\) Therefore, if the kinetic analysis requires a larger excess of electrophile then all of the experiments would need to be repeated. Second, the addition of large excesses of electrophile (i.e. 10.0 eq.) could result in anomalous kinetic data arising from the addition of large volumes of electrophiles that would be added to the reaction. Finally, it would be useful to obtain kinetic data from a reaction which is still conducted for a synthetic purpose allowing the trapped product to be easily isolated at the end. If a large excess of electrophile was added, then this may result in a more complex separation due to the large quantity of unreacted electrophile present.

With this in mind, we decided to use the synthetic reaction conditions and maintain a 2.0 eq. excess of the electrophiles and only use kinetic data from the first 20% of conversion of the trapping reaction, obtaining effectively an initial rate for the trapping reaction. During the
first 20% of conversion, the concentration of the electrophile should only change by a relatively small amount, effectively providing pseudo-first order kinetics with respect to the lithiated intermediate.

The Me$_3$SiCl trapping reaction of 2-lithio pyrrolidine 164 shown in Scheme 4.2 was the first trapping reaction that was subjected to kinetic analysis. A semilogarithmic plot was constructed using ReactIR™ kinetic data for the first 20% conversion of the trapping reaction, to obtain a pseudo-first order $k_{obs}$ for the reaction (Figure 4.1.a). Additionally, a second semilogarithmic plot was constructed which included up to 90% conversion for the trapping reaction. This second plot (Figure 4.1.b) was constructed to identify whether pseudo-first order kinetics were observed over the entirety of the trapping reaction or not. A non-linear correlation in the 90% conversion plot would suggest first order kinetics were not exhibited throughout the reaction, thus suggesting that 2.0 eq. of the Me$_3$SiCl electrophile is not sufficient to provide pseudo-first order reaction conditions throughout.

![Figure 4.1. Semilogarithmic plots for (a) the first 20% conversion and (b) up to 90% conversion for the Me$_3$SiCl trapping of 2-lithio N-Boc pyrrolidine 164](image)

The semilogarithmic plots for both 20% and 90% conversion of 2-lithio pyrrolidine 164 provided strong linear correlations ($R^2 = 0.997$ for both plots, Figure 4.1). This indicated that a pseudo-first order reaction with respect to the lithiated intermediate 164 was observed for the whole Me$_3$SiCl trapping reaction of 2-lithio pyrrolidine 164. This also suggested that 2.0 eq. of the electrophile (Me$_3$SiCl) is sufficient for pseudo-first order conditions to be maintained throughout this particular trapping reaction. Both semilogarithmic plots offered very similar $k_{obs}$ values for the trapping which were within the margins error of one another. Calculation of $k_{obs}$ using the first 20% conversion provided $k_{obs} = (8.55 \pm 0.34) \times 10^{-3}$ s$^{-1}$ and
for 90% conversion \( k_{\text{obs}} = (8.21 \pm 0.11) \times 10^{-3} \text{ s}^{-1} \). To enable easy comparison of the rate of trapping with other substrates and electrophiles, a \( t_{1/2} \) for the trapping of \((81.1 \pm 3.2) \text{ s}\) was calculated using the \( k_{\text{obs}} \) measured for 20% conversion. A detailed procedure for the kinetic analysis carried out for the trapping reactions of the lithiated \( N \)-Boc heterocycles presented in Chapter 4 is detailed in section 6.2 of this thesis.

When a similar kinetic analysis was carried out for the MeI trapping of 2-lithio \( N' \)-Bn \( N \)-Boc piperazine 199, a deviation from pseudo-first order kinetics during the reaction was observed. ReactIR\textsuperscript{TM} monitoring of this reaction indicated that 3.5 h were required for complete trapping to occur, after which the trapped product, 2-methyl piperazine 200 was obtained in 80% yield (Scheme 4.3). By visual inspection of the ReactIR\textsuperscript{TM} trace, it is evident that the curve for the consumption of lithiated intermediate 199 appeared to match that of a multiple order reaction.

**Scheme 4.3. ReactIR\textsuperscript{TM} monitored MeI trapping of 2-lithio \( N' \)-Bn \( N \)-Boc piperazine 199**

Semilogarithmic plots were constructed for both 20% conversion and 90% conversion of the MeI trapping of 2-lithio \( N' \)-Bn piperazine 199 using ReactIR\textsuperscript{TM} kinetic data, as carried out for the Me\textsubscript{3}SiCl trapping of 2-lithio pyrrolidine 164 (Figure 4.2).
The first order plot that was constructed using the kinetic data for up to 90% conversion of 2-lithio N'-Bn piperazine 199 (Figure 4.2.b) did not provide a good linear correlation. It is evident that a deviation from pseudo-first order kinetics occurs roughly 600 s into the trapping reaction. This deviation from first order kinetics in the trapping reaction likely arises from the development of an insufficient excess of electrophile mid-reaction. At this point 600 s into the trapping reaction, second order kinetics are observed as the rate of trapping becomes dependant on both the concentration of lithiated intermediate and electrophile. The semilogarithmic plot of the first 20% conversion for MeI trapping of 2-lithio N'-Bn piperazine 199 (Figure 4.2.a) provided a good linear correlation, indicating that during this initial portion of the trapping reaction, pseudo-first order conditions with respect to the lithiated intermediate 199 were observed. This plot provided a $k_{obs} = (1.22 \pm 0.06) \times 10^{-3}$ s$^{-1}$ and $t_{1/2} = (569 \pm 30)$ s for the MeI trapping of 2-lithio N'-Bn N-Boc piperazine 199.

With a viable method to quantify the rate of the trapping reaction between a lithiated intermediate and electrophile established, our attention centred on investigating the trends in reactivity for both the different lithiated intermediates and different electrophiles. To this end, kinetic data was collected for the Me$_3$SiCl, Me$_2$SO$_4$, MeI and PhCHO trapping reactions of three different lithiated N-Boc heterocycles: 164, cis-201 and 199 (Figure 4.3). It was envisaged that these 12 trapping reactions would provide useful information about the trends in reactivity for both the electrophile and lithiated intermediate.
A variety of different rates of trapping were observed with the different combinations of lithiated intermediate and electrophile used. Many of these combinations of lithiated intermediate and electrophile displayed fast trapping reactions. For trapping reactions where the time for complete trapping was < 3 min, \( k_{\text{obs}} \) and \( t_{1/2} \) were estimated as kinetic analysis could not be carried out as too few data points were available to measure rate constants for the trapping. For these trapping reactions, estimated \( t_{1/2} \) were approximated using \( t_{1/2} \approx t_{\text{trap}} \) (as \( 7 t_{1/2} = 99\% \) conversion), where \( t_{\text{trap}} \) was the time taken for complete trapping. For example, the PhCHO trapping of 2-lithio pyrrolidine 164 was extremely fast (complete within the 1 min time lapse between scans of the ReactIR\textsuperscript{TM}) with a \( t_{1/2} \) of < 8.6 s (Scheme 4.4.a).\textsuperscript{53} After work-up and purification, the PhCHO trapping of 2-lithio pyrrolidine 164 provided a mixture of benzyl alcohol diastereomers 31 in 93% yield. The MeI trapping of 2-lithio phenyl piperidine \textit{cis}-201 also displayed a relatively fast trapping reaction, with \( k_{\text{obs}} = (3.18 \pm 0.02) \times 10^{-3} \text{ s}^{-1} \) and \( t_{1/2} = (218 \pm 1) \text{ s} \) calculated by kinetic analysis of the first 20% conversion of the trapping. After work-up and purification of the MeI trapping of 2-lithio phenyl piperidine \textit{cis}-201, 2-methyl 4-phenyl piperidine \textit{cis}-35 was afforded in 64% yield (Scheme 4.4.b).
Scheme 4.4. (a) PhCHO trapping of 2-lithio N-Boc pyrrolidine 164 and (b) MeI trapping of 2-lithio 4-phenyl piperidine cis-201

![Scheme 4.4](image)

On the other hand, there were trapping reactions of lithiated intermediates that displayed very slow rates of trapping. The Me$_3$SiCl trapping of 2-lithio N'-Bn piperazine 199 was the slowest trapping reaction observed in this investigation, with $k_{obs} = (1.37 \pm 0.01) \times 10^{-5}$ s$^{-1}$ and $t_{1/2} = (51300 \pm 100)$ s measured by kinetic analysis of the first 20% conversion of the trapping. After a 13 h trapping time at –78 °C only partial trapping of 2-lithio N'-Bn piperazine 199 was observed (Scheme 4.5). As the Me$_3$SiCl trapping of 199 was so slow, a second fast trapping electrophile, PhCHO, was added to trap the remaining un-trapped lithiated intermediate 199. This second electrophile was added to ensure that the preceding lithiation was complete and to measure the baseline absorbance at 1648 cm$^{-1}$, which is required for the kinetic analysis. Purification after the addition of both electrophiles provided...
the Me₃SiCl trapped adduct 59 in 40% yield and a 60:40 mixture of PhCHO trapped benzyl alcohols *syn*- and *anti*-202 in 42% yield.

**Scheme 4.5. Me₃SiCl trapping of 2-lithio N'-Bn piperazine 199**

The $k_{obs}$ and $t_{1/2}$ for all 12 trapping reactions with isolated yields of the trapped adduct, are presented in Table 4.1. Due to their faster rates of trapping (time for complete trapping < 3 min), the results from the methylations of 2-lithio N-Boc pyrrolidine 164 and the PhCHO trapping reaction are estimated $k_{obs}$ and $t_{1/2}$ values. All other $k_{obs}$ and $t_{1/2}$ values in Table 4.1 were determined by kinetic analysis of the first 20% of trapping conversion as discussed earlier; in all of these cases the first order plots for up to 20% conversion provided good linear correlations, suggesting that during this initial portion of the trapping reaction, pseudo-first order kinetics with respect to the lithiated intermediate were observed (see section 6.5 for semilogarithmic plots). In fact, for all of the trapping reactions with Me₃SiCl, pseudo-first order kinetics with respect to the lithiated intermediate were observed over the course of the trapping reaction (up to 90% conversion for 164 and *cis*-201, and up to PhCHO trapping for 199). Conversely, all of the trapping reactions with Me₂SO₄ and MeI which were subjected to kinetic analysis showed deviation from pseudo-first order kinetics at some point mid-reaction (after 20% conversion).
Table 4.1. Measured \( k_{\text{obs}} \), \( t_{1/2} \) and isolated yields for the Me\(_3\)SiCl, Me\(_2\)SO\(_4\), MeI and PhCHO trapping reactions of lithiated intermediates 164, cis-201 and 199

<table>
<thead>
<tr>
<th></th>
<th>Me(_3)SiCl</th>
<th>Me(_2)SO(_4)</th>
<th>MeI</th>
<th>PhCHO</th>
</tr>
</thead>
</table>
| 164            | \( k_{\text{obs}} = (8.55 \pm 0.34) \times 10^{-3} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (81.1 \pm 3.2) \text{ s} \)  
|                | (81%)        | \( k_{\text{obs}} \approx 4.1 \times 10^{-2} \text{ s}^{-1} \)  
|                | \( t_{1/2} \approx 17 \text{ s} \)  
|                | (66%)        | \( k_{\text{obs}} = 2.7 \times 10^{-3} \text{ s}^{-1} \)  
|                | \( t_{1/2} = 26 \text{ s} \)  
|                | (40%)        | \( k_{\text{obs}} \approx 8.1 \times 10^{-2} \text{ s}^{-1} \)  
|                | \( t_{1/2} < 8.6 \text{ s} \)  
|                | (93%)        |
| cis-201        | \( k_{\text{obs}} = (7.57 \pm 0.07) \times 10^{-5} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (9160 \pm 80) \text{ s} \)  
|                | (73%)        | \( k_{\text{obs}} = (2.74 \pm 0.05) \times 10^{-4} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (2530 \pm 50) \text{ s} \)  
|                | (63%)        | \( k_{\text{obs}} = (3.18 \pm 0.02) \times 10^{-3} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (218 \pm 1) \text{ s} \)  
|                | (64%)        |
| 199            | \( k_{\text{obs}} = (1.37 \pm 0.01) \times 10^{-5} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (51300 \pm 400) \text{ s} \)  
|                | (40%)        | \( k_{\text{obs}} = (2.14 \pm 0.06) \times 10^{-5} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (32400 \pm 900) \text{ s} \)  
|                | (35%)        | \( k_{\text{obs}} = (1.22 \pm 0.06) \times 10^{-3} \text{ s}^{-1} \)  
|                | \( t_{1/2} = (569 \pm 30) \text{ s} \)  
|                | (80%)        | \( k_{\text{obs}} \approx 8.1 \times 10^{-2} \text{ s}^{-1} \)  
|                | \( t_{1/2} < 8.6 \text{ s} \)  
|                | (52%)        |

\( a \) \( k_{\text{obs}} \) and \( t_{1/2} \)s for these trapping reactions are estimated (\( t_{1/2} \approx \) trapping time / 7)

\( b \) upon addition of MeI, gelation was observed and this provided unreliable kinetics (this is discussed in more detail later)

\( c \) previous in-group work\(^{53}\)

\( d \) the trapping of 2-lithio 4-phenyl piperidine \textit{cis}-201 has been carried out using a cyclobutanone electrophile\(^{53}\) and estimated \( k_{\text{obs}} \approx 8.1 \times 10^{-2} \text{ s}^{-1} \) and \( t_{1/2} \) of < 8.6 s were calculated\(^{a}\)

The reactivities of the different lithiated intermediate and electrophile combinations presented in Table 4.1 were also quantified using initial rate analysis. As the initial concentrations of all reagents were kept constant for each lithiation-trapping experiment it is possible to compare the reactivities of the different lithiated intermediates and electrophiles using the initial reaction rates. Initial rates were calculated by plotting the decaying absorbance of the lithiated intermediate during the trapping reaction and then calculating a gradient of a tangent to the initial consumption where the concentrations of lithiated intermediate and electrophile are known. For example, the initial rate analysis for the Me\(_3\)SiCl trapping of lithiated \( N \)-Boc pyrrolidine 164 provided initial rate, \( \text{rate}_{\text{init}} = (4.99 \pm 0.18) \times 10^{-4} \text{ s}^{-1} \) (Figure 4.4).
The initial rates for the trapping reactions presented in Table 4.1 are presented in Table 4.2 (initial rates for the trapping reactions with PhCHO are not included as these reactions were too rapid for kinetic analysis). The reactivity trends provided by both initial rates and the calculated $k_{obs}$ for the lithiated intermediates and electrophiles are identical, suggesting a good agreement between both methods of trapping rate quantification.

Table 4.2. Measured initial rates ($rate_{init}$) for the Me$_3$SiCl, Me$_2$SO$_4$ and MeI trapping reactions of lithiated intermediates 164, cis-201 and 199

<table>
<thead>
<tr>
<th></th>
<th>Me$_3$SiCl</th>
<th>Me$_2$SO$_4$</th>
<th>MeI</th>
</tr>
</thead>
<tbody>
<tr>
<td>164</td>
<td>rate$_{init}$ = $(4.99 \pm 0.18) \times 10^{-4}$ s$^{-1}$</td>
<td>rate$_{init}$ = $(8.41 \pm 0.13) \times 10^{-2}$ s$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>cis-201</td>
<td>rate$_{init}$ = $(4.76 \pm 0.12) \times 10^{-6}$ s$^{-1}$</td>
<td>rate$_{init}$ = $(1.39 \pm 0.09) \times 10^{-5}$ s$^{-1}$</td>
<td>rate$_{init}$ = $(1.34 \pm 0.31) \times 10^{-4}$ s$^{-1}$</td>
</tr>
<tr>
<td>199</td>
<td>rate$_{init}$ = $(9.70 \pm 0.70) \times 10^{-7}$ s$^{-1}$</td>
<td>rate$_{init}$ = $(2.53 \pm 0.37) \times 10^{-6}$ s$^{-1}$</td>
<td>rate$_{init}$ = $(8.90 \pm 0.46) \times 10^{-5}$ s$^{-1}$</td>
</tr>
</tbody>
</table>

* this initial rate was not calculated as upon addition of MeI, gelation was observed and this provided unreliable kinetics (this is discussed in more detail later)
On inspection of the trapping reaction $t_{1/2}$ and initial rates obtained for the three different lithiated heterocycles and four different electrophiles, trends in reactivity for both the lithiated intermediates and electrophiles are apparent. A clear trend in reactivity of the lithiated intermediates $164$, $cis$-$201$ and $199$ was evident with $Me_3SiCl$, $Me_2SO_4$ and $MeI$ electrophiles, which provided trapping reactions that were slow enough for differences in reactivity of the lithiated intermediates to be observed. For each of these three electrophiles, the same lithiated intermediate reactivity series was observed where $2$-lithio pyrrolidine $164 > 2$-lithio $4$-phenyl piperidine $cis$-$201 > 2$-lithio $N'$-Bn piperazine $199$.

At first glance, the trapping reactivity of these three $N$-Boc heterocycles appears to show no relationship with the lithiation reactivity order for the same substrates (Table 4.3). For example, $N'$-Bn piperazine $57$ affords the fastest lithiation reaction with $s$-$BuLi/TMEDA$ with $t_{1/2} = 18.3$ s but the respective lithiated intermediate $199$ provides the slowest trapping reactions of the three substrates. On closer inspection however, there may be a possible correlation between the lithiation and trapping reactivities of the two $6$-membered heterocycles in Table 4.2, $4$-phenyl $N$-Boc piperidine $cis$-$201$ and $N'$-Bn $N$-Boc piperazine $199$. For these two $6$-membered heterocycles we observe that a more facile lithiation means a slower rate of trapping with $Me_3SiCl$. At present, only kinetic data for the trapping reactions of the two $6$-membered heterocycles $199$ and $201$ has been collected and hence this trend may be an artefact from the small amount of data rather than an actual physical effect. Kinetic analysis of the trapping reactions of other $6$-membered heterocycles would need to be carried out to better determine whether there is an inverse trend between lithiation and trapping reactivities of these $6$-membered heterocycles. If this trend is not an artefact, it is possible that orbital overlap effects may be responsible for this inverse correlation in lithiation and trapping reactivities. In Chapter 2 we proposed that orbital overlap in the $6$-membered heterocycles could facilitate the lithiation $via$ back donation from the C-H $\sigma$ orbital of the $\alpha$-proton making it more acidic. With the lithiated intermediates this same process could result in the stabilisation of the carbanion intermediate $via$ the same back donation process. Therefore, the $6$-membered heterocycle with the most facile lithiation would have the most stabilised carbanion intermediate which would offer the slowest rate of trapping. In this case, $N'$-Bn piperazine $199$ would be the more stable carbanion than $4$-phenyl piperidine $cis$-$201$ resulting in its slower rate of trapping.
Table 4.3. Comparison of the $t_{1/2}$s of Me$_3$SiCl trapping and s-BuLi/TMEDA lithiation for lithiated N-Boc heterocycles 164, cis-201 and 199

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Me$<em>3$SiCl trapping $t</em>{1/2}$s</th>
<th>s-BuLi/TMEDA lithiation $t_{1/2}$s</th>
</tr>
</thead>
<tbody>
<tr>
<td>164</td>
<td>(81.1 ± 3.2) s</td>
<td>(20.7 ± 0.9) s</td>
</tr>
<tr>
<td>cis-201</td>
<td>(9160 ± 80) s</td>
<td>(642 ± 5) s</td>
</tr>
<tr>
<td>199</td>
<td>(51300 ± 400) s</td>
<td>(18.3 ± 0.9) s</td>
</tr>
</tbody>
</table>

The four electrophiles used for the trapping reactions presented in Table 4.1 displayed the same reactivity trend for each of the lithiated intermediates where the rate of trapping followed the order PhCHO $>$ MeI $>$ Me$_2$SO$_4$ $>$ Me$_3$SiCl. For the Me$_2$SO$_4$ and MeI trapping reactions of 2-lithio N-Boc pyrrolidine 164, it appears that the MeI trapping is slower than that for Me$_2$SO$_4$. However, gelation of the reaction mixture was observed upon addition of the MeI electrophile which provides unreliable kinetics due to the inhomogeneity of the reaction. For the MeI trapping reactions of 2-lithio 4-phenyl piperidine cis-201 and 2-lithio N'-Bn piperazine 199, negligible amounts of gelation occurred. A more detailed discussion of the gelation observed with MeI is presented in section 4.2.

For both the lithiated intermediates and electrophiles presented in Tables 4.1 and 4.2, clear reactivity trends are displayed but it is difficult to provide a general rationale for why these differences in reactivity occur. Generalising the trapping reactivity for each of the lithiated intermediates is likely to be misleading, as the reactivity with different electrophiles is probably dictated by different effects that are particular to the electrophile that is used. For example, the reactivity of some electrophiles may be primarily dictated by steric interactions and others due to the electronic properties of the lithiated intermediate. This would mean
that direct comparison of certain properties of the lithiated intermediates may not provide an explanation for all the different trapping reactivities observed. This point is highlighted by the rates of reaction observed for the Me₃SiCl and Me₂SO₄ trapping reactions of 2-lithio bicyclic pyrrolidine 203, which are presented below.

The Me₃SiCl trapping of lithiated bicyclic pyrrolidine 203 is an extremely slow reaction with \( t_{1/2} \approx 166000 \) s (\( t_{1/2} \) is approximate as no second electrophile was added to measure baseline shift) and is much slower than the analogous trapping of 2-lithio N'-Bn piperazine 199 (\( t_{1/2} = 51300 \) s) (Scheme 4.6.a). However, the Me₂SO₄ trapping of 2-lithio bicyclic pyrrolidine 203 is relatively fast with \( t_{1/2} = (1740 \pm 90) \) s and is much faster than the Me₂SO₄ trapping observed with 2-lithio N'-Bn piperazine 199 (\( t_{1/2} = 32400 \) s) (Scheme 4.6.b). This indicated that the lithiated intermediate with the slowest Me₃SiCl trapping does not necessarily mean that it will have the slowest trapping reactions with other electrophiles such as Me₂SO₄. For the case of 2-lithio bicyclic pyrrolidine 203, it is likely that the slow Me₃SiCl trapping results from the steric interactions between the hindered tertiary organolithium and sterically bulky Me₃SiCl electrophile. It is possible that the rate of Me₂SO₄ trapping with 2-lithio bicyclic pyrrolidine 203 is dictated by electronic effects rather than steric effects and this could explain the large difference in reactivity observed between the Me₃SiCl and Me₂SO₄ trapping reactions of lithiated pyrrolidine 203.
Scheme 4.6. Me₃SiCl (a) and Me₂SO₄ (b) trapping reactions of 2-lithio bicyclic pyrrolidine 203

Providing a complete rationale for the reactivity observed with the four electrophiles presented in Table 4.1 is also difficult. The PhCHO trapping reactions of each of the three lithiated intermediates were rapid, with complete trapping occurring between the 1 min time lapse between scans on the ReactIR™ apparatus. In fact, all trapping reactions conducted with PhCHO in this study, which involved five different lithiated intermediates, occurred rapidly with complete trapping occurring within the 1 min window between scans on the ReactIR™ apparatus (Figure 4.5).

Figure 4.5. Lithiated N-Boc heterocycles trapped using PhCHO
Clearly, the carbonyl group is the key to the fast trapping reactions observed with these electrophiles. Both literature and unpublished work by the O’Brien group have also provided evidence that carbonyl electrophiles such as benzophenone 206, cyclobutanone 207 and CO$_2$ also exhibit rapid, < 1 min, trapping reactions (Figure 4.6).

![Figure 4.6. Rapid trapping carbonyl electrophiles](image)

For each of the three lithiated intermediates whose trapping reactions were investigated (Tables 4.1 and 4.2), Me$_3$SiCl provided the slowest trapping reaction. It is well known that the trapping of organolithium reagents with chlorosilane electrophiles can provide slow reactions. It is likely that the slow rate of trapping observed with Me$_3$SiCl is due to the steric bulk of the electrophile which hinders the trapping process. There is evidence that the rate of the trapping reactions with chlorosilane electrophiles does depend on the size of the electrophile. For example, it is known the trapping reactions of organolithiums with the bulkier Ph$_3$SiCl electrophile are slower than those with Me$_3$SiCl.

Two of our key findings from this Chapter, the fact that Me$_3$SiCl trapping reactions tend to be slow and that trapping with carbonyl electrophiles are fast, is mirrored by work conducted by Aggarwal (see scheme 1.50). Aggarwal noted that the slow trapping of a particular enantioenriched lithiated intermediate with Me$_3$SiCl was problematic, as the rates of trapping and racemisation of the intermediate were similar which resulted in the trapped products being obtained in poor er. Conversely, fast trapping electrophiles such as ClCO$_2$Me provided the trapped product in high er as the fast rate of trapping outcompeted the slower rate of lithiated intermediate racemisation.

Both Me$_2$SO$_4$ and MeI electrophiles provided moderate trapping reactivities between those of Me$_3$SiCl and PhCHO. However, the reason why Me$_2$SO$_4$ afforded slower trapping reaction than MeI is currently unclear. Based on a simple analysis, it was perhaps expected that the trapping reactions with the hard alkyllithium and hard Me$_2$SO$_4$ electrophile would be faster than the soft MeI electrophile.
4.2 Investigation of the Gelation of the Reaction Mixture When Using MeI as the Electrophile

As mentioned in section 4.1, the MeI trapping reaction of 2-lithio N-Boc pyrrolidine 164 provided unreliable kinetic data and this was attributed to gelation of the reaction solution occurring upon addition of the MeI electrophile (Table 4.1 and Scheme 4.7). When MeI was added, the bulk reaction mixture solidified, stirring of the reaction ceased and the solution developed a turbid appearance. The ReactIR™ monitoring of the trapping reaction indicated that the reaction stalled mid-reaction (circled in Scheme 4.7.a) and then the trapping continued. It is likely that the lack of stirring and inhomogeneity of the solution are the reason for these anomalous kinetic data.

Scheme 4.7. ReactIR™ monitored MeI trapping of 2-lithio N-Boc pyrrolidine 164 (a) and the observed gelation in the reaction flask (b)

For the MeI trapping reactions of 2-lithio 4-phenyl piperidine cis-201 and 2-lithio N’-Bn piperazine 199, only very small amounts of gelation were visually observed at the edge of the reaction flask. For each of these MeI trapping reactions, no detrimental effects on the kinetic data collected were observed due to the small amounts of gelation. It is possible that the fast rate of trapping between MeI and 2-lithio pyrrolidine 164 may result in the gelation
of the entire bulk solution, whereas slower trapping reactions of lithiated intermediates cis-201 and 199 which require >1 h for complete trapping to occur, may result in only small amounts of gelation. This hypothesis is further supported by the fast MeI trapping of lithiated 4-amino \textit{N}-Boc piperidine \textit{cis}-208 where the complete gelation of the bulk solution also occurred (Scheme 4.8). Upon addition of the MeI electrophile, the ReactIR™ monitoring indicated that trapping reaction had stalled after 15 min. After the work-up, \textsuperscript{1}H NMR spectroscopy of the crude product indicated that 4-amino \textit{N}-Boc piperidine 168 starting material was present and subsequent purification provided methylated product \textit{cis}-209 in 40\% yield and recovered starting material 168 in 21\% yield. The recovery of unreacted starting material likely arises from incomplete trapping where the gelation of the solution prevents complete trapping from occurring, as the lithiation and Me\textsubscript{3}SiCl trapping reaction of 4-amino \textit{N}-Boc piperidine 168 provided complete conversion to the Me\textsubscript{3}SiCl trapped adduct (see section 6.6).

**Scheme 4.8. ReactIR™ monitored MeI trapping of 2-lithio 4-amino piperidine \textit{cis}-208**

The gelation during the trapping reactions of lithiated intermediates was not observed with any electrophiles other than MeI that were used in this investigation. Therefore, we conclude that the gelation may arise from the formation of LiI salts during the trapping reaction. To
probe whether LiI was responsible for the gelation observed, an attempt to recreate the gelation using LiI salts was explored (Scheme 4.9). LiI salt (2.0 mmol), TMEDA (1.30 mmol) and Et₂O (14 mL) were stirred at rt for 30 min and then cooled to −78 °C but no gelation was observed. A second reaction was conducted where s-BuLi (1.3 mmol of a 1.3 M solution in cyclohexane) was added to a stirred solution of TMEDA (1.3 mmol) and MeI (2.00 mmol) at −78 °C. Upon addition of MeI, the solution developed a turbid appearance, similar to that observed during the trapping reactions of 164, cis-201 and 199 and a small amount of gelation was observed. This experiment suggests that the liberation of LiI salts from the reaction between the alkyllithium reagents and MeI may be responsible for the gelation observed. Furthermore, we postulate that rapid trapping reactions with MeI may form the LiI salts over a short period of time which causes the gelation of the entire bulk solution, as observed with the MeI trapping reactions of 2-lithio pyrrolidine 164 and 2-lithio 4-amino piperidine cis-208.

Scheme 4.9. Attempted recreations of the gelation observed with the MeI trapping reaction using (a) LiI and TMEDA and (b) s-BuLi/TMEDA and MeI

(a) Et₂O

1. LiI (2.0 eq.)
2. TMEDA (1.3 eq.)

No Change

No Change

(b) Et₂O, −78 °C

1. MeI (2.0 eq.)

No Change

TMEDA (1.3 eq.)

No Change

s-BuLi (1.3 eq.)

solution becomes turbid and small amount of gelation observed
4.3 Conclusions and Future Work

A comprehensive reactivity study of the trapping reactions of three different lithiated intermediates 164, \textit{cis}-201 and 199 with four different electrophiles (Me$_3$SiCl, Me$_2$SO$_4$, MeI and PhCHO) has provided some interesting details on the reactivity observed in the trapping reactions studied. For this selection of trapping reactions, it was found that for the lithiated intermediates the reactivity was ordered as follows: 2-lithio pyrrolidine 164 > 2-lithio 4-phenyl piperidine \textit{cis}-201 > 2-lithio N’-Bn piperazine 199. For the electrophiles, the order of reactivity observed was: PhCHO >> MeI > Me$_2$SO$_4$ > Me$_3$SiCl (Figure 4.7).

![Figure 4.7. Reactivity series determined for the N-Boc heterocycle lithiated intermediates 164, \textit{cis}-201, 199 and Me$_3$SiCl, Me$_2$SO$_4$, MeI and PhCHO electrophiles used in this investigation.]

Providing a rationale that explained all of the trends in reactivity that were observed in this investigation was not possible. The reactivity data collected suggests that both steric and electronic factors likely influence the rate of the trapping reaction. The dominant effect that determines the rate of the trapping reaction is likely to be different for each different combination of lithiated intermediate and electrophile. Therefore, the use of a general rationale that provides information about the rate of the trapping reaction with a particular lithiated intermediate and electrophile may not be possible.

This inability to predict the reactivity of the trapping reactions of lithiated intermediate highlights how crucial ReactIR™ monitoring can be to ensure that complete trapping occurs. This is particularly important for asymmetric or diastereoselective lithiation-trapping reactions, where warming up the reaction before complete trapping has occurred can erode
the $\text{er/dr}$ of the trapped products. The effect that the rate of the trapping reaction can have on the diastereoselectivity obtained is explored in Chapter 5.

With MeI, an additional complication arose due to the gelation of the reaction mixture that can give poor kinetic data and also results in incomplete trapping. Experiments conducted in this investigation suggest that the formation of LiI salts upon addition of MeI may be responsible for the gelation observed. This suggests that for the methylation of lithiated intermediates, $\text{Me}_2\text{SO}_4$ may be a more suitable electrophile. However, the lower reactivity of $\text{Me}_2\text{SO}_4$ also needs to be considered when evaluating the most suitable methylating electrophile.

At this point in time, it is unclear whether expanding this trapping study further would provide any further useful information about the trapping reaction, as there is evidence that each combination of lithiated intermediate and electrophile may have a rate of trapping that is specific to that combination of reagents. However, the computational modelling of these trapping reactions of lithiated intermediates, similar to that conducted for the $\alpha$-lithiation reaction in Chapter 2, may be able to provide an explanation for the reactivity observed. A computational model may be able to give a predicted reactivity for combinations of lithiated intermediate and electrophile and may be able to distinguish whether steric or electronic effects are primarily responsible for the reactivity observed for a specific trapping reaction. Ultimately, our overall conclusion is that real-time, $\textit{in situ}$ IR spectroscopic monitoring of the lithiation and trapping steps for $N$-Boc heterocycles should be widely adopted.
Chapter 5: Diastereoselective Lithiation-Trapping of a 3,4-
Disubstituted Bicyclic N-Boc Pyrrolidine

The lithiation-trapping reactions of a significant array of N-Boc heterocycles have been reported since Beak’s seminal publication in 1989. However, to date, only a few of these N-Boc heterocycles have included a 3,4-disubstituted pyrrolidine motif as summarised in section 1.2.5.

In this Chapter, we bring together all of the methods and ideas developed in this thesis and apply them to a specific case study. The research presented in this Chapter focuses on the diastereoselective α-lithiation and trapping reactions of one particular 3,4-disubstituted N-Boc pyrrolidine 96 (Scheme 5.1). The effect of both the diamine ligand and the electrophile (E⁺) on the diastereoselectivity of the lithiation-trapping reactions of N-Boc pyrrolidine 96 are investigated.

Scheme 5.1. General α-lithiation-trapping of 3,4-substituted N-Boc pyrrolidine 96

![Scheme 5.1](image)

Since some interesting effects on diastereoselectivity were uncovered, additional experiments were performed and in situ IR spectroscopy was utilised to attempt to elucidate the results and trends that were observed. These experimental results are also complemented with computational DFT calculations in an attempt to model and rationalise the diastereoselectivity observed with the different diamine ligands employed.
5.1 Effect of the Electrophile on the Diastereoselectivity of the Lithiation-Trapping of a Bicyclic N-Boc Pyrrolidine

Bicyclic N-Boc pyrrolidine 96 was selected as a suitable substrate to investigate the diastereoselectivity of a 3,4-disubstituted pyrrolidine for two reasons. First, an asymmetric s-BuLi/(−)-sparteine lithiation-trapping reaction of N-Boc pyrrolidine 96 had previously been reported by Beak and Johnson (see Scheme 1.31). Second, N-Boc pyrrolidine 96 was available via a relatively simple two-step synthesis from imide 210, a commercially available starting material. Reduction of imide 210 with LiAlH₄ and subsequent Boc protection of the secondary amine allowed the synthesis of 3,4-disubstituted N-Boc pyrrolidine 96 (71% yield) in multi-gram quantities (Scheme 5.2).

Scheme 5.2. Two-step synthesis of bicyclic N-Boc pyrrolidine 96

The lithiation of N-Boc pyrrolidine 96 was carried out using 1.3 eq. s-BuLi/TMEDA in Et₂O at −78 °C with a 10 min lithiation time. This lithiation time was selected as the ReactIR™-monitored lithiation of N-Boc pyrrolidine 96 conducted for the reactivity study (see Chapter 2) demonstrated that complete lithiation required just 4 min. The resulting lithiated intermediate was then trapped with a range of different electrophiles which furnished trapped products 99, 211-214 in good yield and anti:syn diastereoselectivity that ranged from 87:13 ≥95:5 (i.e. only one diastereomer detected by ¹H NMR spectroscopy) (Table 5.1).
Table 5.1. \( s\)-BuLi/TMEDA lithiation of \( N\)-Boc pyrrolidine 96 and subsequent trapping with a range of electrophiles

![Diagram of reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>( E^+ )</th>
<th>E</th>
<th>Products</th>
<th>Combined % yield</th>
<th>( anti:syn )^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Me}_3\text{SiCl} )</td>
<td>( \text{SiMe}_3 )</td>
<td>( \text{anti-99} )</td>
<td>75</td>
<td>( \geq 95:5 )</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Me}_2\text{SO}_4 )</td>
<td>( \text{Me} )</td>
<td>( \text{anti} ) and syn-( 211 )</td>
<td>83</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>( \text{CO}_2 )</td>
<td>( \text{COOH} )</td>
<td>( \text{anti} ) and syn-( 212 )</td>
<td>77</td>
<td>87:13</td>
</tr>
<tr>
<td>4</td>
<td>Weinreb amide 215</td>
<td>( \text{COPh} )</td>
<td>( \text{anti} ) and syn-( 213 )</td>
<td>73</td>
<td>87:13</td>
</tr>
<tr>
<td>5</td>
<td>( \text{PhCHO} )</td>
<td>( \text{C(OH)Ph} )</td>
<td>214 - See Figure 5.2</td>
<td>78</td>
<td>87:13</td>
</tr>
</tbody>
</table>

^a% yield of all diastereomers after purification by column chromatography (see text for details)

^b ratio of diastereomers determined by \(^1\)H NMR spectroscopy (see text for details), for \( \text{Me}_3\text{SiCl} \) and \( \text{Me}_2\text{SO}_4 \) trappings the dr was determined from purified products and for \( \text{CO}_2 \), 215 and \( \text{PhCHO} \) electrophiles the dr was determined from the crude product.

For the \( \text{Me}_3\text{SiCl} \) and \( \text{Me}_2\text{SO}_4 \) trapped adducts 99 and 211 (entries 1 and 2), it was not possible for the diastereomeric ratios to be measured directly using \(^1\)H NMR spectroscopy. This was primarily due to rotamers (that arise due to the Boc group) which cause the signals in the \(^1\)H NMR spectra to broaden, which can obscure the diastereomeric peaks. To remove the rotamers and this broadening effect for the \( \text{Me}_3\text{SiCl} \)-trapped product \( \text{anti-99} \), the Boc group was removed and a sulfonamide was formed, for which rotamers do not occur. Removal of the Boc group from \( \text{anti-99} \) was accomplished using TFA and then subsequent treatment of crude amine \( \text{anti-216} \) with \( p\)-TsCl formed sulfonamide \( \text{anti-217} \) in 87% yield (Scheme 5.3). The \(^1\)H NMR spectra of both crude amine \( \text{anti-216} \) and sulfonamide \( \text{anti-217} \) indicated that only one diastereomer was present and indicated that the \( \text{Me}_3\text{SiCl} \)-trapped product \( \text{anti-96} \) had been formed in \( \geq 95:5 \) dr.
The sulfonamide formation procedure was also used to obtain the ratio of methyl-trapped adducts \textit{anti}-211 and \textit{syn}-211. After TFA cleavage of the Boc group and sulfonamide formation using \textit{p}-TsCl, crude sulfonamides \textit{anti}-218 and \textit{syn}-218 were obtained in a 90:10 ratio. This ratio was unaffected by purification and a 90:10 mixture of sulfonamides \textit{anti}-218 and \textit{syn}-218 was obtained in 35\% yield (Scheme 5.4).

Trapping the lithiated intermediate of \textit{N}-Boc pyrrolidine 96 with CO\textsubscript{2} gave an 87:13 mixture of carboxylic acids \textit{anti}-212 and \textit{syn}-212 in a combined 77\% yield (Table 5.1, entry 3). In this case, the dr was measured using the signals for the NCH $\alpha$-proton adjacent to the carboxylic acid functional group in the $^1$H NMR spectrum. This ratio was also confirmed by conversion of carboxylic acids \textit{anti}-212 and \textit{syn}-212 into the corresponding methyl esters, by methylation of the carboxylic acid with Me$_3$Si-diazomethane. This gave an 87:13 mixture of methyl esters \textit{anti}-219 and \textit{syn}-219 in 86\% yield (Scheme 5.5).
Trapping with Weinreb amide 215 afforded an 87:13 mixture of ketones \textit{anti}-213 and \textit{syn}-213 (Table 5.1, entry 4). Ketones \textit{anti}-213 and \textit{syn}-213 were separable by column chromatography and were obtained in 67\% and 6\% yield respectively. PhCHO trapping gave an 87:13 \textit{anti: syn} dr of trapped products (Table 5.1, entry 5) which was the same dr as those obtained by trapping CO$_2$ and Weinreb amide 215 electrophiles. However, the determination of the dr from the PhCHO trapping was a more complex task as it is possible to form four diastereomers of the PhCHO trapped product, due to the additional stereocentre (C4) on the benzylic alcohol (Figure 5.1).

A convention to assign the relative stereochemistry was adopted for the four possible diastereomers formed by the PhCHO lithiation-trapping reaction. As the stereogenic centres C1 and C2 are fixed, it was decided to use stereogenic centres C2, C3 and C4 to define the relative stereochemistry of the product: the first label (\textit{syn} or \textit{anti}) defines the relative stereochemistry of the protons at C2 and C3 and the second label (\textit{syn} or \textit{anti}) defines the relative stereochemistry of the proton at C3 and the hydroxyl group at C4 with the phenyl group adopting the orientation depicted.

The s-BuLi/TMEDA lithiation and PhCHO trapping of N-Boc pyrrolidine 96 (Table 5.1, entry 5) gave a 4:9:29:58 mixture of diastereomeric alcohols \textit{syn-anti}-214, \textit{syn-syn}-214, \textit{anti-syn}-214 and \textit{anti-anti}-214 respectively (measured by $^1$H NMR spectroscopy of the crude product). This gives an 87:13 \textit{anti:syn} ratio for the C2-C3 relative stereochemistry (i.e. ignoring the C4 stereochemistry). After chromatography, products \textit{syn-anti}-214 (3\%), \textit{anti-anti}-214 (1\%)...
syn-214 (23%) and an 80:20 mixture of anti-anti-214 and syn-syn-214 (46%) were isolated by column chromatography, giving a 78% overall yield (Figure 5.2).

Figure 5.2. Diastereomeric alcohol products from the s-BuLi/TMEDA lithiation and PhCHO trapping of N-Boc pyrrolidine 96

To identify the relative stereochemistry of each of the four diastereomers produced from the PhCHO trapping reaction, the alcohols were oxidised to their respective ketones using Dess-Martin periodinane (DMP). This removed the C4 benzylic stereocentre and reduced the number of diastereomers to only two. For the 80:20 mixture of anti-anti-214 and syn-syn-214, DMP oxidation gave a 90:10 mixture of ketones anti-213 and syn-213 which were isolated in 72% yield. The presence of these two diastereomeric ketones indicated that this was a mixture of two diastereomers with different C2/C3 relative stereochemistries. For syn-anti-214, DMP oxidation yielded ketone syn-213 (60%) and DMP oxidation of anti-syn-214 yielded only anti-213 (65%) (Scheme 5.6).

Scheme 5.6. DMP oxidation of diastereomeric alcohols 214 to identify relative stereochemistry
The C3/C4 relative stereochemistry was determined using $^1$H NMR spectroscopy. Literature precedent indicated that for similar PhCHO trapped N-Boc pyrrolidine 31, \textit{anti}-31 had broad signals in its $^1$H NMR spectrum, whereas \textit{syn}-31 did not show a broadening effect (Figure 5.3).\textsuperscript{133} This study also included an X-ray crystal structure which confirmed the relative stereochemistry of \textit{anti}-31. This same phenomenon was observed for the diastereomers of PhCHO-trapped 3,4-disubstituted pyrrolidine 214 which allowed the C3/C4 stereochemistry to be assigned.

This study also included an X-ray crystal structure which confirmed the relative stereochemistry of \textit{anti}-31. This same phenomenon was observed for the diastereomers of PhCHO-trapped 3,4-disubstituted pyrrolidine 214 which allowed the C3/C4 stereochemistry to be assigned.

Figure 5.3. Diastereomeric alcohols \textit{anti}-31 and \textit{syn}-31

For all five lithiation-trapping reactions of \textit{N}-Boc pyrrolidine 96 reported in Table 5.1, the \textit{anti} diastereomer was the major diastereomer in the trapped products. The assignment of the \textit{anti} relative stereochemistry was proved for the Me$_3$SiCl and the Weinreb amide 215/PhCHO-trapped products. For methylated pyrrolidines \textit{syn}-211 and \textit{anti}-211 and carboxylic acids \textit{syn}-212 and \textit{anti}-212, the relative stereochemistry was assigned by analogy.

For the Me$_3$SiCl-trapped adduct \textit{anti}-99, there is literature precedent which also included an X-ray crystal structure for a similar saturated compound \textit{anti}-221.\textsuperscript{4} To further support our assignment of this relative stereochemistry, Me$_3$SiCl-trapped pyrrolidine \textit{anti}-99 was converted into \textit{anti}-221. First, \textit{anti}-99 was hydrogenated with Pd/C and H$_2$ to reduce the alkene. Then, \textit{anti}-220 was treated with TFA and then \textit{p}-TsCl to cleave the Boc group and form the sulfonamide respectively. These transformations yielded sulfonamide \textit{anti}-221 as a single diastereomer ($\geq$95:5 dr) in 59% yield (Scheme 5.7). The $^1$H NMR spectrum of \textit{anti}-221 was identical to that reported in the literature, confirming the \textit{anti} relative stereochemistry.\textsuperscript{4}
Scheme 5.7. Hydrogenation, Boc deprotection and sulfonamide formation for Me₃SiCl-trapped product anti-99

The relative stereochemistry of the minor diastereomer for both the Weinreb amide 215 and PhCHO trapping reactions was proved by X-ray crystal analysis of ketone syn-213. Fortuitously, ketone syn-213 was obtained as a solid after purification by column chromatography which, after recrystallisation, was subjected to X-ray analysis. X-ray analysis of syn-213 confirmed the assignment of syn relative stereochemistry for the minor diastereomer (Figure 5.4).

Figure 5.4. X-ray crystal structure of syn-213 with thermal ellipsoids set at 50%, confirming syn relative stereochemistry

This anti diastereoselectivity can be rationalised as follows. It is likely that the deprotonation of the least sterically hindered α-proton anti to the cyclohexene ring (H_{anti}) will be favoured,
forming lithiated intermediate *anti*-222 as the major diastereomer (Figure 5.5). With N-Boc pyrrolidines, it is believed that the subsequent trapping reaction occurs with retention of stereochemistry, conserving the stereochemistries of lithiated intermediates *anti*-222 and *syn*-222.

![Figure 5.5. Rationale for the *anti* selectivity of the lithiation-trapping of N-Boc pyrrolidine 96](image)

The drs obtained for the five lithiation-trapping reactions of N-Boc pyrrolidine 96 in Table 5.1 (87:13 to ≥95:5) indicate that the reaction has good to excellent diastereoselectivity. However, the variation in the observed drs of the trapped products obtained with different electrophiles (Table 5.1) suggest that the dr of the trapped product does not simply arise from the diastereoselectivity of the lithiation reaction. If diastereoselectivity arose exclusively from the ratio of the lithiated intermediates, the drs of the products obtained by each different electrophile would be the same.

We therefore postulated that the variations in dr of the trapped products shown in Table 5.1 were caused by kinetic effects during the trapping reactions of diastereomeric lithiated intermediates *anti*-222 and *syn*-222. When monitoring the trapping reactions of a similar unsubstituted lithiated N-Boc pyrrolidine 9 at −78 °C, it was noted that the Me3SiCl trapping reaction was relatively slow (t_{1/2} = 86.9 s) compared to other electrophiles such as PhCHO (t_{1/2} < 8.6 s). It is plausible that for a more hindered substrate such as 3,4-disubstituted N-Boc pyrrolidine 96, this trapping reaction may be slower still. If the trapping of the lithiated intermediates *anti*-222 and *syn*-222 is slow, a dynamic kinetic resolution (DKR) could be established. There are many examples where establishing a DKR has been utilised to selectively generate compounds and cases where a DKR can alter the er of an asymmetric lithiation reaction.\(^{134–136}\)

It is possible that a DKR can be established if the trapping reaction is slow and the partially trapped or un-trapped lithiated intermediates are then allowed to warm to room temperature.
before complete trapping has occurred (Scheme 5.8). At a temperature above –78 °C during the warming to room temperature after the trapping is believed to be complete, lithiated intermediates \textit{anti-223} and \textit{syn-223} will become configurationally unstable which enables them to interconvert. The configurational instability of lithiated intermediates at temperatures above –20 °C is well known.\textsuperscript{129,130,137} These rapidly converting lithiated intermediates can then be diastereoselectively trapped with the electrophile, as the rate of trapping for the two diastereomeric lithiated intermediates ($k_1$ and $k_2$) is likely to be different. It is logical that the trapping of lithiated intermediate \textit{anti-223} will be faster than that of \textit{syn-223} as there will be less steric interaction between the incoming electrophile and the cyclohexene ring. This will enrich the dr of the trapped product above that of the lithiated intermediate (> 87:13 for $s$-BuLi/TMEDA), thus giving a larger proportion of the \textit{anti} diastereomer in the trapped product. Conversely, a faster trapping electrophile such as PhCHO (which was shown to trap lithiated intermediates in < 1 min in section 4.1) will trap lithiated intermediates \textit{anti-223} and \textit{syn-223} rapidly at –78 °C, meaning that the configuration of the lithiated intermediates remains stable and the stereochemistry is retained. Therefore, the dr of the trapped products with a fast trapping electrophile should be representative of the diastereoselectivity imparted by the lithiation reaction.
Scheme 5.8. Proposed dynamic kinetic resolution for the trapping of 2-lithio $N$-Boc pyrrolidines $anti$-$223$ and $syn$-$223$

In an attempt to prove this dynamic kinetic resolution hypothesis, several ‘high temperature’ lithiation-trapping experiments were carried out using $N$-Boc pyrrolidine $96$. Lithiation of $N$-Boc pyrrolidine $96$ was conducted at $-20 \, ^\circ C$ and the resulting lithiated intermediate was trapped with Me$_3$SiCl, Me$_2$SO$_4$ and PhCHO electrophiles. It was expected that the lithiated intermediates formed from $N$-Boc pyrrolidine $96$ would be configurationally unstable at $-20 \, ^\circ C$, meaning that the lithiation would effectively impart no diastereoselectivity and diastereoselectivity in the products would be solely due to the trapping reaction.

The lithiation-trapping of $N$-Boc pyrrolidine $96$ at $-20 \, ^\circ C$ with PhCHO gave a 50:50 $anti$:syn mixture of diastereomeric alcohols. This result confirmed that the lithiated intermediates were not configurationally stable at $-20 \, ^\circ C$ and that the fast PhCHO trapping reaction traps
the lithiated intermediates in the ratio that they are formed. The ‘high temperature’ lithiation-trapping of N-Boc pyrrolidine 96 with Me<sub>3</sub>SiCl provided the same dr as when carried out at –78 °C, with only one diastereomer anti-99 (≥95:5 dr) obtained in 64% yield. This indicated that only the trapping of diastereomeric lithiated intermediate anti-222 was feasible at –20 °C, confirming that a DKR process does occur. The ‘high-temperature’ lithiation of pyrrolidine 96 and trapping with Me<sub>2</sub>SO<sub>4</sub> gave a 70:30 mixture of the methylated products anti-211 and syn-211 (measured by <sup>1</sup>H NMR spectroscopy of the respective sulfonamides anti- and syn-218 – see Scheme 5.4). This represented an eroded dr compared to the 90:10 anti:syn dr obtained at –78 °C (see Table 5.1, entry 2). This suggests there is a difference in the rate of the Me<sub>2</sub>SO<sub>4</sub> trapping reactions of the lithiated intermediates anti-222 and syn-222 but the difference in rates was not as significant as for Me<sub>3</sub>SiCl trapping, so both diastereomers of methylated product anti- and syn-211 were still obtained (Scheme 5.9).

Scheme 5.9. ‘High temperature (–20 °C)’ lithiation trapping of N-Boc pyrrolidine 96

Diastereomeric alcohols 214 were obtained in a 1:1:1:1 dr, the 50:50 dr reported ignores the highlighted stereocentre (*)

Further evidence for the occurrence of a dynamic kinetic resolution was provided by <i>in situ</i> IR spectroscopy. The ReactIR<sup>TM</sup> monitored s-BuLi/TMEDA lithiation and PhCHO trapping reaction of N-Boc pyrrolidine 96 at –78 °C confirmed our assumption that, analogous to the PhCHO trapping of unsubstituted N-Boc pyrrolidine 9 (see Table 4.1), PhCHO trapping occurred rapidly at –78 °C. After the lithiation of N-Boc pyrrolidine 96 was complete, PhCHO was added and complete trapping was observed at –78 °C within the one minute time lapse between scans (Scheme 5.10). The crude mixture of diastereomeric alcohol products 214 was oxidised with DMP to make purification and analysis easier and an 87:13 mixture of ketones anti-213 and syn-213 were obtained in 78% yield.
The ReactIR™ monitored lithiation-trapping of N-Boc pyrrolidine 96 with s-BuLi/TMEDA and Me₂SO₄ surprisingly gave a similar kinetic trace to that of the trapping with PhCHO. Following the lithiation of N-Boc pyrrolidine 96, Me₂SO₄ was added and a relatively fast reaction (3 min trapping time) was observed (Scheme 5.11). A 3 min trapping time was also observed for the Me₂SO₄ trapping of lithiated N-Boc pyrrolidine 9 (see section 4.1). MeOH was added after 40 min to ensure that complete trapping had occurred at –78 °C. If any un-trapped lithiated intermediate did remain it would be quenched by MeOH to reform the N-Boc pyrrolidine 96 starting material. No evidence of any further trapping was observed by ReactIR™ and only a small increase in both IR absorbances was observed due to a baseline shift resulting from the addition of MeOH. Additionally, ¹H NMR spectroscopic analysis of the crude product and purification indicated that no starting material was present confirming that complete trapping had occurred. As the trapping with Me₂SO₄ is fast at –78 °C, the lithiated intermediate should remain configurationally stable throughout. There is a slight difference between the 90:10 dr obtained with Me₂SO₄ and 87:13 drs obtained with CO₂, PhCHO and Weinreb amide 215 electrophiles. It is not currently known why this apparently fast trapping reaction provides a different dr to those with other fast trapping electrophiles.

Scheme 5.10. ReactIR™ monitored lithiation-trapping of N-Boc pyrrolidine 96 with s-BuLi/TMEDA and PhCHO

![Scheme 5.10](image-url)
It is possible this small difference in dr may arise due to measurement error in the $^1$H NMR spectroscopic analysis.

Scheme 5.11. ReactIR™ monitored lithiation-trapping of N-Boc pyrrolidine 96 with s-BuLi/TMEDA and Me$_2$SO$_4$

Finally, the s-BuLi/TMEDA lithiation-trapping of N-Boc pyrrolidine 96 was carried out using Me$_3$SiCl to trap the lithiated intermediates. After the 4 min lithiation at −78 °C, Me$_3$SiCl was added and, as expected, a slow trapping reaction was observed by ReactIR™. The reaction is likely impeded by steric effects due to the sterically bulky Me$_3$SiCl electrophile. After 2 h at −78 °C, the consumption of the lithiated intermediate ceased. A second, fast-trapping electrophile, PhCHO, was added to trap any remaining un-trapped lithiated intermediate. Upon addition of PhCHO, the ReactIR™ monitoring indicated further consumption of lithiated intermediate which was complete within 1 min (Scheme 5.12). Clearly, a second trapping event with the PhCHO had occurred. The crude product was then treated with DMP to oxidise the alcohol diastereomers to simplify analysis and purification.
After oxidation, Me$_3$SiCl trapped anti-$99$ and PhCHO trapped and oxidised syn-$213$ were isolated in 53% and 10% yield respectively.

**Scheme 5.12. ReactIR™ monitored lithiation-trapping of N-Boc pyrrolidine 96 with s-BuLi/TMEDA and Me$_3$SiCl/PhCHO**

This result indicated that the trapping of lithiated intermediate syn-$223$ with Me$_3$SiCl is either extremely slow or does not occur. Thus, when Me$_3$SiCl was used as the electrophile only lithiated intermediate anti-$223$ underwent trapping to form 2-silyl product anti-$99$ at $-78 \, ^\circ\text{C}$. In this two-electrophile example, the un-trapped lithiated intermediate syn-$223$ was trapped when the PhCHO electrophile was added. This explains why the two products obtained, anti-$99$ and syn-$213$, are diastereomerically pure. On the other hand, if Me$_3$SiCl was the only electrophile added, the unreacted syn-$223$ lithiated intermediate would lose configurational stability during the warming of the reaction and interconvert into anti-$223$ which is then
trapped by Me$_3$SiCl. This accounts for why trapping with Me$_3$SiCl gives only one observed diastereomer (≥ 95:5 dr, see Table 5.1, entry 1), as the reaction was allowed to warm slowly to room temperature after addition of Me$_3$SiCl.

In conclusion, these lithiated intermediate trapping studies have shown that the electrophile used can have a significant effect on the diastereoselectivity observed for the lithiation-trapping of a 3,4-disubstituted N-Boc pyrrolidine such as 96. A less reactive/slower trapping electrophile can allow a dynamic kinetic resolution to be established, which can then enrich dr of the trapped products beyond that established by the lithiation reaction itself.
5.2 Effect of the Diamine Ligand on the Diastereoselectivity of the Lithiation-Trapping of a Bicyclic N-Boc Pyrrolidine

The effect that the diamine ligand has on the diastereoselectivity of the lithiation-trapping of 3,4-disubstituted N-Boc pyrrolidine 96 was also studied. The study used five of the diamine ligands which had previously been employed for the reactivity study in Chapter 2: TMPDA 179, TMEDA, TMCDA \textit{trans}-161, DPE 177 and tetraisopropyl diamine 178. In addition to these ligands, two bispidine ligands di-\textit{n}-Pr bispidine 105 and di-\textit{i}-Pr bispidine 30 were also used to probe how the identity of the diamine would affect the diastereoselectivity observed (Figure 5.6).

![Diamine ligands used for the lithiation of bicyclic pyrrolidine 96](image)

**Figure 5.6. Diamine ligands used for the lithiation of bicyclic pyrrolidine 96**

Bispidine ligands 105 and 30 have both been prepared and used in previous work conducted by the O’Brien group. However, this previous work was in a different vein where they were used in conjunction with (–)-sparteine for a catalytic purpose.\(^\text{37,138}\) Both di-\textit{i}-Pr bispidine 30 and di-\textit{n}-Pr bispidine 105 were synthesised following an existing optimised procedure.\(^\text{138}\) For di-\textit{i}-Pr bispidine 30, this involved the synthesis of bispidone 225 (in 41\% yield) via a double Mannich reaction of \textit{N-\textit{i}-Pr-piperid}-4-one 224 with paraformaldehyde and \textit{i}-PrNH\(_2\). A subsequent Huang-Minlon modified Wolff-Kishner reduction of the resulting bispidone 225 gave bispidine 30 in a good 91\% yield (Scheme 5.13). The same procedure was used for the synthesis of di-\textit{n}-Pr bispidine 105. The bispidone intermediate was synthesised using a double Mannich reaction with \textit{N-\textit{n}-Pr-piperid}-4-one 226 and \textit{n}-PrNH\(_2\) which gave bispidone 227 in 38\% yield. Next, bispidone 227 was subjected to Wolf-Kishner reduction giving di-\textit{n}-Pr bispidine in 95\% yield. The double Mannich reaction provided only moderate 41\% and 38\% yields of bispidone intermediates 225 and 227; it is likely that the poor yields result from the purification of the intermediates. Bispidones 225 and 227 were purified by vacuum distillation but complete separation from the messy crude product was difficult and
Distillation at higher temperature resulted in decomposition of bispidones 225 and 227. $^1$H NMR spectroscopic analysis of the resulting tar-like residue indicated that significant amounts of the bispidone were still present after distillation. The problematic purification and low yielding double Mannich reaction for a different bispidone has also been reported.\textsuperscript{53}

Scheme 5.13. Synthesis of the di-i-Pr and di-n-Pr bispidone ligands 30 and 105

During the synthesis of the bispidones 225 and 227 and bispidines 30 and 105, another complexity arose when characterising the compounds using $^1$H NMR spectroscopy. It appeared that these compounds were reacting with the CDCl$_3$ NMR solvent. The $^1$H NMR spectra for the bispidones 225 and 227 showed the expected peaks but there was also a complex mixture of products that were unidentifiable (Figure 5.7). NMR samples of 225 and 227 were then prepared using a DMSO-d$_6$ solvent which gave the expected spectra.

Figure 5.7. $^1$H NMR spectra showing 4.5-0.0 ppm region for di-i-Pr bispidone 225 in CDCl$_3$ (left) and DMSO-d$_6$ (right) (peaks at 3.34, 3.31 and 2.50 due to H$_2$O, HOD and DMSO solvent)
When $^1$H NMR spectroscopic analysis of bispidines 30 and 105 was conducted in CDCl$_3$, none of the expected signals were observed and an unidentifiable complex mixture of products was recorded instead. In contrast, when NMR samples of bispidines 30 and 105 were prepared using a DMSO-$d_6$ solvent, the expected well resolved spectra were obtained (Figure 5.8).

![Figure 5.8. $^1$H NMR spectra showing 4.0-0.0 ppm region for di-$n$-Pr bispidine 105 in CDCl$_3$ (left) and DMSO-$d_6$ (right) (peaks at 3.33, 3.31 and 2.50 due to H$_2$O, HOD and DMSO solvent)](image)

As the use of the DMSO-$d_6$ solvent gave the expected spectra for bispidones 225 and 227 and bispidines 30 and 105, it was likely that the CDCl$_3$ solvent was reacting with the diamines. This undesired reaction would account for the complex and messy $^1$H NMR spectra collected in CDCl$_3$. The two tertiary amines on the diamines could perform a nucleophilic attack on CDCl$_3$ forming a chloro-methylene bridge between the amine centres, giving salts 228 and 229 (Scheme 5.14). This type of reaction has been observed between the bispidine (--)sparteine and CH$_2$Br$_2$ but a 12 h reflux was required to form the dibromo salt.$^{139}$ Unpublished work by a researcher at Merck also observed an analogous salt formation (characterised by X-ray crystallography) from an NMR sample of the (+)-sparteine surrogate 17 in CDCl$_2$, stored at room temperature.$^{140}$
Scheme 5.14. Proposed reaction between bispidines 30 and 105 and CDCl$_3$

The selection of diamine ligands in Figure 5.6 were chosen as it was considered that the varying steric bulk on the different diamines may provide a wide range of diastereoselectivities. The use of a more sterically hindered diamine will result in a more sterically bulky $s$-BuLi/diamine lithiation complex. Therefore, this bulky lithiating complex will likely encounter more steric hindrance than $s$-BuLi/TMEDA when the $s$yn proton of $N$-Boc pyrrolidine 96 ($H_{syn}$) is deprotonated due to the interactions between the cyclohexyl substituent and the lithiating complex (Figure 5.9). This will raise further the energy barrier of $H_{syn}$ deprotonation whilst having a negligible effect on the $H_{anti}$ deprotonation barrier. This increased difference between the $H_{syn}$ and $H_{anti}$ deprotonation energies should increase the diastereoselectivity furnishing a higher proportion of the $anti$ trapped product.

Figure 5.9. Disfavoured $H_{syn}$ deprotonation of $N$-Boc pyrrolidine 96 with a bulky diamine ligand

The $s$-BuLi/diamine lithiation and PhCHO trapping at $-78$ °C in Et$_2$O was selected as the control reaction to investigate how the choice of diamine affected the diastereoselectivity of the lithiation of $N$-Boc pyrrolidine 96. PhCHO was selected as the trapping electrophile due to its compatibility with the ReactIR™ and the fast rate of trapping. This fast rate of trapping ensured that the dr of the trapped product should mirror the dr in which the lithiated intermediates were generated, as explained earlier in this chapter. All the lithiation-trapping reactions were monitored using ReactIR™ to ensure that reactions were given enough time for complete lithiation of $N$-Boc pyrrolidine 96 to occur. The crude product was then oxidised with DMP making analysis and purification of the diastereomeric products easier. The lithiation-trapping of $N$-Boc pyrrolidine 96 with the different $s$-BuLi/diamine complexes
provided ketones *anti*-213 and *syn*-213 in good yield over the two steps and in a narrow range of diastereoselectivity (80:20->95:5 dr) (Table 5.2). On the other hand, the lithiation times required for complete lithiation of *N*-Boc pyrrolidine 96 varied significantly with the different s-BuLi/diamine combinations. The lithiation-trapping of *N*-Boc pyrrolidine 96 with s-BuLi/di-*i*-Pr bispidine 30 was problematic and is not included in Table 5.2 – it is discussed later.

**Table 5.2.** s-BuLi/diamine and PhCHO lithiation-trapping procedure for *N*-Boc pyrrolidine 96 to determine the diastereoselectivity of the diamine ligand used

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th><em>dr</em> (<em>anti</em>: <em>syn</em>)</th>
<th>% Yield</th>
<th>Lithiation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMPDA 179</td>
<td>80:20</td>
<td>67</td>
<td>9 h</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA</td>
<td>87:13</td>
<td>78</td>
<td>4 min</td>
</tr>
<tr>
<td>3</td>
<td>TMCDA <em>trans</em>-161</td>
<td>87:13</td>
<td>76</td>
<td>4 min</td>
</tr>
<tr>
<td>4</td>
<td>DPE 177</td>
<td>92:8</td>
<td>86</td>
<td>50 min</td>
</tr>
<tr>
<td>5</td>
<td>di-<em>n</em>-Pr bispidine 105</td>
<td>94:6</td>
<td>86</td>
<td>40 min</td>
</tr>
<tr>
<td>6</td>
<td>178</td>
<td>&gt;95:5</td>
<td>16</td>
<td>&gt; 16 h</td>
</tr>
</tbody>
</table>

*a* *dr* measured by $^1$H NMR spectroscopy of crude mixture of ketones *anti*-213 and *syn*-213 after DMP oxidation

*b* combined isolated yield of ketones *anti*-213 and *syn*-213 after DMP oxidation

*c* ReactIR™ measured lithiation time for the s-BuLi/diamine lithiation of *N*-Boc pyrrolidine 96 at –78 °C

*d* trapping was conducted with CO$_2$, forming acids *anti*-212 and *syn*-212

*e* lithiation was only monitored for the first 7 h by ReactIR™. However, after a 16 h lithiation at –78 °C, ketones *anti*-213 and *syn*-213 were obtained in only 16% yield and a 62% yield of unreacted 96 was recovered
Lithiation of N-Boc pyrrolidine 96 with s-BuLi/TMPDA 179 offered the lowest degree of diastereoselectivity, giving an 80:20 mixture of ketones anti-213 and syn-213 (entry 1). The slow 9 h lithiation time suggests that lithiation may occur with s-BuLi/Et₂O rather than s-BuLi/TMPDA 179, due to poor coordination of the TMPDA 179 ligand to the s-BuLi, as suggested for lithiation of N-Boc pyrrolidine 9 (see Section 2.2). It is therefore possible that the s-BuLi/Et₂O lithiation of N-Boc pyrrolidine 96 is actually responsible for the 80:20 anti:syn dr observed.

The lithiation of N-Boc pyrrolidine 96 with both s-BuLi/TMEDA and s-BuLi/TMCDA trans-161 gave diastereomeric ketones anti-213 and syn-213 in identical 87:13 dr (entries 2 and 3). This is likely due to the structural similarity of both ligands, both having similar steric arrangement around the nitrogen atoms of the amine groups. The rates of the lithiation of N-Boc pyrrolidine 96 with both s-BuLi/TMEDA and s-BuLi/TMCDA trans-161 were similar, with both requiring 4 min for complete lithiation. The same 4 min lithiation time was observed for the s-BuLi/TMEDA and s-BuLi/TMCDA trans-161 lithiations of N-Boc pyrrolidine 9 (see section 2.2) which suggests the substituents of the 3- and 4-positions of the pyrrolidine do not have any significant effect on the rate of lithiation with these diamine ligands.

The s-BuLi/DPE 177 lithiation of N-Boc pyrrolidine 96 provided an enhanced level of diastereoselectivity over that exhibited with s-BuLi/TMEDA, with ketones anti-213 and syn-213 obtained in a 92:8 dr (entry 4). The 50 min lithiation of N-Boc pyrrolidine 96 with s-BuLi/DPE 177 was significantly slower than the lithiation of 96 with s-BuLi/TMEDA. The same reduction in the rate of lithiation was observed for the s-BuLi/DPE 177 lithiation of unsubstituted N-Boc pyrrolidine 9 (60 min lithiation time – see section 2.2). In Chapter 2, it was proposed that s-BuLi/DPE may be significantly more sterically bulky than s-BuLi/TMEDA and hence the slower rate of lithiation. The increased steric bulk of s-BuLi/DPE 177 would also provide a reason for the enriched anti:syn dr measured in the trapped products.

The s-BuLi/di-n-Pr bispidine 105 lithiation of N-Boc pyrrolidine 96 provided further enhancement to the level diastereoselectivity that was afforded, with a 94:6 mixture of acids anti-212 and syn-212 obtained (entry 5). This improvement in diastereoselectivity over the 87:13 dr obtained with s-BuLi/TMEDA (entry 2) most likely arises from the increasing bulk of diamine which further hinders the formation of the syn diastereomer. Lithiation of a
similar bicyclic N-Boc pyrrolidine with s-BuLi/di-n-Pr bispidine 105 and trapping with CO₂ afforded a 95:5 anti:syn ratio of trapped products (see Scheme 1.36).

A 16 h s-BuLi/178 lithiation of N-Boc pyrrolidine 96 provided ketones anti-213 and syn-213 in a promising ≥95:5 dr but in only 16% yield (entry 6). N-Boc pyrrolidine 96 starting material was recovered in 62% yield suggesting that either the lithiated intermediate is not stable with diamine 178 or that lithiation is very slow (> 16 h). A technical issue with the ReactIR™ equipment meant that only the first 7 h of the lithiation was recorded and lithiation was not complete within this 7 h window. This result hints at the fact that the bulky ligands required to achieve complete diastereoselectivity may have an adverse effect on the reactivity, slowing the lithiation reaction. Therefore, a compromise between the reactivity and the diastereoselectivity of the diamine may be required to obtain both a good yield and dr of the trapped product.

The lithiation of N-Boc pyrrolidine 96 was also attempted using the ‘diamine free’ s-BuLi/THF lithiating conditions developed by our group.25 ReactIR™ monitoring of the reaction indicated that, after 4 h, the lithiation of N-Boc pyrrolidine 96 was complete and PhCHO was added. After DMP oxidation of the crude product, a mixture of ketones anti-213 and syn-213 was obtained in a good 93:7 anti:syn dr and 69% yield (Scheme 5.15). We postulate that the increased diastereoselectivity observed in the s-BuLi/THF lithiation of pyrrolidine 96 could be due to the sterically bulky s-BuLi/THF complex (probably with two THF molecules ligating the lithium).

Scheme 5.15 s-BuLi/THF lithiation N-Boc pyrrolidine 96, PhCHO trapping and oxidisation with DMP

As mentioned, the lithiation-trapping of N-Boc pyrrolidine 96 with s-BuLi/di-i-Pr bispidine 30 proved to be problematic. ReactIR™ monitoring indicated that s-BuLi/di-i-Pr bispidine 30 lithiation of 96 was slow, with 5 h required for complete lithiation to occur. Using this lithiation time determined by ReactIR™, the s-BuLi/di-i-Pr bispidine 30 lithiation-trapping
of N-Boc pyrrolidine 96 was carried out using Me₃SiCl, Me₂SO₄ and CO₂ electrophiles (Table 5.3). Trapping with Me₃SiCl provided only recovered starting material (by ⁱH NMR spectroscopic analysis of the crude product) (entry 1). Trapping with Me₂SO₄ provided a 90:10 mixture of methylated pyrrolidines anti-211 and syn-211 in 38% yield together with 34% starting material recovery (entry 2). CO₂ trapping provided a 90:10 mixture of acids anti-212 and syn-212 in 51% yield and 47% recovered starting material (entry 3).

Table 5.3. s-BuLi/di-i-Pr bispidine 30 lithiation of N-Boc pyrrolidine 96 and trapping with Me₃SiCl, Me₂SO₄ and CO₂ electrophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>E⁺</th>
<th>E</th>
<th>dr (anti:syn)ᵃ</th>
<th>% Yieldᵇ</th>
<th>SM, % Yieldᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₃SiCl</td>
<td>SiMe₃</td>
<td>--</td>
<td>--</td>
<td>100ᵈ</td>
</tr>
<tr>
<td>2</td>
<td>Me₂SO₄</td>
<td>Me</td>
<td>90:10</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>CO₂</td>
<td>COOH</td>
<td>90:10</td>
<td>51</td>
<td>47</td>
</tr>
</tbody>
</table>

ᵃ drs measured by ¹H NMR spectroscopy (for Me₂SO₄ trapping, dr measured by sulfonamide formation - see Scheme 5.4)
ᵇ combined isolated yield of anti and syn diastereoisomers
ᶜ % yield of isolated starting material 96 after purification of trapped products
ᵈ ¹H NMR spectroscopy of crude product indicated that only starting material was present

The lithiation-trapping reactions will all three electrophiles indicated that complete trapping had not occurred. In the case of the Me₃SiCl trapping, no trapped product was detected (entry 1) which may result from the bulky di-i-Pr bispidine ligand 30 hindering the trapping process with the bulky Me₃SiCl electrophile (even after warming to room temperature). Both Me₂SO₄ and CO₂ trapping reactions provided a 90:10 mixture of anti and syn products with starting material also recovered. It was anticipated that the dr observed with the di-i-Pr bispidine ligand 30 would be similar or greater than that of the di-n-Pr bispidine 105 due to the additional steric bulk of the i-Pr groups but the drs are potentially unreliable as complete trapping has not occurred. It is possible that the recovery of starting materials may indicate poor stability of the lithiated intermediate with bispidine ligand 30.
For comparative purposes, the lithiation of \( N\)-Boc pyrrolidine \( 96 \) with \( s\)-BuLi/di-\( n\)-Pr bispidine \( 105 \) and trapping with \( \text{Me}_3\text{SiCl} \), \( \text{Me}_2\text{SO}_4 \) and \( \text{CO}_2 \) electrophiles was also conducted. This provided tri-substituted pyrrolidines \( 99, 211-214 \) in drs varying from 90:10-94:6 (\textit{anti}:\textit{syn}) and yields ranging from 64-87\% (Table 5.4).

**Table 5.4.** \( s\)-BuLi/di-\( n\)-Pr bispidine \( 105 \) lithiation of \( N\)-Boc pyrrolidine \( 96 \) and trapping with \( \text{Me}_3\text{SiCl} \), \( \text{Me}_2\text{SO}_4 \) and \( \text{CO}_2 \) electrophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>( E^+ )</th>
<th>( E )</th>
<th>( \text{dr (anti:syn)}^a )</th>
<th>% Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Me}_3\text{SiCl} )</td>
<td>( \text{SiMe}_3 )</td>
<td>( \geq 95:5 )</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Me}_2\text{SO}_4 )</td>
<td>( \text{Me} )</td>
<td>90:10</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>( \text{CO}_2 )</td>
<td>( \text{COOH} )</td>
<td>94:6</td>
<td>86</td>
</tr>
</tbody>
</table>

\( ^a \) drs measured by \(^1\text{H} \) NMR spectroscopy (for \( \text{Me}_2\text{SO}_4 \) trapping, dr measured by sulfonamide formation - see Scheme 5.4)  
\( ^b \) combined isolated yield of \textit{anti} and \textit{syn} diastereoisomers

The \( s\)-BuLi/di-\( n\)-Pr bispidine \( 105 \) lithiation of \( N\)-Boc pyrrolidine \( 96 \) and subsequent trapping with \( \text{CO}_2 \) provided a 94:6 ratio of carboxylic acids of \textit{anti-212} and \textit{syn-212} (entry 3). Presumably, the fast trapping \( \text{CO}_2 \) electrophile will give the trapped products in the dr that the lithiated intermediates are formed in. Trapping with \( \text{Me}_3\text{SiCl} \) provided only the \textit{anti-99} diastereomer and \( \text{Me}_2\text{SO}_4 \) gave a 90:10 \textit{anti}:\textit{syn} dr, both of these results were identical to those using the \( s\)-BuLi/TMEDA lithiating conditions (Table 5.1, entries 1 and 2). These trapping reactions with \( \text{Me}_3\text{SiCl} \) and \( \text{Me}_2\text{SO}_4 \) provide further evidence that a dynamic kinetic resolution likely occurs with the slower trapping electrophiles. The \( s\)-BuLi/di-\( n\)-Pr bispidine and \( \text{Me}_3\text{SiCl} \) lithiation-trapping of \( N\)-Boc pyrrolidine \( 96 \) was also monitored using ReactIR\textsuperscript{TM} to probe the rate of trapping. After lithiation of pyrrolidine \( 96 \) was complete, \( \text{Me}_3\text{SiCl} \) was added and very little or no trapping was observed at \( -78^\circ \text{C} \); it was only upon the warming of the reaction that trapping was observed (Scheme 5.16).
Scheme 5.16. ReactIR™ monitored lithiation-trapping of \(N\)-Boc pyrrolidine 96 with \(s\)-BuLi/di-\(n\)-Pr bispidine 105 and Me₃SiCl

The Me₃SiCl trapping of \(N\)-Boc pyrrolidine 96 with \(s\)-BuLi/di-\(n\)-Pr bispidine 105 displayed slightly different kinetics to that with \(s\)-BuLi/TMEDA (see Scheme 5.12). No trapping occurs at all with \(s\)-BuLi/di-\(n\)-Pr bispidine 105 at \(-78 \, ^\circ\text{C}\) whereas with \(s\)-BuLi/TMEDA, trapping of the \textit{anti-223} lithiated intermediate does occur at \(-78 \, ^\circ\text{C}\). This difference is likely due to the increased steric bulk of the di-\(n\)-Pr bispidine 105 diamine ligand, making the trapping of lithiated intermediate \textit{anti-230} unfeasible at such a low temperature. Conversely, trapping of \textit{anti-223} which is coordinated to the less bulky TMEDA ligand is facile enough to occur at \(-78 \, ^\circ\text{C}\).

To conclude, a range of diamine ligands have been employed to investigate the diastereoselective lithiation of \(N\)-Boc pyrrolidine 96. A narrow range of diastereoselectivity in the lithiation reaction was observed when different \(s\)-BuLi/ligand combinations were employed resulting in the formation in trapped products in good to excellent dr. A trend between the steric bulk of the ligand and diastereoselectivity was discovered. It was also noted that the dynamic kinetic resolution established with slow trapping electrophiles was also observed when a different diamine ligand was employed.
5.3 Computational DFT Modelling of the Diastereoselective Lithiation

An attempt to model the diastereoselective lithiation of 3,4-disubstituted N-Boc pyrrolidine \(96\) with the different \(s\)-BuLi/ligand lithiating complexes was undertaken using DFT, following a similar approach to that used in Chapter 3. This involved modelling prelithiation complexes and transition states for the lithiation of N-Boc pyrrolidine \(96\) for the formation of both lithiated intermediates \emph{anti-222} and \emph{syn-222} (Scheme 5.17). The pro-\emph{syn} and pro-\emph{anti} reaction pathways were modelled using \(i\)-PrLi as the alkylolithium (as detailed in Chapter 3) and models were constructed for each of the different ligands investigated experimentally in Table 5.2.

Scheme 5.17. DFT modelling of the diastereoselective lithiation of \(N\)-Boc pyrrolidine \(96\)

First, the \(i\)-PrLi/TMEDA lithiation of \(N\)-Boc pyrrolidine \(96\) was modelled to explore whether DFT modelling could calculate an energy difference between the pathways for the formation of lithiated intermediates \emph{anti-222} and \emph{syn-222}. The B3LYP and M06 DFT functionals used for modelling in the reactivity study in Chapter 3, were utilised to model this diastereoselective lithiation reaction. Both DFT functionals used gave near identical optimised geometries and the M06/6-31G* optimised transition states for both the \emph{syn} and \emph{anti} diastereomer formation are presented in Figure 5.10.
Figure 5.10. M06/6-31G* optimised transition state geometries for the syn (a) and anti (b) lithiation of N-Boc pyrrolidine 96 – only protons on the pyrrolidine ring shown for clarity

The energies calculated with both DFT functionals did indeed show an energy difference between the anti and syn pathways with both indicating that the anti pathway is favoured (Table 5.5).

Table 5.5. Prelithiation complex and activation free-energies for the anti and syn i-PrLi/TMEDA lithiation of N-Boc pyrrolidine 96 calculated with B3LYP/6-31G* and M06/6-31G*

<table>
<thead>
<tr>
<th>Method</th>
<th>ΔG&lt;sup&gt;a&lt;/sup&gt; /kcal mol&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>syn ΔG&lt;sup&gt;‡&lt;/sup&gt; /kcal mol&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>anti ΔG&lt;sup&gt;‡&lt;/sup&gt; /kcal mol&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>ΔΔG&lt;sup&gt;‡&lt;/sup&gt; /kcal mol&lt;sup&gt;-1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP/6-31G*</td>
<td>0.41</td>
<td>14.07</td>
<td>12.98</td>
<td>1.50</td>
</tr>
<tr>
<td>M06/6-31G*</td>
<td>0.00</td>
<td>12.54</td>
<td>11.52</td>
<td>1.02</td>
</tr>
</tbody>
</table>

<sup>a</sup> difference in free energy between the anti and syn prelithiation complexes (G<sub>syn</sub>-G<sub>anti</sub>)

The B3LYP functional indicated that the anti prelithiation complex was lower in energy than the syn prelithiation complex which was 0.41 kcal mol<sup>-1</sup> higher in energy. However, the M06 functional gave no difference between the free energies of the syn and anti prelithiation
complexes. Both DFT functionals indicated that the major driving force for the diastereoselectivity is due to the significant difference in activation free energies ($\Delta G^\ddagger$) for *anti* and *syn* lithiation. Both DFT functionals calculated that the activation energy for the formation of the *anti* lithiated intermediate was lower than that of the *syn* intermediate. As there is evidence that pre-lithiation complex formation is fast and reversible, as discussed in Chapter 2, the Curtin-Hammett principle can be used to relate these calculated energies to the ratio of diastereomers that should be observed in the reaction. The Curtin-Hammett principle states that the ratio of products (in this case diastereomers) depends on the value $\Delta \Delta G^\ddagger$, the difference in energy of the transition states for the formation of each product.

The energy difference between transition states of *anti* and *syn* lithiation of pyrrolidine 96 ($\Delta \Delta G^\ddagger$) with *i*-PrLi/TMEDA was calculated as 1.50 kcal mol$^{-1}$ with the B3LYP functional and $\Delta \Delta G^\ddagger = 1.02$ kcal mol$^{-1}$ using the M06 functional. These energy differences appear to be small but at a low temperature of $–78 \, ^\circ\text{C}$, this small energy difference can have a marked effect on the selectivity. Use of the Curtin-Hammett equation (Equation 5.1) and the calculated $\Delta \Delta G^\ddagger$ from the DFT modelling allows a predicted *anti*:*syn* ratio to be calculated using the theoretical data (Table 5.6).

$$\frac{\text{anti}}{\text{syn}} = e^{-\frac{\Delta \Delta G^\ddagger}{RT}} \quad \text{(Equation 5.1)}$$

where $\Delta \Delta G^\ddagger$ is the energy difference between the diastereomer transition states (in J mol$^{-1}$), R is the universal gas constant (8.314 J K$^{-1}$) and T is temperature (195 K ≡ $–78 \, ^\circ\text{C}$).

**Table 5.6. Predicted *anti*:*syn* drs for the *i*-PrLi/TMEDA lithiation of *N*-Boc pyrrolidine 96**

<table>
<thead>
<tr>
<th>Entry</th>
<th>DFT Functional</th>
<th>Calculated $\Delta \Delta G^\ddagger$ /kcal mol$^{-1}$</th>
<th>Predicted dr (<em>anti</em>:*syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B3LYP</td>
<td>1.50</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>M06</td>
<td>1.02</td>
<td>93:7</td>
</tr>
</tbody>
</table>

The B3LYP modelled lithiation of *N*-Boc pyrrolidine 96 significantly overestimates the diastereoselectivity of the reaction providing an estimated 98:2 *anti*:*syn* dr. DFT modelling with the M06 function also overestimates the diastereoselectivity of the lithiation, albeit to a lesser extent with a predicted 93:7 *anti*:*syn* dr calculated. However, this is a promising result which is somewhat closer to the experimentally measured 87:13 dr.
With these initial results for TMEDA in hand, the same modelling procedure was conducted for a selection of the ligands used in the experimental diastereoselectivity study. Both the syn and anti lithiated intermediate formation for N-Boc pyrrolidine 96 with TMPDA 179, DPE 177, di-n-Pr bispidine 105 and THF ligands were modelled using the B3LYP and M06 DFT functionals (Tables 5.7 and 5.8). The lithiation of pyrrolidine 96 was not modelled with i-PrLi/TMCDA trans-161 as it provided an identical experimental result to that with TMEDA.

Table 5.7. Calculated diastereoselectivity of the i-PrLi/ligand lithiation of N-Boc pyrrolidine 96 with B3LYP/6-31G*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Calculated ΔΔG‡ /kcal mol⁻¹</th>
<th>Predicted dr (anti: syn)</th>
<th>Experimental dr (anti: syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMPDA 179</td>
<td>1.08</td>
<td>94:6</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA</td>
<td>1.50</td>
<td>98:2</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>DPE 177</td>
<td>0.82</td>
<td>89:11</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>di-n-Pr bispidine 105</td>
<td>1.36</td>
<td>97:3</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>1.17</td>
<td>95:5</td>
<td>93:7</td>
</tr>
</tbody>
</table>

The predicted diastereoselectivities obtained from the B3LYP functional presented in Table 5.7 exhibited very little correlation to the experimental drs. Ligands such as di-n-Pr bispidine 105 (entry 4) and THF (entry 5) which offered improved diastereoselectivity over TMEDA in the experimental study were predicted to be less diastereoselective than TMEDA by the DFT modelling. The B3LYP functional also predicted that lithiation using DPE 177 as the ligand would result in the least diastereoselective lithiation which disagrees with the experimental dr obtained (entry 3). i-PrLi/TMPDA was predicted to afford a good level of diastereoselectivity in the lithiation reaction (entry 1), similar to that of i-PrLi/di-n-Pr bispidine 105 and i-PrLi/THF (entries 4 and 5 respectively). This result conflicted with the experimentally determined drs which indicated that TMPDA imparted the least diastereoselectivity in the lithiation of N-Boc pyrrolidine 96.

The M06 DFT functional provided some predicted diastereoselectivities for the lithiation of N-Boc pyrrolidine 96 that were in slightly better agreement with those observed experimentally (Table 5.8). However, similar to the diastereoselectivities predicted with the
B3LYP DFT functional, most of the drs predicted with the M06 DFT functional were also overestimated.

Table 5.8. Calculated diastereoselectivity of the \( i\)-PrLi/ligand lithiation of \( N\)-Boc pyrroldine 96 with M06/6-31G*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Calculated ( \Delta G^\dagger ) /kcal mol(^{-1})</th>
<th>Predicted dr ((\text{anti:}\text{syn}))</th>
<th>Experimental dr ((\text{anti:}\text{syn}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMPDA 179</td>
<td>1.80</td>
<td>99:1</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA</td>
<td>1.02</td>
<td>97:3</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>DPE 177</td>
<td>0.56</td>
<td>81:19</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>( \text{di-}\text{-}n\text{-Pr bispidine} ) 105</td>
<td>2.26</td>
<td>99.5:0.5</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>3.28</td>
<td>100:0</td>
<td>93:7</td>
</tr>
</tbody>
</table>

Modelling the diastereoselectivity of the lithiation of \( N\)-Boc pyrroldine 96 with the M06 DFT functional did provide two significant outliers. First, as with the results obtained with the B3LYP functional, the M06 functional suggested that \( i\)-PrLi/DPE 177 (entry 3) would offer worse diastereoselectivity than \( i\)-PrLi/TMEDA (entry 2) which contradicted the experimental result. Second, the \( i\)-PrLi/TMPDA 179 lithiation of 96 was predicted to be highly diastereoselective by the DFT modelling (entry 1). This contradicted the experimental results which indicated that \( s\)-BuLi/TMPDA exhibited poorer diastereoselectivity than \( s\)-BuLi/TMEDA for the lithiation of \( N\)-Boc pyrroldine 96. The occurrence of these anomalous results when modelling the lithiation of 96 with \( i\)-PrLi/TMPDA with both B3LYP and M06 DFT functional could arise due to a possible lack of coordination of TMPDA to the alkylolithium; this possibility was suggested previously when the nominal reactivity of the \( s\)-BuLi/TMPDA complex was discussed. A lack of coordination of the alkylolithium and ligand is not accounted for in the computational model where the ligand and alkylolithium are explicitly modelled as being coordinated to each other.

In summary, the computational DFT modelling correctly predicted the \emph{anti} diastereoselectivity observed for the lithiation of \( N\)-Boc pyrroldine 96. However, attempting to predict the dr for the different diamines using both B3LYP and M06 DFT functionals provided no clear overall correlation between the experimental and calculated drs. The narrow range of diastereoselectivity observed for the lithiation of \( N\)-Boc pyrroldine 96 with the different \( s\)-BuLi/ligand combinations further complicated this investigation, as
the relatively small differences in diastereoselectivity require accurate computational calculations to reproduce these small differences in energy between diastereomer formation. This problem is also further exacerbated by the low reaction temperatures used (−78 °C) which mean that small differences in energy between the pathways of anti and syn lithiation can have a significant effect on the dr obtained. More accurate geometry optimisations and energy calculations are difficult to obtain without significant additional computational expense and this is further compounded by the relatively large size of the model (~80 atoms). For this study, DFT was chosen to optimise these models as it is a good compromise between accuracy and performance but for the modelling of diastereoselectivity, the level of theory used may not provide sufficiently accurate energies.

5.4 Conclusions and Future Work

Research in this Chapter has indicated that both the electrophile and the diamine can influence the diastereoselectivity of the lithiation of 3,4-disubstituted N-Boc pyrrolidine 96. The choice of electrophile affects the rate of the trapping reaction between the lithiated intermediate and electrophile, and can therefore affect the dr. Slow trapping electrophiles such as Me3SiCl result in a dynamic kinetic resolution which enriches the dr of the trapped products whereas we presume that fast trapping electrophiles trap the lithiated intermediates in the dr they are formed. The lithiation of N-Boc pyrrolidine 96 with a range of s-BuLi/ligand complexes indicated that the diastereoselectivity of the reaction can also be modified by the ligand employed. A general trend between the diastereoselectivity of the lithiation and steric bulk of the ligand was observed, where bulky ligands enhanced the diastereoselectivity. However, for very bulky ligands such as diamine 178, this comes at a cost with a reduced reactivity of the s-BuLi/diamine complex leading to poor yields of the product.

Computational DFT modelling of the lithiation of N-Boc pyrrolidine 96 correctly predicted that formation of the anti diastereomer was the lowest in energy. However, using DFT to predict the diastereoselectivity of the lithiation of N-Boc pyrrolidine 96 with different s-BuLi/ligand complexes gave disappointing results. There was no clear agreement between the computationally predicted and experimentally obtained drs for both of the DFT functionals used. Therefore, our DFT modelling does not provide useful data about the diastereoselectivity offered by the different s-BuLi/ligand complexes at this point in time.
Attempting to improve the computational prediction of diastereoselectivity for the lithiation of \(N\)-Boc pyrrolidine 96 with different \(s\)-BuLi/ligand complexes could be an interesting avenue for further study. Potential improvements could include modelling the systems with higher levels of theory, use of alternative DFT functionals and the inclusion of solvent effects (discussed in section 3.3). Using higher levels of theory or different DFT functionals, especially those that better describe dispersion interactions, could have a substantial impact on the accuracy of the modelling. As discussed above, accurate energies for the diastereomeric lithiations need to be calculated to provide a better prediction of the diastereoselectivity that will be observed. However, applying higher levels of theory to this system of \(~80\) atoms would greatly increase the computational expense of calculations. Therefore, investigating alternate DFT functionals may be more practical. DFT functionals with included dispersion corrections such as B3LYP-D3, discussed in section 3.4, may be particularly beneficial for this study. This is because the diastereoselectivity likely arises from steric interactions between the \(s\)-BuLi/ligand complex and \(N\)-Boc heterocycle; thus, a computational method which can better accounts for the long-range interactions between these two moieties may provide more accurate calculated energy differences for diastereomer formation. If further work did yield a more accurate computational model for diastereoselectivity then this could potentially be used to design more selective ligands for the lithiation of \(N\)-Boc heterocycles.

Our application of a combination of synthetic, \textit{in situ} IR spectroscopic and computational techniques to investigate the lithiation-trapping of \(N\)-Boc pyrrolidine 96 provides a useful framework for obtaining a better understanding of these types of lithiation-trapping reactions. This could be expanded as a general approach to many other systems, allowing a better understanding of the processes occurring and providing suggestions about optimal reaction conditions and reagents to improve the reaction outcome.
Chapter 6: Experimental

6.1 General

All non-aqueous reactions were carried out under oxygen free Ar using flame-dried glassware. Et$_2$O and THF were freshly distilled from sodium and benzophenone respectively. Alkyllithiums were titrated against N-benzylbenzamide before use.\textsuperscript{141} All diamines used in lithiations were distilled over CaH$_2$ before use. Me$_3$SiCl, Me$_2$SO$_4$, MeI and PhCHO electrophiles were distilled over CaH$_2$ before use. Dry CO$_2(g)$ was generated from solid CO$_2$, flushed through CaCl$_2$ and added into reaction via cannula. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C and was purchased in Winchester quantities. Brine refers to a saturated solution. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F$_{254}$ aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in CHCl$_3$, chemical shifts are quoted in parts per million relative to CHCl$_3$ (δ$_H$ 7.26) and CDCl$_3$ (δ$_C$ 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants ($J$) are quoted in Hertz. Boiling points give for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer with UATR attachment. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. \textit{In situ} ReactIR\textsuperscript{TM} infra-red spectroscopic monitoring was performed on either a Mettler-Toledo ReactIR\textsuperscript{TM} iC10 or ReactIR\textsuperscript{TM} 15 spectrometer equipped with a silicon-tipped (SiComp) or diamond-tipped (DiComp) probe.
6.2 Kinetic Analysis Procedure

Trend fitting and error calculation:
For the kinetic analysis using linear regression (in Chapters 2 and 4) lines of best fit and standard errors were calculated using the LINEST (least squares) function in Microsoft® Excel. Non-linear regression kinetic analyses (Chapter 2) were conducted with Origin 2016 and the curve fitting and standard error calculation were carried out using the Levenberg-Marquardt algorithm (non-linear least squares) included in the software package. The standard errors provided on the kinetic plots are calculated with LINEST (linear regression) and the Levenberg-Marquardt algorithm (curve fitting). The errors quoted on \( k_{obs} \) and \( t_{1/2} \) values presented in this thesis use the standard errors calculated by these fitting methods.

Kinetic analysis of the lithiation reactions of \( N \)-Boc heterocycles (Chapter 2):
When the lithiation reactions of \( N \)-Boc heterocycles were subjected to linear regression analysis, the first ReactIR™ measurement at \( t = 0 \) was discarded to allow the pre-equilibrium approximation to be applied. In addition, subsequent readings after 90% conversion were discarded from the linear regression analysis to minimise the effect of instrument noise on the kinetic analysis. The values of absorbance used in the linear regression plots in this thesis are relative, i.e. the absorbance has been normalised to be zero at the end of the reaction (the end-point of the reactions has been determined by visual inspection of the ReactIR™ data).

For the calculation of the lithiation \( k_{obs} \) using curve fitting, the first ReactIR™ measurement at \( t = 0 \) was discarded to allow the pre-equilibrium approximation to be applied but all subsequent ReactIR™ data for the duration of the reaction were used in the analysis. The absolute absorbance recorded by the ReactIR™ equipment was used in the curve fitting analysis and no normalisation was applied to the absorbance data. To compare the reactivities of the different \( N \)-Boc heterocycles presented in Chapter 2, the \( k_{obs} \) values for the lithiation reactions obtained by the curve fitting analysis were used (Tables 2.4 and 2.5). The kinetic data from the linear regression was not used as it is susceptible to significant variation in \( k_{obs} \) which arises due to selection of the reaction end-point which is not required for the curve fitting, this is discussed in section 2.3 of this thesis.

Percentage errors which compare the error between the lithiation \( k_{obs} \) obtained by analysis of the \( N \)-Boc heterocycle substrate consumption and the prelithiation complex consumption are not presented in this thesis. These % errors were not included as the measurement of \( k_{obs} \)
using the consumption of prelithiation complex is unreliable due to the low concentration and low absorbance of prelithiation complex and overlapping of signals with the uncomplexed starting material and lithiated intermediate (this is discussed in section 2.3).

**Kinetic analysis of the trapping reactions of lithiated N-Boc heterocycles (Chapter 4):**

The trapping reactions of all lithiated intermediates with PhCHO and the trapping of lithiated N-Boc pyrrolidine 164 with MeI and Me₂SO₄ were too rapid for kinetic analysis to be conducted. For these rapid trapping reactions, $k_{\text{obs}}$ and $t_{1/2}$ were estimated by using the trapping times obtained by visual inspection of the ReactIR™ traces ($t_{1/2} \approx \text{trapping time} \div 7$).

The $k_{\text{obs}}$ and $t_{1/2}$ for the trapping reactions of the lithiated intermediates presented in Chapter 4 with Me₃SiCl, MeI and Me₂SO₄ were obtained using linear regression analysis of first order semilogarithmic plots. These first order semilogarithmic plots use the logarithm of relative absorbance (i.e. the absorbance has been normalised to be zero at the end of the reaction). For the kinetic analysis of the trapping reactions the first ReactIR™ measurement at $t = 0$ has been discarded to ensure that the reaction mixture is well mixed and homogenous after the electrophile is added.

For the trapping reactions subjected to kinetic analysis semilogarithmic plots have been included for both 20% and 90% conversion of the lithiated intermediate. Trapping reactions of the lithiated N-Boc heterocycles with both Me₂SO₄ and MeI both displayed a deviation from first order kinetics mid reaction and this is evident in the semilogarithmic plots which present 90% trapping conversion. For this reason, trapping $k_{\text{obs}}$ and $t_{1/2}$ for all substrates have been calculated using the semilogarithmic plots with the first 20% trapping conversion. For this initial portion of the reaction pseudo-first order kinetics are observed (this is discussed in Chapter 4). For consistency, $k_{\text{obs}}$ and $t_{1/2}$ for the trapping reactions with Me₃SiCl have also been calculated using kinetic data for the first 20% of trapping conversion.

The trapping reactions of lithiated intermediates presented in Table 4.1 were also subjected to initial rate analysis. For this initial rate analysis, ReactIR™ absorbance data for the consumption of the lithiated intermediate from $t = 0$ (the start of the trapping reaction) to the end of the reaction has been plotted and then a tangent has been fitted to the decay observed in the initial stage of the trapping reaction. The absorbance data used for the initial rate
analyses uses the absolute absorbance recorded by the ReactIR™ equipment with no normalisation applied to the data. The standard errors quoted on the initial rates obtained (rate_{init}) have been calculated by the LINEST algorithm used for linear regression included in the Microsoft® Excel package.

6.3 General Procedures

**General Procedure A: Lithiation-trapping of N-Boc pyrrolidine 96**

s-BuLi (1.3 M in hexanes, 1.3 eq.) was added dropwise to a stirred solution of N-Boc pyrrolidine 96 (223 mg, 1.0 mmol, 1.0 eq.) and diamine (1.3 eq.) in Et₂O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min, 1 h or 5 h. Then, the electrophile (2.0 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then allowed to slowly warm to rt over 16 h. Saturated NH₄Cl̄_{aq} (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product.

**General Procedure B: High Temperature (–20 °C) Lithiation-trapping of N-Boc pyrrolidine 96**

s-BuLi (1.3 M in hexanes, 1.3 eq.) was added dropwise to a stirred solution of N-Boc pyrrolidine 96 (223 mg, 1.0 mmol, 1.0 eq.) and diamine (1.3 eq.) in Et₂O (7 mL) at –20 °C under Ar. The resulting solution was stirred at –20 °C for 2 min. Then, the electrophile (2.0 eq.) was added and the resulting solution was stirred at –20 °C for 1 h and warmed to rt. Saturated NH₄Cl̄_{aq} (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product.

**General Procedure C: Lithiation-trapping of N-Boc pyrrolidine 96 with CO₂(g)**

s-BuLi (1.3 M in hexanes, 1.3 eq.) was added dropwise to a stirred solution of N-Boc pyrrolidine 96 (223 mg, 1.0 mmol, 1.0 eq.) and diamine (1.3 eq.) in Et₂O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min, 1 h or 5 h. Then, dry CO₂ was bubbled through for 30 min at –78 °C and then allowed to warm to rt over 1 h. Saturated NH₄Cl̄_{aq} (10 mL) was added followed by 2 M HCl̄_{aq} (10 mL) and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic
layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product.

**General Procedure D: DMP oxidation of alcohols**

A solution of the alcohol (1.0 eq.) in CH$_2$Cl$_2$ (5 mL) was added dropwise to a stirred suspension of DMP (1.5 eq.) in CH$_2$Cl$_2$ (10 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and then at rt stirred for 2 h. Saturated NaHCO$_3$(aq) (10 mL) was added and the solution stirred at rt for 16 h. The solids were removed by filtration and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to give the crude ketone product.
6.4 Experimental Procedures for Chapter 2

tert-Butyl pyrrolidine-1-carboxylate 9

Pyrrolidine (4.00 g, 4.70 mL, 56.24 mmol, 1.2 eq.) was added dropwise to a stirred solution of di-tert-butyl dicarbonate (10.28 g, 47.12 mmol, 1.0 eq.) in CH\textsubscript{2}Cl\textsubscript{2} (200 mL) at 0 °C under Ar. The resulting solution was then allowed to warm to rt and stirred for 16 h. 1 M HCl\textsubscript{(aq)} (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 50 mL) and the combined organic layers were dried (MgSO\textsubscript{4}), filtered and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave N-Boc pyrrolidine 9 (6.48 g, 80%) as a colourless oil, bp 115-120°C/3.5 mmHg (lit.,\textsuperscript{142} bp 70-75 °C/0.05 mmHg); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.32-3.28 (m, 4H, NCH\textsubscript{2}), 1.84-1.81 (m, 4H, CH\textsubscript{2}), 1.45 (s, 9H, CMe\textsubscript{3}); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) δ 154.8 (C=O), 79.0 (CMe\textsubscript{3}), 45.9 (NCH\textsubscript{2}), 28.6 (CMe\textsubscript{3}), 25.5 (CH\textsubscript{2}). Spectroscopic data consistent with those reported in the literature.\textsuperscript{142}

Lab Book Reference: AMI_2

\textbf{tert-Butyl 2-(trimethylsilyl)pyrrolidine-1-carboxylate 11}

Et\textsubscript{2}O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR\textsuperscript{TM} probe (ReactIR\textsuperscript{TM} 15, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171
mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 9 min. Then, Me₃SiCl (217 mg, 0.25 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 13 min. Saturated NH₄Cl(aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 Hexane-Et₂O as eluent gave 2-silyl N-Boc pyrrolidine 10 (211 mg, 87%) as a colourless oil, Rₚ (90:10 Hexane- Et₂O) 0.22; ¹H NMR (400 MHz, CDCl₃) δ 3.63-3.38 (m, 1H, NCH), 3.36-3.09 (m, 2H, NCH), 2.11-1.90 (m, 1H, CH), 1.90-1.64 (m, 3H, CH), 1.45 (s, 9H, CMe₃), 0.04 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 155.1 (C=O), 79.3 (CMe₃), 78.5 (CMe₃), 47.8 (NCH), 47.2 (NCH₂), 46.7 (NCH₂), 28.7 (CMe₃), 28.0 (CH), 26.2 (CH₂), 25.0 (CH₂), −2.0 (SiMe₃). Spectroscopic data consistent with those reported in the literature.²⁸

For N-Boc pyrrolidine 9, a peak at 1700 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1678 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1648 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When Me₃SiCl was added (after 9 min total lithiation time), the signal for the lithiated intermediate (νC=O = 1648 cm⁻¹) disappeared after 10 min, indicating complete trapping had occurred. During the trapping process, another peak appeared at 1693 cm⁻¹ which was assigned to the trapped adduct 11.

Kinetic analysis using linear regression indicated that the lithiation of N-Boc pyrrolidine 9 was first order with respect to N-Boc pyrrolidine 9, kobs = (2.70 ± 0.12) s⁻¹ and t₁/₂ = (25.7 ± 1.1) s.
First order exponential decay curves ($y = Ae^{-k_{obs}t} + c$) were fit to the consumption of $N$-Boc pyrrolidine 9 (a) and consumption of the prelithiation complex of 9 (b) for the lithiation of $N$-Boc pyrrolidine 9. Both provided good fit with a first order exponential decay. Curve fitting of $N$-Boc pyrrolidine 9 consumption (a) provided $k_{obs} = (3.34 \pm 0.15) \times 10^{-2}$ s$^{-1}$ and $t_{1/2} = (20.7 \pm 0.9)$ s. Curve fitting of prelithiation complex consumption (b) provided $k_{obs} = (3.89 \pm 0.11) \times 10^{-2}$ s$^{-1}$ and $t_{1/2} = (17.8 \pm 0.5)$ s.

Lab Book Reference: AMI_168
Rapid collect ReactIR™ spectroscopic monitoring of the lithiation and Me$_3$SiCl trapping of N-Boc pyrrolidine 9

Et$_2$O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp using rapid collection mode with 1 scan collected per second) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 11 min. Then, Me$_3$SiCl (217 mg, 0.25 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 12 min.

For N-Boc pyrrolidine 9, a peak at 1700 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1678 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the prelithiation complex. Formation of prelithiation complex and establishment of an equilibrium was complete in < 1 s. A new peak at 1648 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When Me$_3$SiCl was added (after 11 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1648$ cm$^{-1}$) disappeared after 10 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_169
**tert-Butyl piperidine-1-carboxylate 10**

![Chemical Structure](image1.png)

Piperidine (3.00 g, 34.8 mL, 35.23 mmol, 1.3 eq.) was added dropwise to a stirred solution of di-**tert**-butyl dicarbonate (6.14 g, 28.13 mmol, 1.0 eq.) in THF (30 mL) at 0 °C under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 30 min. Then, 10% NaHCO₃(aq) (30 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (2 x 70 mL). The combined organic layers were washed with saturated brine (50 mL), dried (K₂CO₃), filtered and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave **N**-Boc piperidine 10 (5.16 g, 99%) as a colourless oil, bp 90-100 °C/0.5 mmHg (lit., 40 bp 60-70 °C/1.0 mmHg); **¹H** NMR (400 MHz, CDCl₃) δ 3.37-3.34 (m, 4H, NCH₂), 1.58-1.48 (m, 6H, CH₂), 1.45 (s, 9H, CMe₃); **¹³C** NMR (100.6 MHz, CDCl₃) δ 155.1 (C=O), 79.2 (CMe₃), 44.9 (br s, NCH₂), 28.6 (CMe₃), 25.9 (CH₂), 24.6 (CH₂). Spectroscopic data consistent with those reported in the literature. 40

Lab Book Reference: AMI_22

**tert-Butyl 2-(trimethylsilyl)piperidine-1-carboxylate 12**

![Chemical Structure](image2.png)

**Et₂O** (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, **N**-Boc piperidine 10 (185
mg, 1.00 mmol, 1.0 eq.) was added followed by TMEDA (151 mg, 0.20 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at –78 °C for 6 h. Then, Me₃SiCl (217 mg, 0.25 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 12 h. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product as a 90:10 mixture of 2-silyl N-Boc piperidine 12 and N-Boc piperidine 10 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 90:10 hexane-Et₂O as eluent gave 2-silyl N-Boc piperidine 12 (145 mg, 56%) as a colourless oil, Rf (90:10 hexane-Et₂O) 0.27; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 4.20 (br s, 0.5H, NCH), 3.86-3.52 (m, 1.5 H, NCH), 2.95 (br s, 0.5H, NCH), 2.62 (br s, 0.5H, NCH), 1.75-1.32 (m, 6H, CH), 1.45 (s, 9H, CMe₃), 0.08 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.0 (C=O), 79.0 (CMe₃), 45.1 (NCH), 44.4 (NCH), 42.1 (NCH₂), 41.9 (NCH₂), 28.4 (CMe₃), 26.1 (CH₂), 23.5 (CH₂), 22.7 (CH₂), –0.6 (SiMe₃) and N-Boc piperidine 10 (7 mg, 4%) as a colourless oil. Spectroscopic data for 12 consistent with those reported in the literature.³¹

For N-Boc piperidine 10, a peak at 1697 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1674 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1645 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 6 h, incomplete lithiation of N-Boc piperidine 10 to give the lithiated intermediate was observed. When Me₃SiCl was added (after 6 h total lithiation time), the signal for the lithiated intermediate (νC=O = 1645 cm⁻¹) disappeared after 7 h suggesting that complete trapping had occurred.

Kinetic analysis indicated that the lithiation of N-Boc piperidine 10 was first order with respect to N-Boc piperidine 10, kobs = (2.11 ± 0.02) x10⁻⁴ s⁻¹ and t₁/₂ = (3290 ± 30) s.
First order exponential decay curves \( y = A e^{-k_{\text{obs}} t} + c \) were fit to the consumption of \( N \)-Boc piperidine 10 (a) and consumption of the prelithiation complex of 10 (b) for the lithiation of \( N \)-Boc piperidine 10. Both provided good fit with a first order exponential decay. Curve fitting of \( N \)-Boc piperidine 10 consumption (a) provided \( k_{\text{obs}} = (2.17 \pm 0.02) \times 10^{-4} \text{ s}^{-1} \) and \( t_{1/2} = (3190 \pm 30) \text{ s} \). Curve fitting of prelithiation complex consumption (b) provided \( k_{\text{obs}} = (2.43 \pm 0.03) \times 10^{-4} \text{ s}^{-1} \) and \( t_{1/2} = (2850 \pm 30) \text{ s} \).

(a) \[ k_{\text{obs}} = (2.17 \pm 0.02) \times 10^{-4} \text{ s}^{-1} \quad R^2 = 0.993 \]

(b) \[ k_{\text{obs}} = (2.43 \pm 0.03) \times 10^{-4} \text{ s}^{-1} \quad R^2 = 0.991 \]
A solution of \textit{cis}-1,2,3,6-tetrahydropthalimide (2.00 g, 13.23 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to a stirred suspension of LiAlH$_4$ (3.01 g, 79.39 mmol, 6.0 eq.) in THF (90 mL) at 0 °C under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solution was then cooled to 0 °C and quenched by careful dropwise addition of H$_2$O (3 mL), 20% NaOH(aq) (6 mL) and H$_2$O (3 mL). The resulting mixture was allowed to warm to rt, stirred for 30 min and MgSO$_4$ was added. The solids were removed by filtration through Celite® and washed with 9:1 CH$_2$Cl$_2$/MeOH (50 mL). The solvent was evaporated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (15 mL). After cooling to 0 °C, a solution of di-\textit{tert}-butyl dicarbonate in CH$_2$Cl$_2$ (10 mL) was added dropwise and the resulting solution was stirred at rt for 16 h. Saturated NaHCO$_3$(aq) (15 mL) and CH$_2$Cl$_2$ (25 mL) were added and the two layers were separated. The organic layer was dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using CH$_2$Cl$_2$ and then 96:4 CH$_2$Cl$_2$-Et$_2$O as eluent gave 3,4-disubstituted pyrrolidine \textit{96} (1.87 g, 63%) as a pale orange oil, $R_f$ (96:4 CH$_2$Cl$_2$-Et$_2$O) 0.31; IR (CHCl$_3$) 2934, 2894, 2838, 2798, 1657 (C=O), 1453, 1391, 1345, 1153, 1111 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.61 (s, 2H, =CH), 3.37 (dd, $J$ = 10.0, 6.5 Hz, 2H, NCH), 3.09 (br dd, $J$ = 10.0, 4.5 Hz, 2H, NCH), 2.34-2.12 (m, 4H, CH), 1.87 (dd, $J$ = 16.0, 4.0 Hz, 2H, CH), 1.43 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.4 (C=O), 124.5 (=CH), 79.0 (CMe$_3$), 51.0 (NCH$_2$), 33.9 (br, CH), 28.6 (CMe$_3$), 24.8 (CH$_2$); HRMS (ESI) $m/z$ calcd for C$_{13}$H$_{21}$NO$_2$ (M + Na)$^+$ 246.1465, found 246.1459 (+2.3 ppm error).

Lab Book Reference: AMI_1
Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, SiComp) at rt under Ar. After cooling to –78 °C, a solution of N-Boc pyrrolidine 96 (226 mg, 1.01 mmol, 1.0 eq.) was added followed by TMEDA (153 mg, 1.31 mmol, 1.3 eq., 0.20 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.35 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at –78 °C for 10 min. Then, Me₂SO₄ (255 mg, 2.02 mmol, 2.0 eq., 0.19 mL) was added and the solution was stirred for a further 45 min at –78 °C. Then, saturated NH₄Cl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 90:10 mixture (by ¹H NMR spectroscopy of sulfonamides anti-218 and syn-218) of 2,3,4-trisubstituted pyrrolidines anti-211 and syn-211 (192 mg, 80%) as a colourless oil, Rf (85:15 hexane-EtOAc) 0.30; IR (ATR) 2970, 2935, 1690 (C=O), 1388, 1363, 1174, 1128, 1104, 1090, 664 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) for anti-211 δ 5.63 (s, 2H, =CH), 3.58-3.37 (br m, 1H, NCH), 3.40 (dd, J = 10.5, 7.0 Hz, 1H, NCH), 3.18 (br s, 1H, NCH), 2.39 (br s, 1H, CH), 2.24-2.18 (m, 2H, CH), 1.89-1.83 (m, 3H, CH), 1.46 (s, 9H, CMe₃), 1.22 (d, J = 6.0 Hz, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) for anti-211 (rotamers) δ 155.3 (C=O), 124.8 (=CH), 124.8 (=CH), 124.5 (=CH), 124.4 (=CH), 79.1 (CMe₃), 78.9 (CMe₃), 58.9 (NCH), 58.6 (NCH), 51.1 (NCH₂), 50.9 (NCH₂), 41.9 (CH), 40.8 (CH), 32.3 (CH), 31.8

(15S*,3aS*,7aR*) and (1R*,3aS*,7aR*)-tert-Butyl-1-methyl-2,3,3a,4,7,7a-hexahydro-1H-isooindole-2-carboxylate anti-211 and syn-211
For N-Boc pyrrolidine 96, a peak at 1702 cm\(^{-1}\) was observed and assigned to \(\nu_{C=O}\). After addition of \(s\)-BuLi, a new peak at 1651 cm\(^{-1}\) was observed which was assigned to \(\nu_{C=O}\) in the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed. When \(\text{Me}_2\text{SO}_4\) was added (after a 10 min total lithiation time), the signal for the lithiated intermediate \((\nu_{C=O} = 1651 \text{ cm}^{-1})\) disappeared after 3 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_96

**tert-Butyl N-[4-hydroxycyclohexyl]carbamate trans-171**

![Chemical Structure](image)

1 M NaOH\(_{\text{aq}}\) (40 mL) was added to a stirred suspension of trans-aminocyclohexanol hydrochloride trans-170 (5.00 g, 32.98 mmol, 1.0 eq.) in 1,4-dioxane (180 mL) at 0 °C. The resulting solution was then stirred at 0 °C for 15 min. Then, a solution of di-\(\text{tert}\)-butyl dicarbonate (7.90 g, 36.20 mmol, 1.1 eq.) in 1,4-dioxane (60 mL) was added dropwise. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. 1 M HCl\(_{\text{aq}}\) was added until pH > 7 was reached and EtOAc (100 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organics were washed with 1 M HCl\(_{\text{aq}}\) (50 mL), H\(_2\)O (50 mL) and brine (50 mL), dried (Na\(_2\)SO\(_4\)), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 70:30 EtOAc-hexane as eluent gave N-Boc aminocyclohexanol trans-171 (6.13 g, 86%) as a white solid, mp 158-160 °C; \(R_f\) (70:30 EtOAc, hexane) 0.24; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.38 (br s, 1H, NH), 3.63-3.56 (m, 1H, NCH), 3.48-3.36 (m, 1H, CHOH), 2.03-1.94 (m, 4H, CH), 1.44 (CMe\(_3\)), 1.36-1.12 (m, 4H, CH); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.4 (C=O), 79.4 (CMe\(_3\)), 70.0 (OCH), 49.0 (NCH),
34.1 (CH₂), 31.3 (CH₂), 28.5 (CMe₃). Spectroscopic data consistent with those reported in the literature.¹⁴³

Lab book Reference: AMI_125

_**tert-Butyl 7-azabicyclo[2.2.1]heptane-7-carboxylate 84**_

![Diagram of tert-Butyl 7-azabicyclo[2.2.1]heptane-7-carboxylate 84](image)

Methanesulfonyl chloride (2.40 g, 20.98 mmol, 1.5 eq., 1.62 mL) was added dropwise to a stirred solution of _N_-Boc aminocyclohexanol _trans_-171 (3.01 g, 13.99 mmol, 1.0 eq.) and Et₃N (2.12 g, 20.98 mmol, 1.5 eq., 2.93 mL) in CH₂Cl₂ (120 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. Then, saturated NaHCO₃(aq) (60 mL) was added dropwise with vigorous stirring. The two layers were separated and the organic layer was washed with H₂O (50 mL), dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the intermediate mesylate as a white solid. KOt-Bu (785 mg, 7.00 mmol, 0.5 eq.) was added to a stirred solution of the crude mesylate in THF (120 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. KOt-Bu (2.355, 21.00 mmol, 1.5 eq.) was added and the resulting solution was stirred at rt for 16 h. After cooling to 0 °C, 1 M HCl(aq) (60 mL) was added followed by Et₂O (100 mL) and the two layers were separated. The organic layer was washed with brine (50 mL), dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave bicyclic compound 84 (1.27 g, 46%) as a colourless oil, _R_f_ (90:10 hexane-EtOAc) 0.40; ¹H NMR (400 MHz, CDCl₃) δ 4.19-4.17 (m, 2H, NCH), 1.78-1.73 (m, 4H, CH), 1.44 (s, 9H, CMe₃), 1.38 (d, _J_ = 7.0 Hz, 4H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.0 (C=O), 79.4 (CMe₃), 56.3 (NCH), 29.7 (CH₂), 28.4 (CMe₃). Spectroscopic data consistent with those reported in the literature.⁹⁹

Lab Book Reference: AMI_129
*tert*-Butyl 1-[hydroxy(phenyl)methyl]-7-azabicyclo[2.2.1]heptane-7-carboxylate 231

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC10, DiComp) at rt under Ar. After cooling to −78 °C, a solution of bicyclic pyrrolidine 84 (196 mg, 0.99 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (150 mg, 0.19 mL, 1.29 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 35 min. Then, PhCHO (211 mg, 0.20 mL, 1.99 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 5 min. The solution was then allowed to warm to rt over 30 min and saturated NH₄Cl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 99.5:0.5 CH₂Cl₂-acetone as eluent gave 2-substituted bicyclic pyrrolidine 231 (204 mg, 68%) as a white solid, mp 100-102 °C; *R*ₙ (99.5:0.5 CH₂Cl₂-acetone) 0.22; IR (ATR) 3269 (OH), 2979, 2873, 1663 (C=O), 1402, 1367, 1150, 1128, 1053, 713 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.37 (m, 2H, Ph), 7.31-7.21 (m, 3H, Ph), 5.61 (br s, 1H, OH), 5.32 (s, 1H, OCH), 4.28 (dd, *J* = 5.0, 5.0 Hz, 1H, NCH), 2.29 (dddd, *J* = 12.0, 12.0, 3.5, 3.5 Hz, 1H, CH), 1.81-1.67 (m, 3H, CH₂), 1.48 (s, 9H, CMe₃), 1.36-1.28 (m, 2H, CH), 1.19-1.12 (m, 1H, CH), 1.09-1.04 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.9 (C=O), 141.0 (*ipso*-Ph), 128.0 (Ph), 127.6 (Ph), 127.5 (Ph), 80.5 (CMe₃), 73.8 (CHO), 72.8 (NC), 58.4 (NCH), 35.1 (CH₂), 29.2 (CH₂), 29.1 (CH₂), 28.6 (CMe₃), 28.1 (CH₂); HRMS (ESI) *m/z* calcd for C₁₈H₂₄NO₃ (M + Na)⁺ 326.1727, found 326.1718 (+2.1 ppm error).
For bicyclic pyrrolidine 84, a peak at 1705 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1682 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the prelithiation complex. A new peak at 1641 cm$^{-1}$ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 15 min, complete lithiation of bicyclic pyrrolidine 84 to give the lithiated intermediate was observed. When PhCHO was added (after a 15 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1641$ cm$^{-1}$) disappeared after 1 min, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of bicyclic pyrrolidine 84 was first order with respect to bicyclic pyrrolidine 84, $k_{\text{obs}} = (6.39 \pm 0.31) \times 10^{-3}$ s$^{-1}$ and $t_{1/2} = (108 \pm 5)$ s.

First order exponential decay curves ($y = Ae^{-k_{\text{obs}}t} + c$) were fit to the consumption of bicyclic pyrrolidine 84 (a) and consumption of the prelithiation complex of 84 (b) for the lithiation of bicyclic pyrrolidine 84. Both provided good fit with a first order exponential decay. Curve fitting of bicyclic pyrrolidine 84 consumption (a) provided $k_{\text{obs}} = (8.16 \pm 0.43) \times 10^{-3}$ s$^{-1}$ and $t_{1/2} = (84.9 \pm 4.4)$ s. Curve fitting of prelithiation complex consumption (b) provided $k_{\text{obs}} = (6.87 \pm 0.26) \times 10^{-3}$ s$^{-1}$ and $t_{1/2} = (101 \pm 4)$ s.
tert-Butyl 4-(dimethylamino)piperidine-1-carboxylate 168

Me₂NH.HCl (326 mg, 4.00 mmol, 2.0 eq.) and Ti(O-i-Pr)₄ (1.137 g, 4.00 mmol, 2.0 eq., 1.18 mL) were added to a stirred solution of N-Boc piperidin-4-one (399 mg, 2.00 mmol, 1.0 eq.) and Et₃N (405 mg, 4.00 mmol, 2.0 eq., 0.56 mL) in EtOH (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, NaBH₄ (113 mg, 3.0 mmol, 1.5 eq.) was added and the mixture was stirred at rt for 16 h. 2 M NH₄OH (aq) (10 mL) was added to the solution and the solids were removed by filtration and washed with CH₂Cl₂ (2 x 20 mL). The two layers of the filtrate were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organics were extracted with 2 M HCl (aq) (2 x 10 mL). 10% NaOH (aq) was added to the combined aqueous extracts until pH > 10 was reached and then this solution was extracted with CH₂Cl₂ (2 x 25 mL). These combined organics were dried (K₂CO₃), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:9.9:0.1 CH₂Cl₂-MeOH-Et₃N as eluent gave dimethyl N-Boc piperidine 168 (180 mg, 40%) as a yellow oil, \( R_f \) (90:10 CH₂Cl₂-MeOH) 0.16; IR (ATR) 2933, 2861, 2771, 1690 (C=O), 1419, 1364, 1239, 1155, 1057, 879 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 4.14 (br s, 2H, NCH), 2.77-2.63 (m, 2H, NCH), 2.37-2.27 (m, 2H, NCH), 2.02-1.95 (m, 2H, NCH), 1.34-1.28 (m, 2H, NCH), 1.10-1.05 (m, 2H, NCH), 0.86-0.81 (m, 2H, NCH), 0.20-0.15 (m, 2H, NCH).
7H, NCH + NMe₂), 1.86-1.78 (m, 2H, CH), 1.45 (s, 9H, CMe₃), 1.44-1.32 (m, 2H, CH); \(^{13}\)C NMR (100.6 MHz, CDCl₃) δ 154.9 (C=O), 79.5 (CMe₃), 62.3 (NCH), 43.2 (NCH₂), 41.7 (NMe₂), 28.5 (CMe₃), 28.4 (CH₂); HRMS (ESI) m/z calced for C\(_{12}\)H\(_{24}\)N\(_2\)O\(_2\) (M + Na)+ 229.1911, found 229.1903 (+3.4 ppm error).

**Lab book Reference:** AMI_118

**tert-Butyl (2R\(^*\),4R\(^*\))-4-(dimethylamino)-2-(trimethylsilyl)piperidine-1-carboxylate cis-232**

Et\(_2\)O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of 4-amino piperidine \(168\) (228 mg, 1.00 mmol, 1.0 eq.) in Et\(_2\)O (2 mL) was added followed by TMEDA (151 mg, 195 µL, 1.31 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.31 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 2 h. Then, Me\(_3\)SiCl (217 mg, 0.254 µL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 9 h. Saturated NH\(_4\)Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et\(_2\)O (3 x 10 mL) and the combined organics were dried (MgSO\(_4\)), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:5:1 CH\(_2\)Cl\(_2\)-MeOH-NH\(_4\)OH as eluent gave 2-silyl N-Boc piperidine *cis-232* (197 mg, 66%) as a pale orange oil, \(R_F\) 0.14 (93:5:1 CH\(_2\)Cl\(_2\)-MeOH-NH\(_4\)OH), IR (ATR) 2941, 2820, 2769, 1687 (C=O), 1422, 1365, 1243, 1158, 1068,
837 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.96 (br s, 1H, NCH), 2.84 (br s, 1H, NCH), 2.36-2.10 (m, 2H, NCH), 2.27 (s, 6H, NMe\(_2\)), 1.84-1.71 (m, 2H, CH), 1.42 (s, 9H, CMe\(_3\)), 1.39-1.21 (m, 2H, CH), 0.06 (s, 9H, SiMe\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.2 (C=O), 79.2 (CMe\(_3\)), 63.9 (NCH), 49.2 (NCH), 46.8 (NCH\(_2\)), 41.6 (NMe\(_2\)), 35.5 (CH\(_2\)), 29.1 (CH\(_2\)), 28.5 (CMe\(_3\)), –0.8 (SiMe\(_3\)); HRMS (ESI) \(m/z\) calcd for C\(_{15}\)H\(_{32}\)N\(_2\)O\(_2\)Si (M + H)\(^+\) 301.2306, found 301.2300 (+2.1 ppm error). The stereochemistry of cis-232 has not been proven but is assumed from literature precedent.\(^{38}\)

For 4-amino piperidine 168, a peak at 1697 cm\(^{-1}\) was observed and assigned to \(\nu_{C=O}\). After addition of s-BuLi, a new peak at 1676 cm\(^{-1}\) was observed which was assigned to \(\nu_{C=O}\) in the prelithiation complex. A new peak at 1645 cm\(^{-1}\) was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 2 h, complete lithiation of 4-amino piperidine 168 to give the lithiated intermediate was observed. When Me\(_3\)SiCl was added (after 2 h total lithiation time), the signal for the lithiated intermediate (\(\nu_{C=O} = 1645\) cm\(^{-1}\)) disappeared after 8.5 h, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of 4-amino N-Boc piperidine 168 was first order with respect to 4-amino N-Boc piperidine 168, \(k_{obs} = (6.26 \pm 0.14) \times 10^{-4}\) s\(^{-1}\) and \(t_{1/2} = (1110 \pm 20)\) s.

First order exponential decay curves (\(y = Ae^{-k_{obs}t} + c\)) were fit to the consumption of 4-amino N-Boc piperidine 168 (a) and consumption of the prelithiation complex of 168 (b) for the lithiation of 4-amino N-Boc piperidine 168. Both provided good fit with a first order exponential decay. Curve fitting of 4-amino N-Boc piperidine 168 consumption (a) provided
\( k_{\text{obs}} = (6.64 \pm 0.15) \times 10^{-4} \text{ s}^{-1} \) and \( t_{1/2} = (1040 \pm 20) \text{ s} \). Curve fitting of prelithiation complex consumption (b) provided \( k_{\text{obs}} = (8.60 \pm 0.25) \times 10^{-4} \text{ s}^{-1} \) and \( t_{1/2} = (806 \pm 24) \text{ s} \).

Lab Book Reference: AMI_266

**tert-Butyl 4-hydroxypiperidine-1-carboxylate 233**

NaBH₄ (200 mg, 7.50 mmol, 1.5 eq.) was added to a stirred solution of \( N \)-Boc piperidin-4-one (1.00 g, 5.00 mmol, 1.0 eq.) in EtOH (5 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 4 h. Then, the mixture was cooled to 0 °C and saturated NH₄Cl(aq) (20 mL) was added dropwise. The solvent was evaporated under reduced pressure and EtOAc (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organics were dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 CH₂Cl₂-acetone as eluent gave \( N \)-Boc-4-hydroxy piperidine 233 (913 mg, 91 %) as a white solid, mp 66-68 °C (lit., 144 64.6-66.5 °C); \( R_F \) (90:10 CH₂Cl₂-acetone) 0.21; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 3.89-3.80 (m, 3H, NCH + OCH), 3.02 (ddd, \( J = 13.0, 10.0, 3.0 \) Hz, 2H, NCH), 2.17 (br s, 1H, OH), 1.89-1.81 (m, 2H,
tert-Butyl 4-\{tris(propan-2-yl)silyl\}oxy}piperidine-1-carboxylate 39

Triisopropysilyl chloride (3.48 g, 3.87 mL, 18.07 mmol, 1.2 eq.) was added dropwise to a stirred solution of 4-hydroxy piperidine 233 (3.03 g, 15.06 mmol, 1.0 eq.) and imidazole (2.56 g, 37.65 mmol, 2.5 eq.) in DMF (40 mL) at rt under Ar. The resulting solution was stirred at rt for 6 h. Saturated NaHCO$_3$(aq) (40 mL) and Et$_2$O (40 mL) were added and the two resulting layers were separated. The aqueous layer was then extracted with Et$_2$O (4 x 30 mL) and the combined organics were washed with brine (50 mL), dried (Na$_2$SO$_4$), filtered evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:7 hexane:EtOAc as eluent gave 4-OTIPS piperidine 39 (4.84 g, 90%) as a colourless oil, $R_f$ (93:7 hexane:EtOAc) 0.28; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.99 (tt, $J = 6.5$, 3.3 Hz, 1H, OCH), 3.60 (ddd, $J = 12.0$, 8.0, 3.5 Hz, 2H, NCH), 3.28 (ddd, $J = 12.0$, 7.0, 4.0 Hz, 2H, NCH), 1.78-1.67 (m, 2H, CH), 1.58-1.49 (m, 2H, CH), 1.45 (s, 9H, CMe$_3$), 1.08-1.03 (m, 21H, Si(i-Pr)$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.1 (C=O), 79.4 (CMe$_3$), 67.2 (OCH), 40.9 (NCH$_2$), 34.5 (CH$_2$), 28.6 (CMe$_3$), 18.2 (SilCHCH$_3$), 12.4 (SilCHCH$_3$). Spectroscopic data consistent with those reported in the literature.
**tert-Butyl (2R*,4R*)-2-(trimethylsilyl)-4-{[tris(propan-2-yl)silyl]oxy}piperidine-1-carboxylate cis-234**

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of 4-OTIPS piperidine 39 (355 mg, 0.99 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 50 min. Then, Me₃SiCl (215 mg, 0.25 mL, 1.98 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 14.5 h. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 98:2-95:5 hexane:Et₂O as eluent gave 2-silyl piperidine cis-234 (301 mg, 70%) as a colourless oil, Rf (95:5 hexane:Et₂O) 0.30; IR (ATR) 2943, 2866, 1691, 1464, 1422, 1245, 1150, 1104, 880, 826 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.92 (br s, 1H, CHO), 3.84-3.69 (m, 1H, NCH₂), 2.83 (br s, 1H, NCH₂), 2.26 (br s, 1H, NCH), 1.90-1.80 (m, 2H, CH), 1.49-1.34 (m, 2H, CH), 1.43 (s, 9H, CMe₃), 1.08-1.01 (m, 21H, Si(i-Pr)₃), 0.07 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1 (C=O), 79.2 (CMe₃), 66.0 (CHO), 36.4 (NCH₂), 30.5 (NCH), 28.5 (CMe₃), 18.2 (SiCHCH₃), 12.5 (SiCHCH₃), −0.7 (SiMe₃); HRMS (ESI) m/z calcd for C₂₂H₄₇NO₃Si₂ (M + Na)⁺ 452.2987,
found 452.3007 (+2.8 ppm error). The stereochemistry of cis-234 has not been proven but is assumed from literature precedent.\(^\text{38}\)

For 4-OTIPS piperidine 39, a peak at 1698 cm\(^{-1}\) was observed and assigned to \(\nu_{C=O}\). After addition of s-BuLi, a new peak at 1676 cm\(^{-1}\) was observed which was assigned to \(\nu_{C=O}\) in the prelithiation complex. A new peak at 1645 cm\(^{-1}\) was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 45 min, complete lithiation of 4-OTIPS piperidine 39 to give the lithiated intermediate was observed. When Me\(_3\)SiCl was added (after 50 min total lithiation time), the signal for the lithiated intermediate (\(\nu_{C=O} = 1645\) cm\(^{-1}\)) disappeared after 14.5 h, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of 4-OTIPS N-Boc piperidine 39 was first order with respect to 4-OTIPS N-Boc piperidine 39, \(k_{\text{obs}} = (2.07 \pm 0.06) \times 10^{-3}\) s\(^{-1}\) and \(t_{1/2} = (335 \pm 9)\) s.

First order exponential decay curves (\(y = Ae^{-k_{\text{obs}}t} + c\)) were fit to the consumption of 4-OTIPS N-Boc piperidine 39 (a) and consumption of the prelithiation complex of 39 (b) for the lithiation of 4-OTIPS N-Boc piperidine 39. Both provided good fit with a first order exponential decay. Curve fitting of 4-OTIPS N-Boc piperidine 39 consumption (a) provided \(k_{\text{obs}} = (2.16 \pm 0.05) \times 10^{-3}\) s\(^{-1}\) and \(t_{1/2} = (321 \pm 8)\) s. Curve fitting of prelithiation complex consumption (b) provided \(k_{\text{obs}} = (2.46 \pm 0.09) \times 10^{-3}\) s\(^{-1}\) and \(t_{1/2} = (281 \pm 10)\) s.
tert-Butyl piperazine-1-carboxylate 235

A solution of Boc₂O (7.00 g, 32.07 mmol, 1.0 eq.) in CH₂Cl₂ (50 mL) was added dropwise over 1 h to a stirred solution of piperazine (5.53 g, 64.15 mmol, 2.0 eq.) in CH₂Cl₂ (180 mL) at rt. The resulting solution was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give a white solid. H₂O (100 mL) was added and the insoluble solids were removed by filtration and washed with H₂O (50 mL). The aqueous filtrate was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organics were evaporated under reduced pressure to give N-Boc piperazine 235 (4.35 g, 73%) as a white solid, mp 43-45 °C (lit., 145 42.5-45 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.38 (t, J = 5.0 Hz, 4H, NCH₂), 2.80 (t, J = 5.0 Hz, 4H, NCH₂), 1.65 (s, 1H, NH), 1.45 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.6 (C=O), 79.4 (CMe₃), 45.6 (NCH₂), 44.6 (NCH₂), 28.4 (CMe₃). Spectroscopic data consistent with those reported in the literature.¹⁴⁵

Lab Book Reference: AMI_182
tert-Butyl 4-benzylpiperazine-1-carboxylate 57

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\text{N-Boc piperazine 235 (4.35 g, 23.37 mmol, 1.0 eq.) and K}_2\text{CO}_3 (6.46 g, 46.74 mmol, 2.0 eq.) were added portionwise to a stirred solution of benzyl chloride (2.96 g, 2.69 mL, 23.37 mmol, 1.0 eq.) in EtOH (80 mL) at rt. The resulting white suspension was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure and the residue was partitioned between H}_2\text{O (50 mL) and CH}_2\text{Cl}_2 (50 mL). The two layers were separated and the aqueous layer was extracted with CH}_2\text{Cl}_2 (3 x 25 mL). The combined organic layers were dried (MgSO}_4, filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave N-Boc N'-Bn piperazine 57 (5.10 g, 79%) as a pale yellow solid, mp 74-76 °C (lit., 146 72-75 °C); } R_F (80:20 hexane-EtOAc) 0.19; \^H NMR (400 MHz, CDCl}_3) \delta 7.38-7.29 (m, 4H, Ph), 7.28-7.23 (m, 1H, Ph), 3.51 (s, 2H, CH}_2\text{Ph), 3.42 (t, } J = 5.0 \text{ Hz, 4H, NCH}_2\text{), 2.39 (t, } J = 5.0 \text{ Hz, 4H, NCH}_2\text{), 1.45 (s, 9H, CMe}_3\text{); } \^{13}\text{C NMR (100.6 MHz, CDCl}_3) \delta 154.9 (C=O), 138.0 (ipso-Ph), 129.3 (Ph), 128.4 (Ph), 127.3 (Ph), 79.7 (CMe}_3\text{, 63.2 (CH}_2\text{Ph), 53.0 (NCH}_2\text{), 44.2 (NCH}_2\text{), 28.6 (CMe}_3\text{); Spectroscopic data consistent with those reported in the literature.}

Lab Book Reference: AMI_187
ReactIR™ spectroscopic monitoring of the s-BuLi/TMEDA lithiation and PhCHO trapping of $N'$-Bn $N$-Boc piperazine 57

Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to $-78$ °C, a solution of $N'$-Bn piperazine 57 (278 mg, 1.00 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (151 mg, 0.20 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at $-78$ °C for 12 min. Then, PhCHO (212 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at $-78$ °C for a further 8 min. Saturated NH$_4$Cl$_{(aq)}$ (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and combined organic extracted were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. $^1$H NMR spectroscopic analysis of the crude product indicated that no unreacted $N'$-Bn $N$-Boc piperazine 57 was present, confirming complete lithiation of $N'$-Bn $N$-Boc piperazine 57 had occurred.

For $N'$-Bn $N$-Boc piperazine 57, a peak at 1701 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1678 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the prelithiation complex. A new peak at 1644 cm$^{-1}$ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of $N'$-Bn $N$-Boc piperazine 57 to give the lithiated intermediate was observed. When PhCHO was added (after 12 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1644$ cm$^{-1}$) disappeared after 1 min, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of $N'$-Bn $N$-Boc piperazine 57 was first order with respect to $N'$-Bn $N$-Boc piperazine 57, $k_{obs} = (3.09 \pm 0.18) \times 10^{-2}$ s$^{-1}$ and $t_{1/2} = (22.5 \pm 1.3)$ s.
First order exponential decay curves (\( y = Ae^{-k_{obs}t} + c \)) were fit to the consumption of \( N'\text{-}Bn \) \( N\text{-}Boc \) piperazine 57 (a) and consumption of the prelithiation complex of 57 (b) for the lithiation of \( N'\text{-}Bn \) \( N\text{-}Boc \) piperazine 57. Both provided good fit with a first order exponential decay. Curve fitting of \( N'\text{-}Bn \) \( N\text{-}Boc \) piperazine 57 consumption (a) provided \( k_{obs} = (3.79 \pm 0.19) \times 10^{-2} \text{ s}^{-1} \) and \( t_{1/2} = (18.3 \pm 0.9) \text{ s} \). Curve fitting of prelithiation complex consumption (b) provided \( k_{obs} = (4.58 \pm 0.49) \times 10^{-2} \text{ s}^{-1} \) and \( t_{1/2} = (15.2 \pm 1.6) \text{ s} \).

Lab Book Reference: AMI_191
tert-Butyl 4-methylpiperazine-1-carboxylate 58

A solution of di-tert-butyl dicarbonate (7.20 g, 33.00 mmol, 1.1 eq.) in CH$_2$Cl$_2$ (20 mL) was added dropwise to a stirred solution of N-methyl piperazine (3.00 g, 30.00 mmol, 1.0 eq., 3.3 mL) in CH$_2$Cl$_2$ at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Water (50 mL) and 20% NaOH$_{aq}$ (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave N-Boc-N’-methyl piperazine 58 (5.44 g, 91%) as a colourless oil, bp 92-97°C/ 0.5 mmHg; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.42 (t, $J$ = 5.0 Hz, 4H, NCH$_2$), 2.32 (t, $J$ = 5.0 Hz, 4H, NCH$_2$), 2.28 (s, 3H, NMe), 1.44 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 154.9 (C=O), 79.7 (CMe$_3$), 55.0 (NCH$_2$), 46.3 (NMe), 43.6 (br, NCH$_2$), 28.5 (CMe$_3$). Spectroscopic data consistent with those reported in the literature.$^{146}$

Lab Book Reference: AMI_156

ReactIR™ spectroscopic monitoring of the s-BuLi/TMEDA lithiation and PhCHO trapping of N’-Me N-Boc piperazine 58

Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of N’-Me N-Boc piperazine 58 (199 mg, 0.99 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (150 mg, 0.19 mL, 1.29 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 12
min. Then, PhCHO (210 mg, 0.20 mL, 1.99 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 5 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. ¹H NMR spectroscopic analysis of the crude product indicated that no unreacted N’-Me N-Boc piperazine 58 was present, confirming complete lithiation of N’-Me N-Boc piperazine 58 had occurred.

For N’-Me N-Boc piperazine 58, a peak at 1701 cm⁻¹ was observed and assigned to ʋC=O. After addition of s-BuLi, a new peak at 1681 cm⁻¹ was observed which was assigned to ʋC=O in the prelithiation complex. A new peak at 1645 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N’-Me N-Boc piperazine 58 to give the lithiated intermediate was observed. When PhCHO was added (after 12 min total lithiation time), the signal for the lithiated intermediate (ʋC=O = 1645 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of N’-Me N-Boc piperazine 58 was first order with respect to N’-Me N-Boc piperazine 58, kₜₐₑₛ = (3.54 ± 0.31) x 10⁻² s⁻¹ and t₁/₂ = (19.6 ± 1.7) s.

First order exponential decay curves (y = Aₑᵏₒₜₑₛᵗ + c) were fit to the consumption of N’-Me N-Boc piperazine 58 (a) and consumption of the prelithiation complex of 58 (b) for the lithiation of N’-Me N-Boc piperazine 58. Both provided good fit with a first order exponential decay. Curve fitting of N’-Me N-Boc piperazine 58 consumption (a) provided
Curve fitting of prelithiation complex consumption (b) provided $k_{\text{obs}} = (7.41 \pm 5.24) \times 10^{-2}$ s$^{-1}$ and $t_{1/2} = (9.36 \pm 6.62)$ s.

Lab Book Reference: AMI_238

**tert-Butyl morpholine-4-carboxylate 169**

Di-tert-butyl dicarbonate (5.51 g, 25.25 mmol, 1.1 eq.) was added to a stirred solution of morpholine (2.00 g, 22.96 mmol, 1.0 eq., 2.0 mL) in H$_2$O (30 mL) at rt. The resulting solution was stirred at rt for 10 min and EtOAc (30 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave N-Boc morpholine 169 (2.40 g, 56%) as a white solid, mp 55-58 °C, $R_F$ (80:20 hexane:EtOAc) 0.25; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.64 (t, $J = 4.5$ Hz, 4H, CH$_2$), 3.41 (t, $J = 4.5$ Hz, 4H, CH$_2$), 1.46 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 154.9 (C=O), 80.0 (CMe$_3$), 66.8 (CH$_2$), 44.0 (CH$_2$), 28.5 (CMe$_3$). Spectroscopic data consistent with those reported in the literature.$^{147}$

Lab Book Reference: AMI_157
ReactIR™ spectroscopic monitoring of the lithiation of N-Boc morpholine 169 using s-BuLi/TMEDA

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of solution of N-Boc morpholine 169 (187 mg, 1.00 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (300 mg, 2.60 mmol, 2.6 eq., 0.39 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.60 mmol, 2.6 eq.) was added. The resulting solution was stirred at −78 °C for 15 min.

For N-Boc morpholine 169, a peak at 1703 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1645 cm⁻¹ was observed which was assigned to νC=O in the lithiated intermediate. After a lithiation time of 1 min, complete lithiation of N-Boc morpholine 169 to give the lithiated intermediate was observed.

Lab Book Reference: AMI_282

**tert-Butyl 1,4-dioxoa-8-azaspiro[4.5]decane-8-carboxylate 34**

![Chemical structure of tert-Butyl 1,4-dioxoa-8-azaspiro[4.5]decane-8-carboxylate 34]

A solution of N-Boc-4-piperidone (3.00g, 15.06 mmol, 1 eq.), p-toluenesulfonic acid monohydrate (0.20g, 1.05 mmol, 0.07 eq.) and ethylene glycol (9.35 g, 150.56 mmol, 10 eq., 8.40 mL) in toluene (75 mL) was stirred and heated at reflux under Dean-Stark conditions for 72 h. After cooling to rt, the solvent was evaporated under reduced pressure and CH₂Cl₂ (30 mL) was added. The organic solution was washed with sat. NaHCO₃(aq) (30 mL), dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product.
Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-ketal piperidine 34 (2.91 g, 79%) as a colourless oil, $R_F$ (70:30 hexane-EtOAc) 0.26; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.96 (s, 4H, OCH$_2$), 3.50 (dd, $J = 5.5, 5.5$ Hz, 4H, NCH$_2$), 1.65 (dd, $J = 5.5, 5.5$ Hz, 4H, CH$_2$), 1.45 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) 154.8 (C=O), 107.3 (OCO), 79.7 (CMe$_3$), 64.5 (OCH$_2$), 41.9 (NCH$_2$), 35.0 (CH$_2$), 28.5 (CMe$_3$). Spectroscopic data consistent with those reported in the literature.$^{25}$

Lab Book Reference: AMI_223

**tert-Butyl 7-(trimethylsilyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate 47**

Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR$^{\text{TM}}$ probe (ReactIR$^{\text{TM}}$ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of acetal 34 (240 mg, 0.99 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (149 mg, 192 μL, 1.28 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^{\text{TM}}$). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 70 min. Then, Me$_3$SiCl (214 mg, 250 μL, 1.97 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 14.5 h. Saturated NH$_4$Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min. The two layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave 2-substituted $N$-Boc piperidine 47 (220 mg, 71%) as a yellow solid, mp 62-64 °C; $R_F$ (85:15 hexane-EtOAc) 0.3; IR (ATR) 2975, 2948,
2924, 2896, 1678 (C=O), 1361, 1166, 1100, 836, cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.95 (s, 4H, OCH\(_2\)), 3.71 (br s, 1H, NCH), 3.27 (br s, 1H NCH\(_2\)), 2.94 (br s, 1H, NCH\(_2\)), 1.78–1.57 (m, 4H, CH), 1.44 (s, 9H, CMe\(_3\)), 0.07 (s, 9H, SiMe\(_3\)); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.1 (C=O), 107.7 (OCH\(_2\)), 79.4 (CMe\(_3\)), 64.6 (OCH\(_2\)), 64.4 (OCH\(_2\)), 44.2 (NCH\(_2\)), 35.6 (CH\(_2\)), 28.5 (CMe\(_3\)), –0.08 (SiMe\(_3\)); HRMS (ESI) \(m/z\) calcd for C\(_{15}\)H\(_{29}\)NO\(_4\)Si (M + Na)\(^+\) 338.1758, found 338.1750 (+1.5 ppm error). Spectroscopic data consistent with those reported in the literature.\(^{148}\)

For 4-ketal \(N\)-Boc piperidine 34, a peak at 1700 cm\(^{-1}\) was observed and assigned to \(\nu\)\(_{C=O}\). After addition of s-BuLi, a new peak at 1674 cm\(^{-1}\) was observed which was assigned to \(\nu\)\(_{C=O}\) in the prelithiation complex. A new peak at 1646 cm\(^{-1}\) was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 70 min, complete lithiation of 4-ketal \(N\)-Boc piperidine 34 to give the lithiated intermediate was observed. When Me\(_3\)SiCl was added (after 70 min total lithiation time), the signal for the lithiated intermediate (\(\nu\)\(_{C=O}\) = 1646 cm\(^{-1}\)) disappeared after 8.5 h, indicating complete trapping had occurred.

Kinetic analysis indicated that the lithiation of 4-ketal \(N\)-Boc piperidine 34 was first order with respect to 4-ketal \(N\)-Boc piperidine 34, \(k_{obs} = (1.09 \pm 0.03) \times 10^{-3} \text{s}^{-1}\) and \(t_{1/2} = (636 \pm 18)\) s.

First order exponential decay curves (\(y = Ae^{k_{obs}t} + c\)) were fit to the consumption of 4-ketal \(N\)-Boc piperidine 34 (a) and consumption of the prelithiation complex of 34 (b) for the lithiation of 4-ketal \(N\)-Boc piperidine 34. Both provided good fit with a first order exponential decay. Curve fitting of 4-ketal \(N\)-Boc piperidine 34 consumption (a) provided
\( k_{\text{obs}} = (1.11 \pm 0.04) \times 10^{-3} \text{ s}^{-1} \) and \( t_{1/2} = (624 \pm 22) \text{ s} \). Curve fitting of prelithiation complex consumption (b) provided \( k_{\text{obs}} = (2.23 \pm 0.14) \times 10^{-3} \text{ s}^{-1} \) and \( t_{1/2} = (311 \pm 19) \text{ s} \).

**Lab Book Reference:** AMI_236

**tert-Butyl 4-phenyl-1,2,3,6-tetrahydropyridine-1-carboxylate 236**

\( n\)-BuLi (6.48 mL of a 2.3 M solution in hexanes, 15.04 mmol, 1.0 eq.) was added dropwise to a solution of bromobenzene (2.36 g, 15.04 mmol, 1.0 eq.) in THF (80 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min. A solution of N-Boc piperidin-4-one (3.00 g, 15.04 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred for a further 1 h at –78 °C and then allowed to warm to rt and stirred at rt for a further 1 h. The reaction was then cooled to –78 °C and methanesulfonyl chloride (6.89 g, 4.66 mL, 60.16 mmol, 4.0 eq.) and Et$_3$N (12.18 g, 16.8 mL, 120.32 mmol, 8.0 eq.) were added dropwise. The reaction mixture was then allowed to warm to rt and stirred at rt for 15 h. Saturated NaHCO$_3$(aq) (60 mL) was then added with vigorous stirring followed by addition of EtOAc (2 x 40 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organics were washed with brine (50 mL), dried (MgSO$_4$), filtered and evaporated under
reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane:EtOAc as eluent gave tetrahydropyridine \textbf{236} (2.61 g, 67\%) as a colourless oil, \( R_f \) (90:10 hexane:EtOAc) 0.21; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.40-7.31 (m, 4H, Ph), 7.28-7.23 (m, 1H, Ph), 6.03 (br s, 1H, =CH), 4.10-4.04 (m, 2H, NCH), 3.64 (dd, \( J = 5.5, 5.5 \) Hz, 2H, NCH), 2.53 (br s, 2H, CH\(_2\)), 1.49 (s, 9H, CMe\(_3\)); \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 154.5 (C=O), 141.4 (ipso-Ph), 135.1 (=C), 128.6 (Ph), 128.4 (Ph), 126.9 (Ph), 124.5 (=CH), 79.7 (CMe\(_3\)), 43.6 (NCH\(_2\)), 40.0 (NCH\(_2\)), 28.6 (CMe\(_3\)), 27.3 (CH\(_2\)). Spectroscopic data consistent with those reported in the literature.\(^{149}\)

Lab Book Reference: AMI_180

\textit{tert-}Butyl 4-phenylpiperidine-1-carboxylate \textbf{32}

\[
\begin{array}{c}
\text{Ph} \\
\text{Boc} \\
\text{32}
\end{array}
\]

Pd/C (261 mg, 10\% w/w, 0.25 mmol) was added to a solution of tetrahydropyridine \textbf{236} (2.61 g, 10.00 mmol) in MeOH (80 mL). The resulting suspension was degassed and then H\(_2\) gas (1 atm) was supplied \textit{via} a balloon. The suspension was stirred at rt under a H\(_2\) atmosphere (balloon) for 16 h. The solids were removed by filtration through Celite\(^\circledR\) and washed with MeOH (10 mL). The solvent was evaporated to give the crude product as a colourless oil. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave 4-phenyl N-Boc piperidine \textbf{32} (1.93 g, 74\%) as a colourless oil, \( R_f \) (90:10 hexane:EtOAc) 0.22; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.35-7.28 (m, 2H, Ph), 7.24-7.18 (m, 3H, Ph), 4.24 (br s, 2H NCH), 2.89-2.71 (m, 2H, NCH), 2.64 (tt, \( J = 12.0, 3.5 \) Hz, 1H, CHPh), 1.87-1.77 (m, 2H, CH), 1.68-1.57 (m, 2H, CH), 1.48 (s, 9H, CMe\(_3\)); \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 155.0 (C=O), 145.9 (ipso-Ph), 128.6 (Ph), 126.9 (Ph), 126.4 (Ph), 79.5 (CMe\(_3\)), 44.6 (NCH\(_2\)), 42.8 (CHPh), 33.3 (CH\(_2\)), 28.6 (CMe\(_3\)). Spectroscopic data consistent with those reported in the literature.\(^{150}\)

Lab Book Reference: AMI_186
*tert*-Butyl (2$R^*$, 4$R^*$)-2-methyl-4-phenylpiperidine-1-carboxylate cis-35

\[ \text{Et}_2\text{O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR}^\text{TM} \text{ probe (ReactIR}^\text{TM} 15, \text{DiComp} \text{) at rt under Ar. After cooling to –78 °C, a solution of 4-Phenyl N-Boc piperidine 32 (261 mg, 1.00 mmol, 1.0 eq.) in Et}_2\text{O (2 mL) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR}^\text{TM}). \text{Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 2 h. Then, MeI (283 mg, 0.13 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 4 h. Saturated NH}_4\text{Cl(aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et}_2\text{O (3 x 10 mL) and the combined organics were dried (MgSO}_4\text{), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 Hexane-EtOAc as eluent gave 2-methyl N-Boc piperidine cis-35 (175 mg, 64%) as a colourless oil, R}_f (95:5 Hexane-EtOAc) 0.13; }^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.33-7.27 (m, 2H, Ph), 7.24-7.17 (m, 3H, Ph), 4.01-3.92 (m, 1H, NCH), 3.81 (ddd, $J = 14.0, 7.5, 3.0$ Hz, 1H, NCH), 3.25 (ddd, $J = 14.0, 10, 6.5$ Hz, 1H, NCH), 2.80-2.72 (m, 1H, CHPh), 2.21-2.11 (m, 1H, CH), 1.92 (ddd, $J = 13.5, 6.0, 3.5, 1.0$ Hz, 1H, CH), 1.65-1.57 (m, 2H, CH), 1.50 (s, 9H, CMe$_3$), 1.21 (d, $J = 6.5$ Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.5 (C=O), 146.2 ($ipso$-Ph), 128.6 (Ph), 127.0 (Ph), 126.2 (Ph), 79.3 (CMe$_3$), 50.2 (NCH), 38.1 (CHPh), 37.7 (NCH$_2$), 37.2 (CH$_2$), 31.4 (CH$_2$), 28.7 (CMe$_3$), 20.0 (CHMe). Spectroscopic data consistent with those reported in the literature.$^{151}$

For 4-phenyl N-Boc piperidine 32, a peak at 1697 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1678 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$
in the prelithiation complex. A new peak at 1644 cm\(^{-1}\) was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 90 min, complete lithiation of 4-phenyl N-Boc piperidine 32 to give the lithiated intermediate was observed. When MeI was added (after 100 min total lithiation time), the signal for the lithiated intermediate (\(\nu_{\text{C=O}} = 1641 \text{ cm}^{-1}\)) disappeared after 90 min, indicating that complete trapping had occurred.

Kinetic analysis indicated that the lithiation of 4-phenyl N-Boc piperidine 32 was first order with respect to 4-phenyl N-Boc piperidine 32, \(k_{\text{obs}} = (1.045 \pm 0.001) \times 10^{-3} \text{ s}^{-1}\) and \(t_{1/2} = (663 \pm 6) \text{ s}\).

First order exponential decay curves (\(y = Ae^{-k_{\text{obs}}t} + c\)) were fit to the consumption of 4-phenyl N-Boc piperidine 32 (a) and consumption of the prelithiation complex of 32 (b) for the lithiation of 4-phenyl N-Boc piperidine 32. Both provided good fit with a first order exponential decay. Curve fitting of 4-phenyl N-Boc piperidine 32 consumption (a) provided \(k_{\text{obs}} = (1.08 \pm 0.01) \times 10^{-3} \text{ s}^{-1}\) and \(t_{1/2} = (642 \pm 5) \text{ s}\). Curve fitting of prelithiation complex consumption (b) provided \(k_{\text{obs}} = (1.38 \pm 0.02) \times 10^{-3} \text{ s}^{-1}\) and \(t_{1/2} = (502 \pm 7) \text{ s}\).
Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of $N'$-t-Bu $N$-Boc piperazine 66 (241 mg, 0.99 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (150 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then $s$-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 22 min. Then, MeI (281 mg, 0.13 mL, 1.98 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 3.5 h. Saturated NH$_4$Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered
and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 CH₂Cl₂-MeOH as eluent gave 2-methyl N-Boc piperazine 237 (177 mg, 69%) as a white solid, mp 46-48 °C, R<sub>f</sub> (95:5 CH₂Cl₂-MeOH) 0.22; IR (ATR) 2968, 2811, 1680 (C=O), 1418, 1230, 1155, 1100, 1016, 894, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.20-4.10 (m, 1H, NCH), 3.77 (br d, J = 13.0 Hz, 1H, NCH), 2.98 (ddd, J = 12.5, 12.5, 3.5 Hz, 1H NCH), 2.87 (ddd, J = 11.0, 5.5, 2.5 Hz, 1H, NCH), 2.71 (ddd, J = 11.0, 2.0, 2.0 Hz, 1H, NCH), 2.24 (dd, J = 11.0, 3.5, 1.0, 1H, NCH), 2.05 (ddd, J = 12.0, 11.0, 3.5 Hz, 1H, NCH), 1.44 (s, 9H, OCMe<sub>3</sub>), 1.18 (d, J = 6.5 Hz, 3H, CHMe), 1.00 (s, 9H, NCM<sub>e</sub>), 1.00 (s, 9H, NCM<sub>e</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 155.0 (C=O), 79.2 (OCMe<sub>3</sub>), 53.2 (NCMe<sub>e</sub>), 50.7 (NCH<sub>2</sub>), 47.5 (NCH), 46.1 (NCH<sub>2</sub>), 40.2 (NCH<sub>2</sub>), 28.6 (NCMe<sub>3</sub>), 26.1 (OCMe<sub>3</sub>), 15.8 (CHMe); HRMS (ESI) m/z calcd for C<sub>14</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 257.2224, found 257.2221 (+0.7 ppm error).

For N'<t-Bu N-Boc piperazine 66, a peak at 1700 cm<sup>-1</sup> was observed and assigned to ν<sub>C=O</sub>. After addition of s-BuLi, a new peak at 1678 cm<sup>-1</sup> was observed which was assigned to ν<sub>C=O</sub> in the prelithiation complex. A new peak at 1648 cm<sup>-1</sup> was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 22 min, complete lithiation of N'<t-Bu N-Boc piperazine 66 to give the lithiated intermediate was observed. When MeI was added (after 22 min total lithiation time), the signal for the lithiated intermediate (ν<sub>C=O</sub> = 1645 cm<sup>-1</sup>) disappeared after 27 min, indicating complete trapping had occurred. During the trapping process, another peak appeared at 1697 cm<sup>-1</sup> which was assigned to the trapped adduct 237.

Kinetic analysis of the lithiation of N'<t-Bu N-Boc piperazine 66 using the consumption of N'<t-Bu N-Boc piperazine 66 with a semilogarithmic plot of up to 90 % lithiation conversion (a) suggested that the reaction may involve two consecutive first order processes. A first order exponential decay curve was also fitted to consumption of N'<t-Bu N-Boc piperazine 66 throughout the lithiation provided only a moderate fit suggesting that two consecutive first order processes may occur.
For this reason, the lithiation of $N'$-t-Bu N-Boc piperazine 66 was modelled as two consecutive first order processes. The lithiation of $N'$-t-Bu N-Boc piperazine 66 between 15 and 165 s was first order with respect to $N'$-t-Bu N-Boc piperazine 66 with $k_{\text{obs}} = (6.56 \pm 0.18) \times 10^{-3} \text{ s}^{-1}$ and $t_{1/2} = (105 \pm 3)$ s. From 180s to 90% conversion (570 s) the lithiation of $N'$-t-Bu N-Boc piperazine 66 was first order with respect to $N'$-t-Bu N-Boc piperazine 66 with $k_{\text{obs}} = (3.71 \pm 0.13) \times 10^{-3} \text{ s}^{-1}$ and $t_{1/2} = (186 \pm 7)$ s.
Kinetic analysis of the lithiation of $N'$-t-Bu $N$-Boc piperazine 66 using the consumption of $N'$-t-Bu $N$-Boc piperazine 66 prelithiation complex also suggested the lithiation proceeds via two consecutive first order reactions. The lithiation of $N'$-t-Bu $N$-Boc piperazine 66 between 15 and 165 s was first order with respect to the $N'$-t-Bu $N$-Boc piperazine 66 prelithiation complex with $k_{\text{obs}} = (1.06 \pm 0.06) \times 10^{-3} \text{ s}^{-1}$ and $t_{1/2} = (65 \pm 4) \text{ s}$. From 180s to 90% conversion (570 s) the lithiation of $N'$-t-Bu $N$-Boc piperazine 66 was first order with respect to $N'$-t-Bu $N$-Boc piperazine 66 with $k_{\text{obs}} = (4.65 \pm 0.51) \times 10^{-3} \text{ s}^{-1}$ and $t_{1/2} = (149 \pm 16) \text{ s}$.

At present, the reason why the lithiation of $N'$-t-Bu $N$-Boc piperazine 66 appears to follow two consecutive first order reactions is not known. It is possible that the changing excess of the s-BuLi/TMEDA reagent or the build-up of the lithiated product during the reaction could cause the lithiation to proceed via a different mechanism. To compare the reactivity of $N'$-t-Bu $N$-Boc piperazine 66 with the other $N$-Boc heterocycles presented in this thesis the rate of the initial first order process has been used. This initial first order process has been selected for the kinetic comparison as the reagent quantities will more closely mirror those
present in the lithiation reactions of the other N-Boc heterocycles at the beginning of the reaction. In addition, if the lithiated product or another intermediate species formed during the reaction is changing the mechanistic pathway of the reaction, this effect will be less pronounced during the initial stages of the reaction where the concentrations of intermediates and products will be smaller.

Lab Book Reference: AMI_193

1-\(\text{[2-(pyrrolidin-1-yl)ethyl]pyrrolidine 177}\)

A mixture of 1,2-dichloroethane (4.3 mL, 55.0 mmol, 1.0 eq.), pyrrolidine (10.7 mL, 132.0 mmol, 2.4 eq.), \(\text{K}_{2}\text{CO}_3\) (9.88 g, 71.5 mmol, 1.3 eq.) and \(\text{H}_2\text{O}\) (10 mL) were stirred and heated at reflux for 16 h. The resulting mixture was then allowed to cool to rt and toluene (10 mL) was added. The two layers were separated and the aqueous layer was extracted with toluene (2 x 10 mL). The combined organics were dried (KOH), filtered and evaporated under reduced pressure to give the crude product. Purification by vacuum distillation, collecting the distillate between 120-140 °C/5 mmHg gave diamine 177 (6.02 g, 65%) as a colourless oil, bp 78-85°C/1 mmHg; \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 2.63 (s, 4H, NCH\(_2\)), 2.54-2.51 (m, 8H, NCH\(_2\)), 1.79-1.75 (m, 8H, CH\(_2\)); \(^{13}\text{C NMR}\) (100.6 MHz, CDCl\(_3\)) \(\delta\) 55.8 (NCH\(_2\)), 54.7 (NCH\(_2\)), 23.5 (CH\(_2\)). Spectroscopic data consistent with those reported in the literature.\(^{105}\)

Lab Book Reference: AMI_94
ReactIR™ spectroscopic monitoring of the lithiation of N-Boc pyrrolidine 9 using s-BuLi/di-pyrrolidino ethane 177

$\text{Et}_2\text{O} (12 \text{ mL})$ was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, SiComp) at rt under Ar. After cooling to $–78$ °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by a solution of di-pyrrolidino ethane 177 (219 mg, 1.30 mmol, 1.3 eq.) in $\text{Et}_2\text{O}$ (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at $–78$ °C for 1 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at $–78$ °C for a further 10 min. Saturated $\text{NH}_4\text{Cl(aq)}$ (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with $\text{Et}_2\text{O}$ (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Analysis of the crude product by $^1\text{H}$ NMR spectroscopy indicated no N-Boc pyrrolidine 9 starting material was present.

For N-Boc pyrrolidine 9, a peak at 1700 cm$^{-1}$ was observed and assigned to $\nu_{\text{C}=\text{O}}$. After addition of s-BuLi, a new peak at 1679 cm$^{-1}$ was observed which was assigned to $\nu_{\text{C}=\text{O}}$ in the prelithiation complex. A new peak at 1648 cm$^{-1}$ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 46 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. The PhCHO trapping was not monitored by ReactIR™. $^1\text{H}$ NMR analysis of the crude indicated no N-Boc pyrrolidine 9 starting material was present.

Lab Book Reference: AMI_144
Formaldehyde (9.1 mL of a 37% w/v solution in H₂O, 128.87 mmol, 7.0 eq.) was added dropwise to a stirred solution of trans-diaminocyclohexane (2.00 g, 17.51 mmol, 1.0 eq., 2.1 mL) and formic acid (7.0 mL, 185.53 mmol, 10.6 eq.) at 0 °C. The resulting solution was stirred and heated at reflux for 2 h. The solution was then cooled to 0 °C and NaOH(s) was added until pH = 12 was reached. The mixture was extracted with Et₂O (3 x 20 mL) and the combined organic layers were dried (KOH), filtered and evaporated under reduced pressure to give the crude product. Then, acetyl chloride (5.50 g, 70.04 mmol, 4.0 eq., 5.0 mL) was added dropwise to a stirred solution of the crude product and EtOH (4.1 mL, 70.04 mmol, 4.0 eq.) in EtOAc (25 mL) at 0 °C under Ar. The resulting suspension was allowed to warm to rt over 1 h. The solids were collected by filtration through a sintered glass funnel and washed with EtOAc (2 x 10 mL). Recrystallisation from hot EtOH gave the bis-hydrochloride salt as a white solid. 20% NaOH(aq) (20 mL) and Et₂O (20 mL) were added to the recrystallised solid and the layers separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude diamine. Purification by Kugelrohr distillation gave TMCDA trans-161 (1.25 g, 42%) as a colourless oil, bp 66-71 °C/2.6 mmHg (lit.,¹⁵² bp 50 °C/0.1 mmHg);¹⁵¹ ¹H NMR (400 MHz, CDCl₃) δ 2.43-2.37 (m, 2H, NCH), 2.29 (s, 12H, NMe₂), 1.87-1.84 (m, 2H, CH), 1.75-1.71 (m, 2H, CH). 1.19-1.06 (m, 4H, CH);¹⁵¹ ¹³C NMR (100.6 MHz, CDCl₃) δ 64.0 (NCH), 40.3 (NMe₂), 25.8 (CH₂), 23.0 (CH₂). Spectroscopic data consistent with those reported in the literature.¹⁵¹

Lab Book Reference: AMI_69
ReactIR™ spectroscopic monitoring of the lithiation of N-Boc pyrrolidine 9 using s-BuLi/TMCDA *trans*-161

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, SiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by a solution of TMCDA *trans*-161 (170 mg, 1.30 mmol, 1.3 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 25 min. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 10 min. Saturated NH₄Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ¹H NMR spectroscopy indicated that no N-Boc pyrrolidine 9 starting material was present.

For N-Boc pyrrolidine 9, a peak at 1702 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1644 cm⁻¹ was observed which was assigned to νC=O in the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When PhCHO was added (after a 25 min total lithiation time), the signal for the lithiated intermediate (νC=O = 1644 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_109
The lithiumation of N-Boc pyrrolidine 9 using s-BuLi/THF

THF (14 mL) was added to a flask equipped with a stirrer bar and ReactIR\textsuperscript{TM} probe (iC10, SiComp) at rt under Ar. After cooling to $-78 \, ^\circ \text{C}$, N-Boc pyrrolidine 9 (171 mg, 0.175 mL, 1.0 mmol, 1.0 eq.) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR\textsuperscript{®}). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added. The resulting solution was stirred at $-78 \, ^\circ \text{C}$ for 5 h.

For N-Boc pyrrolidine 9, a peak at 1696 cm\textsuperscript{-1} was observed and assigned to $\nu_{\text{C}=\text{O}}$. New peaks at 1663 cm\textsuperscript{-1} and 1648 cm\textsuperscript{-1} were observed and assigned to $\nu_{\text{C}=\text{O}}$ in the lithiated intermediate. After a lithiation time of 5 h, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed.

Lab Book Reference: AI_77

$N^1,N^1$, $N^2,N^2$-Tetraisopropylethane-1,2-diamine 178

Oxalyl chloride (0.43 mL, 5.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of diisopropylamine (1.40 mL, 10.0 mmol, 2.0 eq.) and Et$_3$N (1.81 mL, 13.0 mmol, 2.6 eq.) in CH$_2$Cl$_2$ (10 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. CH$_2$Cl$_2$ (10 mL) and 1 M HCl(aq) (10 mL) were added and the two layers were separated. The aqueous
layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were washed with H$_2$O (20 mL) and brine (20 mL), dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude bisamide as a pale brown solid. A solution of the crude bisamide in THF (10 mL) was added dropwise to a stirred suspension of LiAlH$_4$ (0.94 g, 24.65 mmol, 5.0 eq.) in THF (30 mL) at 0 °C under Ar. The resulting suspension was stirred and heated at reflux for 16 h. The suspension was then cooled to 0 °C and quenched by careful addition of H$_2$O (1 mL), 20% NaOH$_{aq}$ (2 mL) and H$_2$O (1 mL). The resulting mixture was allowed to warm to rt, stirred for 30 min and MgSO$_4$ was added. The solids were removed by filtration through Celite® and washed with 9:1 CH$_2$Cl$_2$-MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude diamine product. Purification by Kugelrohr distillation gave diamine 178 (788 mg, 69%) as a colourless oil, bp 95-100 °C/5.0 mmHg (lit.,$^{153}$ bp 110-115 °C/16 mmHg); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.98 (sept, $J = 6.5$ Hz, 4H, NCH), 2.36 (s, 4H, NCH$_2$), 1.01 (d, $J = 6.5$ Hz, 24H, Me); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 21.0 (Me), 48.1 (NCH$_2$), 49.4 (NCH). Spectroscopic data consistent with those reported in the literature.$^{153}$

Lab Book Reference: AMI_ 92

**ReactIR$^\text{TM}$ spectroscopic monitoring of the lithiation of N-Boc pyrrolidine 9 using s-BuLi/178**

Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR$^\text{TM}$ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by a solution of tetra-isopropyl ligand 178 (297 mg, 1.30 mmol, 1.3 eq.) in Et$_2$O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^\text{TM}$). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 17 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a
further 15 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ¹H NMR spectroscopy indicated no N-Boc pyrrolidine 9 starting material was present.

For N-Boc pyrrolidine 9, a peak at 1701 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1676 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1657 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 8 h, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When PhCHO was added (after a 17 h total lithiation time), the signal for the lithiated intermediate (νC=O = 1657 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_145

** tert-Butyl (2S*)-2-[(R*) and (S*)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate anti-31 and syn-31**

Et₂O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by TMPDA 179 (170 mg, 0.22 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The
resulting solution was stirred at –78 °C for 16 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 10 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 98:2 CH₂Cl₂-acetone as eluent gave 2-substituted pyrrolidine syn-31 (188 mg, 68%) as a colourless oil, Rᵥ (98:2 CH₂Cl₂-acetone) 0.30; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.27 (m, 5H, Ph), 4.70 (s, 1H, OH), 4.54 (br d, J = 8.0 Hz, 1H, OCH), 4.09 (ddd, J = 8.0, 3.5 Hz, 1H, NCH), 3.50-3.43 (m, 1H, NCH), 3.37-3.29 (m, 1H, NCH), 1.77-1.44 (m, 4H, CH), 1.52 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 158.4 (C=O), 141.1 (ipso-Ph), 128.7 (Ph), 128.5 (Ph), 127.9 (Ph), 127.7 (Ph), 127.4 (Ph), 127.1 (Ph), 80.9 (CMe₃), 79.4 (CHO), 65.5 (NCH), 64.3 (NCH), 47.8 (NCH₂), 28.8 (CH₂), 28.6 (CMe₃), 23.9 (CH₂) and anti-31 (81 mg, 29%) as a colourless oil, Rᵥ (98:2 CH₂Cl₂-acetone) 0.21; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.24 (m, 5H, Ph), 4.94 (br s, 1H, OCH), 4.23 (br s, 1H, NCH), 3.42-3.30 (m, 1H, NCH), 2.94 (br s, 1H, NCH), 1.89-1.75 (m, 2H, CH), 1.52 (s, 9H, CMe₃), 1.46-1.22 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.4 (C=O), 141.4 (ipso-Ph), 128.1 (Ph), 127.4 (Ph), 127.1 (Ph), 80.49 (CMe₃), 80.47 (CHO), 63.4 (NCH), 48.0 (NCH₂), 28.6 (CMe₃), 27.6 (CH₂), 23.6 (CH₂). Spectroscopic data consistent with those reported in the literature.

For N-Boc pyrrolidine 9, a peak at 1700 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1680 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1656 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 14 h, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When PhCHO was added (after a 16 h total lithiation time), the signal for the lithiated intermediate (νC=O = 1656 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_128
ReactIR™ spectroscopic monitoring of the lithiation of N-Boc pyrrolidine 9 using s-BuLi/Et₂O

Et₂O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 16 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 15 min. Saturated NH₄Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ¹H NMR spectroscopy indicated no N-Boc pyrrolidine 9 starting material was present.

For N-Boc pyrrolidine 9, a peak at 1700 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1674 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1659 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 11 h, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When PhCHO was added (after a 16.5 h total lithiation time), the signal for the lithiated intermediate (νC=O = 1659 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_132
tert-Butyl 4-chloropiperidine-1-carboxylate 48

A solution of hexachloroethane (7.25 g, 30.62 mmol, 2.0 eq.) in CH₂Cl₂ (25 mL) was added to a stirred solution of N-Boc 4-hydroxy piperidine 223 (3.05 g, 15.31 mmol, 1.0 eq.) and PPh₃ (8.03 g, 30.62 mmol, 2.0 eq.) in CH₂Cl₂ (75 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 80:20 hexane-Et₂O gave 4-chloro N-Boc piperidine 48 (1.27 g, 38%) as a colourless oil, Rₛ (80:20 hexane-Et₂O) 0.26; ¹H NMR (400 MHz, CDCl₃) δ 4.20 (tt, J = 7.5, 3.5 Hz, 1H, CHCl), 3.70 (ddd, J = 13.0, 7.0, 3.5 Hz, 2H, NCH), 3.30 (ddd, J = 13.0, 7.5, 3.5 Hz, 2H, NCH), 2.02 (ddddd, J = 13.5, 7.0, 3.5, 3.5 Hz, 2H, CH), 1.79 (ddddd, J = 13.5, 7.5, 7.5, 3.5 Hz, 2H, CH), 1.46 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.8 (C=O), 79.9 (CMe₃), 57.1 (CHCl), 41.3 (br, NCH₂), 35.0 (CH₂), 28.6 (CMe₃). Spectroscopic data consistent with those reported in the literature.⁴⁴

Lab Book Reference: AMI_152

ReactIR™ spectroscopic monitoring of the lithiation of 4-chloro N-Boc piperidine 48 using s-BuLi/di-pyrrolidino ethane 177

Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of solution of 4-chloro N-Boc piperidine 48 (215 mg, 0.98 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed
by a solution of di-pyrrolidino ethane **177** (429 mg, 2.55 mmol, 2.6 eq.) in Et$_2$O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^\text{TM}$). Then s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.55 mmol, 2.6 eq.) was added. The resulting solution was stirred at –78 °C for 30 min.

For 4-chloro N-Boc piperidine **48**, a peak at 1700 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1652 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 5 min, complete lithiation of 4-chloro N-Boc piperidine **48** to give the lithiated intermediate was observed.

Lab Book Reference: AMI_154

*tert*-Butyl 4-{(2,4,6-tris(propan-2-yl)benzenesulfonyl)oxy}piperidine-1-carboxylate **167**

![Image](image_url)

Trisopropylsulfonyl chloride (5.95 g, 19.66 mmol, 1.3 eq.) was added portionwise to a stirred solution of N-Boc 4-hydroxy piperidine **223** (3.04 g, 15.12 mmol, 1.0 eq.), Et$_3$N (1.68 g, 16.63 mmol, 1.1 eq., 2.32 mL) and DMAP (18 mg, 0.15 mmol, 0.01 eq.) in CH$_2$Cl$_2$ (50 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, H$_2$O (20 mL) was added and the two layers were separated. The organic layer was washed with 1 M HCl$_{\text{aq}}$ (20 mL), dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 80:20 hexane-EtOAc gave 4-O-trisyl N-Boc piperidine **167** (696 mg, 10%) as a white solid, mp 70-74 °C; $R_f$ (80:20 hexane-EtOAc) 0.19; IR (ATR) 2961, 2865, 1694 (C=O), 1425, 1344, 1240, 1178, 1014, 952, 830, 565 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.17 (s, 2H, Ar), 4.83 (tt, $J = 7.5$, 3.5 Hz, 1H, CHOSO$_2$Ar), 4.15 (sept, $J = 7.0$ Hz, 2H, CHMe$_2$), 3.69-3.63 (m, 2H, NCH), 3.25 (ddd, $J = 13.5$, 8.0, 4.0 Hz, 2H, NCH), 2.91 (sept, $J = 7.0$ Hz, 1H, CHMe$_2$), 1.90-1.83 (m, 2H, NCH), 1.78-1.70 (m, 2H, CH), 1.44 (s, 9H, CMe$_3$), 1.26 (d, $J = 7.0$ Hz, 12H, CHMe$_2$), 1.26 (d, $J = 7.0$ Hz, 6H, CHMe$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$
154.7 (C=O), 153.8 (ipso-Ar), 150.5 (ipso-Ar), 130.8 (ipso-Ar), 123.9 (Ar), 80.0 (CMe₃), 77.0 (CHOSO₂Ar), 34.4 (CHMe₂), 31.7 (br, NCH₂), 29.7 (br, CH₂), 29.7 (CHMe₂), 28.5 (CMe₃), 24.8 (CHMe₂), 23.7 (CHMe₂); HRMS (ESI) m/z calcd for C₂₅H₄₁NO₅S (M + Na)⁺ 490.2598, found 490.2575 (+4.2 ppm error).

Lab Book Reference: AMI_151

ReactIR™ spectroscopic monitoring of the lithiation of 4-O-trisyl N-Boc piperidine 167 using s-BuLi/di-pyrrolidino ethane 177

Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of 4-O-trisyl N-Boc piperidine 167 (489 mg, 1.04 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by a solution of di-pyrrolidino ethane 177 (457 mg, 2.72 mmol, 2.6 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (2.1 mL of a 1.3 M solution in hexanes, 2.72 mmol, 2.6 eq.) was added. The resulting solution was stirred at −78 °C for 15 min.

For of 4-O-trisyl N-Boc piperidine 167, a peak at 1700 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1648 cm⁻¹ was observed which was assigned to νC=O in the lithiated intermediate. After a lithiation time of 2 min, complete lithiation of 4-O-trisyl N-Boc piperidine 167 to give the lithiated intermediate was observed.

Lab Book Reference: AMI_155
ReactIR™ spectroscopic monitoring of the lithiation of N-Boc morpholine 169 using s-BuLi/di-pyrrolidino ethane 177

Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of N-Boc morpholine 169 (187 mg, 1.00 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by a solution of di-pyrrolidino ethane 177 (436 mg, 2.60 mmol, 2.6 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol, 2.6 eq.) was added. The resulting solution was stirred at –78 °C for 8 min.

For N-Boc morpholine 169, a peak at 1704 cm⁻¹ was observed and assigned to νₐ₃=O. After addition of s-BuLi, a new peak at 1639 cm⁻¹ was observed which was assigned to νₐ₃=O in the lithiated intermediate. After a lithiation time of 15 s, complete lithiation of N-Boc morpholine 169 to give the lithiated intermediate was observed.

Lab Book Reference: AMI_160
ReactIR\textsuperscript{TM} spectroscopic monitoring of the lithiation of \(N'\)-Me \(N\)-Boc piperazine 58 using \(s\)-BuLi/di-pyrrolidino ethane 177

\[
\text{Et}_2\text{O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR\textsuperscript{TM} probe (ReactIR\textsuperscript{TM} 15, DiComp) at rt under Ar. After cooling to } -78^\circ \text{C, a solution of } N'\text{-Me } N\text{-Boc piperazine 58 (205 mg, 1.02 mmol, 1.0 eq.) in Et}_2\text{O (2 mL) was added followed by a solution of di-pyrrolidino ethane 177 (223 mg, 1.33 mmol, 1.3 eq.) in Et}_2\text{O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR\textsuperscript{TM}). Then } s\text{-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added. The resulting solution was stirred at } -78^\circ \text{C for 50 min.}
\]

For \(N'\)-Me \(N\)-Boc piperazine 58, a peak at 1700 cm\(^{-1}\) was observed and assigned to \(\nu_{C=O}\). After addition of \(s\)-BuLi, a new peak at 1677 cm\(^{-1}\) was observed which was assigned to \(\nu_{C=O}\) in the prelithiation complex. A new peak at 1644 cm\(^{-1}\) was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 35 min, complete lithiation of \(N\)-Boc \(N'\)-Me \(N\)-Boc piperazine 58 to give the lithiated intermediate was observed.

Lab Book Reference: AMI_161
### 6.5 Experimental Procedures for Chapter 3

#### 6.5.1 General Computational Procedures

All computational MP2 and DFT calculations were performed using GAUSSIAN 09. Both MP2 calculations and DFT calculations were used with a Pople 6-31G(d) split valence basis set. MP2 calculations were performed with calculation of the Hessian matrix for each iteration of the geometry optimisation (GAUSSIAN keyword = CalcAll) due to the flat nature of the potential energy surface. All DFT calculations used a pruned (99, 950) grid for numerical integrations, GAUSSIAN keyword = Int(UltraFine). All geometry optimisations used the deprecated GDIIS algorithm which assisted in the location of minima.

All ground states were confirmed by the absence of imaginary frequencies and transition states were confirmed by the presence of one imaginary frequency. The vibrational modes of the imaginary frequencies obtained for transition states were inspected to ensure the mode corresponded to the \( \alpha \)-lithiation of the substrate. The XYZ coordinates of all optimised geometries are included (as .xyz files) in the electronic supplementary information included with this thesis. Frequency calculations were performed after geometry optimisation at the same level of theory; enthalpies (\( H \)) and free-energies (\( G \)) were corrected to a temperature of 195 K (\(-78 \, ^\circ C\)), the temperature at which these reactions were conducted.

For optimisation of the prelithiation complexes the following parameters were used:

\[
\text{# Opt(GDIIS, Tight) Temperature=195 Freq Int=UltraFine –only for DFT}
\]

For optimisation of the transition states the following parameters were used:

\[
\text{# Opt(TS, GDIIS, CalcFC, NoEigen, Tight) Temperature=195 Freq Int=UltraFine – only for DFT}
\]
6.5.2 *N*-Boc piperidine IRC calculation results:

*N*-Boc piperidine 10 ‘side-on’ lithiation:

B3LYP/6-31G(d) calculated reaction coordinate for the *i*-PrLi/di-methyl bispidine 195 ‘side-on’ lithiation of *N*-Boc piperidine 10 (a) and an output geometry from the forward path showing formation of the lithiated intermediate and *i*-propane (b).

![Graph showing reaction coordinate](image)

*N*-Boc piperidine 10 ‘side-on’ lithiation:

B3LYP/6-31G(d) calculated reaction coordinate for the *i*-PrLi/di-methyl bispidine 195 ‘top’ lithiation of *N*-Boc piperidine 10 (a) and an output geometry from the forward path showing formation of the lithiated intermediate and *i*-propane (b).

![Graph showing reaction coordinate](image)
6.6 Experimental Procedures for Chapter 4

*tert*-Butyl 2-(trimethylsilyl)pyrrolidine-1-carboxylate 11

For experimental procedure for the lithiation-trapping of *N*-Boc pyrrolidine 9 with Me₃SiCl, see Chapter 6.3. Kinetic analysis of the Me₃SiCl trapping of 2-lithio *N*-Boc pyrrolidine 9 indicated that trapping was pseudo first order with respect to 2-lithio *N*-Boc pyrrolidine 9. Semilogarithmic plots for both 90% conversion (a) and the first 20% of conversion (b) of the trapping reaction indicated that pseudo-first order conditions were maintained throughout the reaction. A pseudo-first order $k_{obs}$ of $(8.55 \pm 0.34) \times 10^{-3}$ s⁻¹ and $t_{1/2} = (81.1 \pm 3.2)$ s were measured for the trapping reaction using the semilogarithmic plot for 20% conversion.

Initial rate analysis of the Me₃SiCl trapping of lithiated *N*-Boc pyrrolidine 9 provided an initial rate of trapping, $rate_{init} = (4.99 \pm 0.18) \times 10^{-4}$ s⁻¹ (initial rate tangent is displayed on the plot in red).
Et₂O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 10 min. Then, Me₂SO₄ (252 mg, 0.19 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 5 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x
10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 Hexane-EtOAc as eluent gave 2-methyl N-Boc pyrrolidine 14 (122 mg, 66%) as a colourless oil, $R_f$ (90:10 Hexane-EtOAc) 0.23; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.98-3.78 (m, 1H, NCH), 3.44-3.22 (m, 2H, NCH), 2.05-1.92 (m, 1H, CH), 1.92-1.82 (m, 1H, CH), 1.82-1.71 (m, 1H, CH), 1.61-1.49 (m, 1H, CH), 1.46 (s, 9H, CMe$_3$), 1.21-1.09 (m, 3H, NCHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) (mixture of rotamers) $\delta$ 154.6 (C=O), 78.9 (CMe$_3$), 52.9 (NCH), 46.5 (NCH$_2$), 46.2 (NCH$_2$), 33.4 (CH$_2$), 32.7 (CH$_2$), 28.7 (CMe$_3$), 23.7 (CH$_2$), 23.1 (CH$_2$), 20.9 (NCH$_2$Me), 20.3 (NCH$_2$Me). Spectroscopic data consistent with those reported in the literature.$^{40}$

For N-Boc pyrrolidine 9, a peak at 1701 cm$^{-1}$ was observed and assigned to $\nu$C=O. After addition of s-BuLi, a new peak at 1648 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When Me$_2$SO$_4$ was added (after a 9 min total lithiation time), the signal for the lithiated intermediate ($\nu$C=O = 1641 cm$^{-1}$) disappeared after 1 min, indicating complete trapping had occurred.

Initial rate analysis of the Me$_2$SO$_4$ trapping of lithiated N-Boc pyrrolidine 9 provided an initial rate of trapping, $\text{rate}_{\text{init}} = (8.41 \pm 0.13) \times 10^{-2}$ s$^{-1}$ (initial rate tangent is displayed on the plot in red).

![Graph showing absorbance at 1648 cm$^{-1}$ vs time (s)](attachment:image.png)

Lab Book Reference: AMI_177
Et₂O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 9 (171 mg, 1.00 mmol, 0.18 mL, 1.0 eq.) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 10 min. Then, MeI (283 mg, 0.13 mL, 2.00 mmol, 2.0 eq.) was added, the solution rapidly gelated and the stirring ceased, the gel was held at −78 °C for a further 10 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 Hexane-EtOAc as eluent gave 2-methyl N-Boc pyrrolidine 14 (75 mg, 40%) as a colourless oil.

For N-Boc pyrrolidine 9, a peak at 1700 cm⁻¹ was observed and assigned to ṽC=O. After addition of s-BuLi, a new peak at 1648 cm⁻¹ was observed which was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 9 to give the lithiated intermediate was observed. When Me₂SO₄ was added (after 10 min total lithiation time), the signal for the lithiated intermediate (ṽC=O = 1648 cm⁻¹) disappeared after 3 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_174
**tert-Butyl (2*R*, 4*R*)-4-phenyl-2-(trimethylsilyl)piperidine-1-carboxylate cis-238**

![Chemical Structure](image)

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of 4-Phenyl N-Boc piperidine 32 (264 mg, 1.01 mmol, 0.18, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (153 mg, 0.20 mL, 1.31 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 2 h. Then, Me₃SiCl (219 mg, 0.26 mL, 2.02 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 16 h. Saturated NH₄Cl(aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 97.5:2.5 Hexane-Et₂O as eluent gave 2-silyl N-Boc piperidine **cis-238** (247 mg, 73%) as a colourless oil, Rₚ (97.5:2.5 Hexane-Et₂O) 0.25; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.29 (m, 2H, Ph), 7.25-7.19 (m, 3H, Ph), 4.12 (br d, J = 13.0 Hz, 1H, NCH), 2.97 (br t, J = 12.0 Hz, 1H, NCH), 2.76-2.68 (tt, 1H, 1H, CHPh), 2.43 (br d, J = 12.0 Hz, 1H, NCH), 1.88-1.76 (m, 2H, CH), 1.68-1.51 (m, 2H, CH), 1.48 (s, 9H, CMe₃), 0.09 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.3 (C=O), 146.4 (ipso-Ph), 128.6 (Ph), 127.0 (Ph), 126.4 (Ph), 79.2 (CMe₃), 51.2 (NCH), 48.1 (NCH₂), 45.0 (CHPh), 34.4 (CH₂), 33.7 (CH₂), 28.6 (CMe₃), −0.6 (SiMe₃). Spectroscopic data consistent with those reported in the literature.²⁶
For 4-phenyl N-Boc piperidine 32, a peak at 1697 cm\(^{-1}\) was observed and assigned to \(\nu_{C=O}\). After addition of \(s\)-BuLi, a new peak at 1644 cm\(^{-1}\) was observed which was assigned to the lithiated intermediate. After a lithiation time of 90 min, complete lithiation of 4-phenyl N-Boc piperidine 32 to give the lithiated intermediate was observed. When \(\text{Me}_3\text{SiCl}\) was added (after 2 h total lithiation time), the signal for the lithiated intermediate (\(\nu_{C=O} = 1644 \text{ cm}^{-1}\)) disappeared after 15.5 h, indicating complete trapping had occurred.

Kinetic analysis of the \(\text{Me}_3\text{SiCl}\) trapping of 2-lithio 4-phenyl N-Boc piperidine 32 indicated that trapping was pseudo first order with respect to 2-lithio 4-phenyl N-Boc piperidine 32. Semilogarithmic plots for both 90% conversion (a) and the first 20% of conversion (b) of the trapping reaction indicated that pseudo-first order conditions were maintained throughout the reaction. A pseudo-first order \(k_{\text{obs}}\) of \((7.57 \pm 0.07) \times 10^{-5} \text{ s}^{-1}\) and \(t_{1/2} = (9160 \pm 80) \text{ s}\) were measured using the semilogarithmic plot for 90% conversion of the trapping reaction.

Initial rate analysis of the \(\text{Me}_3\text{SiCl}\) trapping of lithiated 4-phenyl N-Boc piperidine 32 provided an initial rate of trapping, \(\text{rate}_{\text{init}} = (4.76 \pm 0.12) \times 10^{-6} \text{ s}^{-1}\) (initial rate tangent is displayed on the plot in red).
Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR$^\text{TM}$ probe (ReactIR$^\text{TM}$ 15, DiComp) at rt under Ar. After cooling to $-78$ °C, a solution of 4-Phenyl N-Boc piperidine 32 (264 mg, 1.01 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (152 mg, 0.20 mL, 1.31 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^\text{TM}$). Then $s$-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at $-78$ °C for 2 h. Then, Me$_2$SO$_4$ (254 mg, 0.19 mL, 2.02 mmol, 2.0 eq.) was added and the solution was stirred at $-78$ °C for a further 16 h. Saturated NH$_4$Cl$_{(aq)}$ was added and the solution was then allowed
to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 10 mL) and the combined organics were dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 Hexane-EtOAc as eluent gave 2-methyl N-Boc piperidine <i>cis</i>-35 (175 mg, 63%) as a colourless oil. For spectroscopic data see section 6.4.

For 4-phenyl N-Boc piperidine 32, a peak at 1697 cm<sup>-1</sup> was observed and assigned to v<sub>C=O</sub>. After addition of s-BuLi, a new peak at 1644 cm<sup>-1</sup> was observed which was assigned to the lithiated intermediate. After a lithiation time of 90 min, complete lithiation of 4-phenyl N-Boc piperidine 32 to give the lithiated intermediate was observed. When Me<sub>2</sub>SO<sub>4</sub> was added (after 2 h total lithiation time), the signal for the lithiated intermediate (v<sub>C=O</sub> = 1641 cm<sup>-1</sup>) disappeared after 12 h, indicating complete trapping had occurred.

Kinetic analysis of the Me<sub>2</sub>SO<sub>4</sub> trapping of 2-lithio 4-phenyl N-Boc piperidine 32 indicated that trapping was pseudo first order with respect to 2-lithio 4-phenyl N-Boc piperidine 32. A semilogarithmic plot for 90% conversion of the trapping (a) indicated that pseudo-first order conditions were not maintained throughout the reaction, with deviation from pseudo-first order kinetics occurring at ~2500 s. However, the semilogarithmic plot for the first 20% of conversion indicated that pseudo-first order behaviour was observed in this portion of the reaction. Therefore, a pseudo-first order k<sub>obs</sub> of (2.74 ± 0.05) x10<sup>-4</sup> s<sup>-1</sup> and t<sub>1/2</sub> = (2530 ± 50) s were measured using the semilogarithmic plot for 20% conversion of the trapping reaction.

Initial rate analysis of the Me<sub>2</sub>SO<sub>4</sub> trapping of lithiated 4-phenyl N-Boc piperidine 32 provided an initial rate of trapping, rate<sub>init</sub> = (1.39 ± 0.09)<sub>°</sub> s<sup>-1</sup> (initial rate tangent is displayed on the plot in red).
For experimental procedure for the lithiation-trapping of 4-Phenyl N-Boc piperidine 32 with MeI, see Chapter 6.3. Kinetic analysis of the MeI trapping of 2-lithio 4-Phenyl N-Boc piperidine 32 indicated that trapping was pseudo first order with respect to of 2-lithio 4-Phenyl N-Boc piperidine 32. A semilogarithmic plot for 90% conversion of the trapping (a) indicated that pseudo-first order conditions were not maintained throughout the reaction with deviation from pseudo-first order kinetics occurring at ~500 s. However, the semilogarithmic plot for the first 50% of conversion indicated that pseudo-first order behaviour was observed in this portion of the reaction. 55% trapping conversion was used rather than 20% due to the faster rate of reaction and lesser amount of data collected with ReactIR™. A pseudo-first order $k_{obs}$ of $(3.18 \pm 0.02) \times 10^{-3} \text{ s}^{-1}$ and $t_{1/2} = (218 \pm 1) \text{ s}$ were measured for the trapping reaction using the semilogarithmic plot for 55% conversion of the trapping reaction.
Initial rate analysis of the MeI trapping of lithiated 4-phenyl N-Boc piperidine 32 provided an initial rate of trapping, rate_{init} = (1.34 ± 0.31) \times 10^{-4} \text{ s}^{-1} (initial rate tangent is displayed on the plot in red).

Lab Book Reference: AMI_189
**tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 59 and tert-butyl (2R®)-4-benzyl-2-[(S®) and (R®)-hydroxy(phenyl)methyl]piperazine-1-carboxylate anti-202 and syn-202**

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of N'-Bn N-Boc piperazine 57 (275 mg, 1.00 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (150 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR®). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 15 min. Then, Me₂SiCl (216 mg, 0.25 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 13 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for an additional 30 min. Saturated NH₄Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et₂O as eluent gave 2-silyl N'-Bn N-Boc piperazine 59 (140 mg, 40%) as a colourless oil, R<sub>f</sub>(50:50 hexane-Et₂O) 0.6, <sup>1</sup>H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 7.35-7.29 (m, 4H, Ph), 7.28-7.22 (m, 1H, Ph), 4.03 (br s, 0.6H, NCH), 3.79 (br s, 0.4H, NCH), 3.67-3.50 (m, 1H, NCH), 3.43 (d, J = 13.0 Hz, CH₃H₃Ph), 3.40 (d, J = 13.0 Hz, CH₃H₃Ph), 3.13-2.85 (m, 1H, NCH), 2.79 (d, J = 11.5 Hz, 1H, NCH), 2.76-2.57 (m, 1H, NCH), 2.24 (br s, 1H, NCH), 1.92 (td, J = 11.5, 3.2 Hz, 1H, NCH), 1.44 (s, 9H, CMe₃), 0.07 (s, 9H, SiMe₃); <sup>13</sup>C NMR (100.6 MHz, CDCl₃) (rotamers) δ 154.6 (C=O), 138.4 (ipso-Ph), 129.2 (Ph), 128.0
(Ph), 127.2 (Ph), 79.1 (CMe$_3$), 63.5 (NCH$_2$), 54.3 (NCH$_2$), 53.1 (NCH$_2$), 45.2 (NCH), 41.5 (NCH), 28.5 (CMe$_3$), –0.7 (SiMe$_3$) and anti-202 (99 mg, 26%) as a yellow solid, $R_f$ (50:50 hexane-Et$_2$O) 0.3; mp 99-102 °C; IR (ATR) 3203 (OH), 2970, 2781, 1659 (C=O), 1428, 1387, 1346, 1301, 1196, 1150 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43-7.36 (m, 3H, Ph), 7.28-7.21 (m, 2H, Ph), 7.21-6.97 (m, 5H, Ph), 6.33 (br s, 1H, CHO), 5.05 (br s, 1H, CCHOH), 4.13-4.01 (m, 1H, NCH), 3.98-3.86 (m, 1H, NCH), 3.62 (d, $J = 12.0$ Hz, 1H, CH$_2$Ph), 3.10-2.94 (m, 1H, NCH), 2.96 (d, $J = 12.0$ Hz, 1H, CH$_2$Ph), 2.34-2.17 (m, 1H, NCH), 1.99 (dd, $J = 12.0, 3.5$ Hz, 1H, NCH), 1.71-1.57 (m, 1H, NCH), 1.50 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) (rotamers) δ 155.1 (C=O), 143.3 (ipso-Ph), 136.5 (ipso-Ph), 129.6 (Ph), 128.7 (Ph), 128.1 (Ph), 127.7 (Ph), 126.6 (Ph), 126.4 (Ph), 125.4 (Ph), 80.4 (CMe$_3$), 80.2 (CMe$_3$), 79.1 (CHOH), 63.2 (NCH$_2$Ph), 55.7 (NCH), 54.5 (NCH), 52.9 (NCH$_2$), 50.3 (NCH$_2$), 42.2 (NCH$_2$), 41.0 (NCH$_2$), 28.5 (CMe$_3$); HRMS (ESI) m/z calcd for C$_{23}$H$_{30}$N$_2$O$_3$ (M + H)$^+$ 383.2329, found 383.2339 (–1.9 ppm error) and syn-202 (61 mg, 16%) as a white solid, $R_f$ (50:50 hexane-Et$_2$O) 0.2; mp 120-123 °C; IR (ATR) 3155 (OH), 2965, 1654 (C=O), 1434, 1388, 1347, 1277, 1231, 1195, 1152 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (50:50 mixture of rotamers) δ 7.39-7.15 (m, 10H, Ph), 5.99 (br s, 0.5H, OH), 5.27 (br s, 0.5H, OH), 5.17-5.04 (m, 1H, CCHOH), 4.34-4.27 (m, 0.5 H, NCH), 4.17-4.10 (m, 1H, NCH), 3.88 (br d, $J = 13.0$ Hz, 0.5 H, NCH), 3.67-3.41 (m, 3H, NCH + CH$_2$Ph), 3.12 (d, $J = 11.5$ Hz, 0.5 H, NCH), 2.97-2.80 (m, 1.5 H, NCH), 2.43 (dd, $J = 11.5, 4.0$ Hz, 0.5 H, NCH), 2.31-2.26 (m, 0.5H, NCH), 2.19-2.05 (m, 1H, NCH), 1.29 (s, 4.5 H, CMe$_3$), 1.08 (s, 4.5 H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) (rotamers) δ 154.5 (C=O), 141.5 (ipso-Ph), 137.2 (ipso-Ph), 136.6 (ipso-Ph), 129.1 (Ph), 128.7 (Ph), 128.6 (Ph), 128.3 (Ph), 128.1 (Ph), 127.7 (Ph), 127.5 (Ph), 127.2 (Ph), 126.7 (Ph), 80.0 (CMe$_3$), 79.6 (CHOH), 63.2 (NCH$_2$Ph), 56.3 (NCH$_2$), 54.9 (NCH), 54.5 (NCH), 52.7 (NCH$_2$), 52.4 (NCH$_2$), 41.8 (NCH$_2$), 41.0 (NCH$_2$), 28.1 (CMe$_3$), 27.9 (CMe$_3$); HRMS (ESI) m/z calcd for C$_{23}$H$_{30}$N$_2$O$_3$ (M + H)$^+$ 383.2329, found 383.2336 (–2.1 ppm error). Spectroscopic data for 2-silyl N'-Bn N-Boc piperazine 59 is consistent with those reported in the literature.$^{25}$ The relative stereochemistry of syn-202 has been determined by X-ray crystallography conducted previously in-group.$^{53}$

For N'-Bn N-Boc piperazine 57, a peak at 1701 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1645 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 2 min, complete lithiation of N'-Bn N-Boc piperazine 57 to give the lithiated intermediate was observed. When Me$_3$SiCl was added
(after 15 min total lithiation time), the signal for the lithiated intermediate (νC=O = 1645 cm⁻¹) began to disappear and when PhCHO was added 13 h after the previous addition of Me₃SiCl the signal for the lithiated intermediate disappeared after 1 min, indicating complete trapping had occurred.

Kinetic analysis of the Me₃SiCl trapping of 2-lithio N'-Bn N-Boc piperazine 57 indicated that trapping was pseudo first order with respect to 2-lithio N'-Bn N-Boc piperazine 57. Semilogarithmic plots for both ~46% conversion (a) and the first 20% of conversion (b) of the trapping reaction indicated that pseudo-first order conditions were maintained throughout the reaction. A pseudo-first order $k_{\text{obs}}$ of $(1.37 \pm 0.01) \times 10^{-5}$ s⁻¹ and $t_{1/2} = (51300 \pm 400)$ s were measured using the semilogarithmic plot for up to 20% conversion of the trapping reaction.

Initial rate analysis of the Me₃SiCl trapping of lithiated N'-Bn N-Boc piperazine 57 provided an initial rate of trapping, $\text{rate}_{\text{init}} = (9.70 \pm 0.70) \times 10^{-7}$ s⁻¹ (initial rate tangent is displayed on the plot in red).
Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe (ReactIR 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of N’-Bn N-Boc piperazine 57 (271 mg, 0.98 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (148 mg, 0.19 mL, 1.28 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR®). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.28 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 15 min. Then, Me₂SO₄ (247 mg, 0.19 mL, 1.96 mmol, 2.0 eq.) was added and the
solution was stirred at –78 °C for a further 16.5 h. Then, PhCHO (208 mg, 0.20 mL, 1.96 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for an additional 30 min. Saturated NH$_4$Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave 2-methyl $N'$-Bn piperazine 200 (100 mg, 35%) as a colourless oil, $R_F$ (60:40 hexane:EtOAc) 0.4. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.26 (m, 4H, Ph), 7.24-7.18 (m, 1H, Ph), 4.15 (br s, 1H, NCH), 3.77 (br d, $J = 13.0$ Hz, 1H, NCH), 3.50 (d, $J = 13.5$ Hz, 1H, CH$_A$H$_B$Ph), 3.37 (d, $J = 13.5$ Hz, 1H, CH$_A$H$_B$Ph), 3.08 (td, $J = 12.5, 3.5$ Hz, 1H, NCH), 2.74-2.71 (m, 1H, NCH), 2.56 (dt, $J = 11.0, 1.5$ Hz, 1H, NCH), 2.09 (dd, $J = 11.0, 4.0$ Hz, 1H, NCH), (ddd, $J = 12.0, 11.5, 3.5, 1$H, NCH), 1.43 (s, 9H, CMe$_3$), 1.21 (d, $J = 7.0$ Hz, 3H, CHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 154.9 (C=O), 138.5 ($ipso$-Ph), 128.8 (Ph), 128.3 (Ph), 127.1 (Ph), 79.4 (CMe$_3$), 62.9 (NCH$_2$), 57.5 (NCH$_2$), 53.3 (NCH$_2$), 47.2 (NCH$_2$), 39.2 (NCH$_2$), 28.6 (CMe$_3$), 16.0 (Me) and alcohol anti-202 (68 mg, 18%) as a white solid and alcohol syn-202 (45 mg, 12%) as white solid. Spectroscopic data for 2-methyl $N'$-Bn piperazine 200 consistent with those reported in the literature.$^{154}$

For $N'$-Bn N-Boc piperazine 57, a peak at 1700 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1645 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of $N'$-Bn N-Boc piperazine 57 to give the lithiated intermediate was observed. When Me$_2$SO$_4$ was added (after 15 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1645$ cm$^{-1}$) began to disappear and when PhCHO was added 16.5 h after the previous addition of Me$_2$SO$_4$ the signal for the lithiated intermediate disappeared after 1 min, indicating complete trapping had occurred.

Kinetic analysis of the Me$_2$SO$_4$ trapping of 2-lithio $N'$-Bn N-Boc piperazine 57 indicated that trapping was pseudo first order with respect to 2-lithio $N'$-Bn N-Boc piperazine 57. A semilogarithmic plot for 90% conversion of the trapping (a) indicated that pseudo-first order conditions were not maintained throughout the reaction, with deviation from pseudo-first order kinetics occurring at ~6000 s. However, the semilogarithmic plot for the first 20% of conversion indicated that pseudo-first order behaviour was observed in this portion of the
reaction. Therefore, a pseudo-first order $k_{obs}$ of $(2.14 \pm 0.06) \times 10^{-5}$ s$^{-1}$ and $t_{1/2} = (32400 \pm 900)$ s were measured using the semilogarithmic plot for 20% conversion of the trapping reaction.

Initial rate analysis of the Me$_2$SO$_4$ trapping of lithiated N'-Bn N-Boc piperazine 57 provided an initial rate of trapping, $r_{init} = (2.53 \pm 0.37) \times 10^{-6}$ s$^{-1}$ (initial rate tangent is displayed on the plot in red).

Lab Book Reference: AMI_246
Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of N’-Bn N-Boc piperazine 57 (276 mg, 1.00 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 10 min. Then, MeI (284 mg, 0.13 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 3.5 h. Saturated NH$_4$Cl(aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 Hexane-EtOAc as eluent gave 2-methyl N-Boc piperazine 200 (231 mg, 80%) as a colourless oil.

For N’-Bn N-Boc piperazine 57, a peak at 1700 cm$^{-1}$ was observed and assigned to $\nu$C=O. After addition of s-BuLi, a new peak at 1645 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of piperazine 57 to give the lithiated intermediate was observed. When MeI was added (after 10 min total lithiation time), the signal for the lithiated intermediate ($\nu$C=O = 1645 cm$^{-1}$) disappeared after 3.5 h, indicating complete trapping had occurred.
Kinetic analysis of the MeI trapping of 2-lithio \( N'\)-Bn \( N\)-Boc piperazine 57 indicated that trapping was pseudo first order with respect to 2-lithio \( N'\)-Bn \( N\)-Boc piperazine 57. A semilogarithmic plot for 90% conversion of the trapping (a) indicated that pseudo-first order conditions were not maintained throughout the reaction, with deviation from pseudo-first order kinetics occurring at \(~600\) s. However, the semilogarithmic plot for the first 20% of conversion indicated that pseudo-first order behaviour was observed in this portion of the reaction. Therefore, a pseudo-first order \( k_{\text{obs}} \) of \( (1.22 \pm 0.06) \times 10^{-3} \text{ s}^{-1} \) and \( t_{1/2} = (568 \pm 30) \text{ s} \) were measured using the semilogarithmic plot for 20% conversion of the trapping reaction.

![Graph](attachment:image1.png)

Initial rate analysis of the MeI trapping of lithiated \( N'\)-Bn \( N\)-Boc piperazine 57 provided an initial rate of trapping, \( r_{\text{init}} = (8.90 \pm 0.46) \times 10^{-5} \text{ s}^{-1} \) (initial rate tangent is displayed on the plot in red).

![Graph](attachment:image2.png)

Lab Book Reference: AMI_230
tert-Butyl-1-methyl-7-azabicyclo[2.2.1]heptane-7-carboxylate 205

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of bicyclic pyrrolidine 84 (201 mg, 1.02 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (154 mg, 0.19 mL, 1.32 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.32 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 30 min. Then, Me₂SO₄ (257 mg, 0.19 mL, 2.04 mmol, 2.0 eq.) was added and the solution was stirred at –78 °C for a further 9.5 h. Saturated NH₄Cl(aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 petrol-EtOAc as eluent gave 2-methyl bicyclic pyrrolidine 205 (130 mg, 60%) as a colourless oil, Rᵥ (95:5 petrol-EtOAc) 0.15; IR (ATR) 2968, 2872, 1690 (C=O), 1455, 1364, 1341, 1163, 1129, 1025, 874 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.23 (dd, J = 5.0, 5.0 Hz, 1H, NCH), 1.81-1.72 (m, 2H, CH), 1.65-1.57 (m, 2H, CH), 1.60 (s, 3H, Me), 1.53-1.47 (ddd, J = 11.0, 9.0, 4.5 Hz, 2H, CH), 1.43 (s, 9H, CMe₃), 1.39-1.33 (ddd, J = 11.0, 9.0, 4.5 Hz, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.0 (C=O), 79.2 (CMe₃), 64.8 (NCMe), 58.6 (NCH), 37.5 (CH₂), 29.3 (CH₂), 28.5 (CMe₃), 20.6 (Me); HRMS (ESI) m/z calcd for C₁₂H₂₁NO₂(M + Na)⁺ 234.1464, found 234.1462 (+1.2 ppm error).

For bicyclic pyrrolidine 84 a peak at 1704 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1641 cm⁻¹ was observed which was assigned to the lithiated intermediate. After a lithiation time of 15 min, complete lithiation of bicyclic pyrrolidine 84
to give the lithiated intermediate was observed. When PhCHO was added (after 30 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1641 \text{ cm}^{-1}$) disappeared after 6.5 h, indicating complete trapping had occurred.

Kinetic analysis of the Me$_2$SO$_4$ trapping of lithiated bicyclic pyrrolidine 84 indicated that trapping was pseudo first order with respect to lithiated bicyclic pyrrolidine 84. A semilogarithmic plot for 90% conversion of the trapping (a) indicated that pseudo-first order conditions were not maintained throughout the reaction, with deviation from pseudo-first order kinetics occurring at $\sim$1200 s. However, the semilogarithmic plot for the first 20% of conversion indicated that pseudo-first order behaviour was observed in this portion of the reaction. Therefore, a pseudo-first order $k_{obs}$ of $(3.99 \pm 0.21) \times 10^{-4} \text{ s}^{-1}$ and $t_{1/2} = (1740 \pm 90)$ s were measured using the semilogarithmic plot for 20% conversion of the trapping reaction.

Lab Book Reference: AMI_210
**tert-Butyl-1-(trimethylsilyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate 204**

![Structure of 204](image)

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to −78 °C, a solution of bicyclic pyrrolidine 84 (195 mg, 0.99 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (149 mg, 0.19 mL, 1.28 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.28 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 20 min. Then, Me₃SiCl (215 mg, 0.25 mL, 1.98 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 14 h. Saturated NH₄Cl (aq) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 petrol-EtOAc as eluent gave 2-silyl bicyclic pyrrolidine 204 (42 mg, 16%) as a white solid, mp 75-75 °C; Rₚ (95:5 petrol-EtOAc) 0.21; IR (ATR) 2953, 1679, 1390, 1364, 1240, 1156, 1113, 1095, 835, 765 cm⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 4.28 (dd, J = 4.5, 4.5 Hz, 1H, NCH), 1.76 - 1.61 (m, 4H, CH), 1.42 (s, 9H, CMe₃), 1.41 - 1.28 (m, 4H, CH), 0.15 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.9 (C=O), 79.0 (CMe₃), 59.0 (NCH), 55.4 (NCSi), 33.5 (CH₂), 30.1 (CH₂), 28.5 (CMe₃), −1.6 (SiMe₃); HRMS (ESI) m/z calcd for C₁₄H₂₇NO₂Si (M + Na)⁺ 292.1703, found 292.1703 (−0.2 ppm error) and bicyclic pyrrolidine 84 (114 mg, 58%) as a colourless oil.

For bicyclic pyrrolidine 84 a peak at 1704 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1641 cm⁻¹ was observed which was assigned to the lithiated
intermediate. After a lithiation time of 15 min, complete lithiation of bicyclic pyrrolidine \textbf{84} to give the lithiated intermediate was observed. When Me$_3$SiCl was added (after 20 min total lithiation time), the signal for the lithiated intermediate ($\nu_{\text{C=O}} = 1641$ cm$^{-1}$) only partly decreased after 14.5 h, indicating that incomplete trapping had occurred.

Kinetic analysis of the Me$_3$SiCl trapping of lithiated bicyclic pyrrolidine \textbf{84} indicated that trapping was pseudo first order with respect to lithiated bicyclic pyrrolidine \textbf{84}. As no baseline absorbance for the signal at 1641 cm$^{-1}$ was collected at the end of reaction only an approximate $k_{\text{obs}}$ for the trapping could be measured. An approximate pseudo-first order $k_{\text{obs}}$ of $(4.17 \pm 0.08) \times 10^{-6}$ s$^{-1}$ and $t_{1/2} = (166000 \pm 3000)$ s were measured using the semilogarithmic plot for the partial trapping ($\sim 20\%$ conversion).

Lab Book Reference: AMI_277

s-BuLi (1.0 mL of a 1.3M solution in hexanes, 1.34 mmol, 1.3 eq.) was added dropwise to a stirred solution of bicyclic pyrrolidine \textbf{84} (204 mg, 1.03 mmol, 1.0 eq.) and TMEDA (156 mg, 1.34 mmol, 0.20 mL, 1.3 eq.) in Et$_2$O (7 mL) under Ar. The resulting solution was stirred at $-78$ °C for 40 min and then Me$_3$SiCl (224 mg, 2.06 mmol, 0.26 mL, 2.0 eq.) was added. The reaction mixture was allowed to warm to rt over 16 h and then saturated NH$_4$Cl$_{\text{(aq)}}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column
chromatography on silica using 95:5 hexane-Et₂O as eluent gave silyl pyrrolidine 204 (224 mg, 81%) as a white solid.

Lab Book Reference: AMI_278

tert-Butyl (2R*,4R*)-4-(dimethylamino)-2-methylpiperidine-1-carboxylate cis-209

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (ReactIR™ 15, DiComp) at rt under Ar. After cooling to –78 °C, a solution of 4-amino piperidine 168 (225 mg, 0.99 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (149 mg, 192 µL, 1.28 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.28 mmol, 1.3 eq.) was added. The resulting solution was stirred at –78 °C for 130 min. Then, MeI (280 mg, 122 µL, 1.97 mmol, 2.0 eq.) was added, the solution rapidly gelated and the stirring ceased, the gel was held at –78 °C for a further 1.5 h. Saturated NH₄Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:6:1 CH₂Cl₂-MeOH-NH₄OH as eluent gave 2-methyl piperidine cis-209 (96 mg, 40%) as a colourless oil, Rₚ (93:6:1 CH₂Cl₂-MeOH-NH₄OH) 0.13; IR (ATR) 2972, 2870, 2813, 2771, 1681 (C=O), 1410, 1362, 1152, 1074, 768 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.93-3.83 (m, 1H, NCH), 3.74 (ddd, J = 13.5, 7.0, 2.5 Hz, 1H, NCH), 3.06 (ddd, J = 13.5, 11.0, 5.5 Hz, 1H, NCH), 2.33-2.25 (m, 1H, NCH), 2.22 (s, 6H, NMe₂), 1.90-1.77 (m, 2H, CH), 1.60-1.49 (m, 1H, CH), 1.47-1.38 (m, 1H, CH), 1.44 (s, 9H, CMe₃), 1.21 (d, J = 6.5 Hz, 3H,
$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.2 (C=O), 79.2 (CMe$_3$), 58.9 (NCH), 48.6 (NCH), 42.5 (NMe$_2$), 36.4 (NCH$_2$), 32.3 (CH$_2$), 28.6 (CMe$_3$), 27.0 (CH$_2$), 19.9 (NCHMe); HRMS (ESI) $m/z$ calcd for C$_{13}$H$_{26}$N$_2$O$_2$ (M + H)$^+$ 243.2067, found 243.2064 (+2.8 ppm error) and 4-amino piperidine 168 (47 mg, 21%) as a colourless oil. The stereochemistry of cis-209 has not been proven but is assumed from literature precedent.\textsuperscript{38} 

For 4-amino piperidine 168, a peak at 1697 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of $s$-BuLi, a new peak at 1644 cm$^{-1}$ was observed which was assigned to the lithiated intermediate. After a lithiation time of 2 h, complete lithiation of 4-amino piperidine 168 to give the lithiated intermediate was observed. When MeI was added (after 2 h total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O}$ = 1645 cm$^{-1}$) plateaued after 15 min. $^1$H NMR spectroscopy of the crude product indicated starting material 168 was present so complete trapping had not occurred.

Lab Book Reference: AMI_279
6.7 Experimental Procedures for Chapter 5

*tert*-Butyl (1$^S$, 3a$^S$,7a$^R$)-1-(trimethylsilyl)-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate anti-$^{99}$

Using general procedure A, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), N-Boc pyrrolidine $^{96}$ (223 mg, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 0.19 mL, 1.3 mmol, 1.3 eq.) in Et$_2$O (7 mL) for 10 min and then Me$_3$SiCl (217 mg, 0.25 mL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave a single diastereomer (by $^1$H NMR spectroscopy of amine anti-$^{99}$) of 2,3,4-trisubstituted pyrrolidine anti-$^{99}$ (222 mg, 75%) as a colourless oil, $R_F$ (90:10 hexane-EtOAc) 0.18; IR (ATR) 2929, 1686 (C=O), 1389, 1364, 1246, 1168, 1113, 1073, 835, 766 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (50:50 mixture of rotamers) $\delta$ 5.62 (s, 2H, =CH), 3.30-3.27 (m, 1.5 H, NCH), 3.18-3.14 (m, 0.5H, NCH), 3.04 (d, $J = 3.5$ Hz 0.5H, NCH), 2.98 (d, $J = 3.5$ Hz 0.5H, NCH), 2.29-2.17 (m, 4H, CH), 1.90-1.79 (m, 2H, CH), 1.47 (s, 4.5H, CMe$_3$), 1.44 (s, 4.5H, CMe$_3$), 0.07 (s, 4.5H, SiMe$_3$), 0.06 (s, 4.5H, SiMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) (rotamers) $\delta$ 155.4 (C=O), 125.0 (=CH), 124.7 (=CH), 124.4 (=CH), 124.3 (=CH), 79.4 (CMe$_3$), 78.6 (CMe$_3$), 55.7 (NCH), 54.7 (NCH), 51.2 (NCH$_2$), 50.8 (NCH$_2$), 36.7 (CH), 36.1 (CH), 34.7 (CH), 33.9 (CH), 28.8 (CMe$_3$), 28.7 (CMe$_3$), 27.4 (CH$_2$), 27.2 (CH$_2$), 24.7 (CH$_2$), 24.6 (CH$_2$), –1.6 (SiMe$_3$); HRMS (ESI) $m/z$ calcd for C$_{16}$H$_{29}$NO$_2$Si (M + Na)$^+$ 318.1860, found 318.1852 (+2.0 ppm error). Spectroscopic data consistent with those reported in the literature.$^4$ The stereochemistry of anti-$^{99}$ has not been proven but is assumed from literature precedent.$^4$

Lab Book Reference: AMI_5
TFA (240 mg, 0.13 mL, 1.69 mmol, 10.0 eq.) was added dropwise to a stirred solution of 2-silyl N-Boc pyrrolidine \textit{anti-99} (50 mg, 0.169 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (2 mL) at rt under Ar. The resulting solution was stirred at rt for 3 h. Then, saturated NaHCO$_3$(aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The two layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organics were dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to give crude amine \textit{anti-216} (17 mg, 52\%) as a brown oil. The $^1$H NMR spectrum indicated the presence of only one diastereomer. Diagnostic signals for \textit{anti-216}: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.79-5.71 (m, 2H, =CH), 3.08 (dd, $J = 10.5$, 5.5 Hz, 1H), 2.62 (dd, $J = 10.5$, 5.0 Hz, 1H).

\textbf{Lab Book Reference: AMI_11}

TFA (1.94 g, 1.30 mL, 17.01 mmol, 36.0 eq.) was added dropwise to a stirred solution of 2-silyl N-Boc pyrrolidine \textit{anti-99} (140 mg, 0.47 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (13 mL) at rt under Ar. The resulting solution was stirred at rt for 1 h. Then, saturated NaHCO$_3$(aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The two layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organics were dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (5 mL) and Et$_3$N (119 mg, 0.17 mL, 1.18 mmol, 2.5 eq.) and $p$-TsCl (108 mg, 0.57 mmol, 1.2 eq.) were added. The resulting solution was stirred at rt for 1 h. Then, CH$_2$Cl$_2$ (10 mL) and 0.1 M HCl (aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were dried
(MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 85:15 hexane-Et₂O as eluent gave sulfonamide anti-217 (164 mg, 87%) as a white solid, mp 94-96 °C; \( R_f \) (80:20 hexane-Et₂O) 0.18; IR (ATR) 2930, 2895, 1345, 1248, 1166, 1100, 870, 837, 817, 657 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta 7.72-7.67 \) (m, 2H, Ar), 7.30 (d, \( J = 8.0 \) Hz, 2H, Ar), 5.46-5.39 (m, 1H, =CH), 5.33-5.23 (m, 1H, =CH), 3.42 (dd, \( J = 9.0, 7.5 \) Hz, 1H, NCH), 2.87 (dd, \( J = 10.5, 9.0 \) Hz, 1H, NCH), 2.80 (d, \( J = 2.0 \) Hz, 1H, NCH), 2.44-2.33 (m, 1H, CH) 2.43 (s, 3H, Ar-Me), 2.20-2.01 (m, 2H, CH), 1.79-1.66 (m, 2H, CH), 0.74-0.62 (m, 1H, CH), 0.15 (s, 9H, SiMe₃); \(^{13}\)C NMR (100.6 MHz, CDCl₃) \( \delta 143.2 \) (ipso-Ar), 134.0 (Ar), 129.6 (Ar), 127.9 (Ar), 124.2 (=CH), 123.7 (=CH), 59.1 (NCH), 52.0 (NCH₂), 36.5 (CH), 34.9 (CH), 26.8 (CH₂), 23.8 (CH₂), 21.7 (Ar-Me), -1.7 (SiMe₃); HRMS (ESI) \( m/z \) calcd for C₁₈H₂₅NO₂Si (M + H)⁺ 350.1605, found 350.1599 (+0.5 ppm error).

Lab Book Reference: AMI_271

(1S*,3aS*,7aR*)-2-(4-Methylbenzenesulfonyl)-1-(trimethylsilyl)-octahydro-1H-isooindole anti-221

\[ \text{anti-221} \]

Pd/C (25 mg, 25% w/w, 0.025 mmol) was added to a stirred solution of 2,3,4-trisubstituted pyrrolidine anti-99 (101 mg, 0.340 mmol, 1.0 eq.) in EtOAc (5 mL) at rt. The resulting suspension was degassed and then H₂ gas (1 atm) was supplied via a balloon. The suspension was stirred at rt under a H₂ atmosphere (balloon) for 3 h. The solids were removed by filtration through Celite® and washed with EtOAc (10 mL). The filtrate was evaporated under reduced pressure and the residue was dissolved in CH₂Cl₂ (5 mL) and TFA (0.26 mL, 3.40 mmol, 10.0 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 3 h. Then, saturated NaHCO₃(aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organics were dried (Na₂SO₄), filtered and evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ (2 mL) and Et₃N (0.06 mL, 0.408 mmol, 1.2 eq.) and p-TsCl (78 mg, 0.408 mmol,
1.2 eq.) were added. The resulting solution was stirred at rt for 16 h. Then, CH$_2$Cl$_2$ (10 mL) and 0.1 M HCl(aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 50:50 hexane-Et$_2$O as eluent gave sulfonamide anti-221 (71 mg, 59%) as a grey solid, mp 130-135 °C (lit.,$^4$ bp 120-121 °C), $R_f$ (50:50 hexane-Et$_2$O) 0.29; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J$ = 8.0 Hz, 2H, Ar), 7.31 (d, $J$ = 8.0 Hz, 2H, Ar), 3.27 (dd, $J$ = 9.5, 8.0 Hz, 1H, NCH), 3.13-3.03 (m, 1H, NCH), 2.80 (d, $J$ = 2.0 Hz, 1H, NCH), 2.43 (s, 3H, Ar-Me), 2.30 (m, 1H, CH), 1.89 (ddddd, $J$ = 7.5, 5.5, 5.5, 2.0 Hz, 1H, CH), 1.63-0.93 (m, 8H, CH), 0.12 (s, 9H, SiMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 143.2 (ipso-Ar), 134.2 (Ar), 129.5 (Ar), 128.0 (Ar), 58.7 (NCH), 50.3 (NCH$_2$), 40.5 (CH), 37.1 (CH), 28.7 (CH$_2$), 24.8 (CH$_2$), 24.5 (CH$_2$), 21.7 (Ar-Me), 21.1 (CH$_2$), –1.9 (SiMe$_3$). Spectroscopic data consistent with those reported in the literature.$^4$

Lab Book Reference: AMI_21

Using general procedure A, s-BuLi (1.26 mL of a 1.3 M solution in hexanes, 1.64 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (282 mg, 1.26 mmol, 1.0 eq.) and TMEDA (190 mg, 0.25 mL, 1.64 mmol, 1.3 eq.) in Et$_2$O (7 mL) for 10 min and then Me$_2$SO$_4$ (318 mg, 0.24 mL, 2.52 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 90:10 mixture (by $^1$H NMR spectroscopy of sulfonamides anti-218 and syn-218) of 2,3,4-trisubstituted pyrrolidines anti-211 and syn-211 (249 mg, 83%) as a colourless oil. For spectroscopic data see section 6.4.

Lab Book Reference: AMI_6
(15S,3aS*,7aR*) and (1R*,3aS*,7aR*)-1-Methyl-2-(4-methylbenzenesulfonyl)-2,3,3a,4,7,7a-hexahydro-1H-isoindole anti-218 and syn-218

TFA (259 mg, 0.17 mL, 2.30 mmol, 10 eq.) was added to a stirred solution of 2,3,4-trisubstituted pyrrolidine 211 (54 mg, 0.23 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (7 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated NaHCO$_3$(aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (4 mL) and Et$_3$N (28 mg, 0.04 mL, 0.28 mmol, 1.2 eq.) and p-TsCl (28 mg, 0.28 mmol, 1.2 eq.) were added. The resulting solution was stirred at rt for 16 h. Then, CH$_2$Cl$_2$ (10 mL) and 0.1 M HCl (aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product, which contained a 90:10 mixture (by $^1$H NMR spectroscopy) of anti-218 and syn-218. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 90:10 mixture of sulfonamides anti-218 and syn-218 (33 mg, 48%) as a white solid, mp 92-97 °C, $R_F$ (50:50 Hexane-Et$_2$O) 0.29; IR (CHCl$_3$) 1337 (S=O), 1162, 1098, 816, 664, 593, 548 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74-7.70 (m, 2H, Ar), 7.33-7.29 (m, 2H, Ar), 5.70-5.57 (m, 0.2H, =CH), 5.47-5.35 (m, 1.8H, =CH), 3.59-3.53 (m, 0.1H, NCH), 3.48 (dd, $J$ = 9.0, 6.5 Hz, 0.9H, NCH), 3.40-3.30 (m, 1H, NCH), 2.95-2.91 (m, 0.9H, NCH), 2.49-2.44 (br, m, 1H, CH), 2.42 (s, 3H, Ar-Me), 2.19-1.80 (m, 4H, CH), 1.60 (br s, 1H, CH), 1.36 (d, $J$ = 6.5 Hz, 2H, NCHMe), 1.35 (d, $J$ = 6.5 Hz, 0.9H, NCHMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 143.3 (Ar$_{anti}$), 141.9 (Ar$_{syn}$), 135.1 (Ar$_{anti}$), 134.7 (Ar$_{syn}$), 129.7 (Ar$_{syn}$), 129.6 (Ar$_{anti}$), 127.7 (Ar$_{syn}$), 127.5 (Ar$_{anti}$), 125.0 (=CH$_3$), 124.7 (=CH$_3$), 124.2 (=CH$_3$), 123.9 (=CH$_3$), 61.9 (NCH$_{anti}$), 60.4 (NCH$_{syn}$), 53.4 (NCH$_{2syn}$), 52.5 (NCH$_{2anti}$), 41.5 (CH$_{anti}$), 38.5 (CH$_{syn}$), 33.9 (CH$_{syn}$), 32.5 (CH$_{anti}$), 25.0 (CH$_{2syn}$), 24.4 (CH$_{2anti}$), 23.9 (CH$_{2syn}$), 23.8 (CH$_{2anti}$), 22.1 (NCHMe$_{anti}$), 21.73(Ar-Me$_{syn}$), 21.68 (Ar-Me$_{anti}$), 17.7 (NCHMe$_{syn}$); HRMS (ESI) $m/z$ calcd for C$_{16}$H$_{21}$NO$_2$S (M + Na)$^+$ 314.1185, found 314.1171 (+3.4 ppm error).

Lab Book Reference: AMI_7
(1R*,3aS*,7aR*) and (1S*,3aS*,7aR*)-2-[(tert-Butoxy)carbonyl]-2,3,3a,4,7,7a-hexahydro-1H-isoinole-1-carboxylic acid anti-212 and syn-212

Using general procedure C, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.38 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (237 mg, 1.06 mmol, 1.0 eq.) and TMEDA (160 mg, 0.21 mL, 1.38 mmol, 1.3 eq.) in Et₂O (7 mL) for 10 min and then dry CO₂ was bubbled through for 30 min to give the crude product, which contained an 87:13 mixture (by ¹H NMR spectroscopy) of carboxylic acids anti-212 and syn-212. Purification by flash column chromatography on silica using 50:49.5:0.5 EtOAc-hexane-AcOH as eluent gave an 87:13 mixture of carboxylic acids anti-212 and syn-212 (218 mg, 77%) as a white solid, mp 110-112 °C, R_f (50:49.5:0.5 EtOAc-hexane-AcOH) 0.16; IR 2973, 2928, 1727 (C=O, CO₂H), 1632 (C=O, Boc), 1431, 1235, 1139, 913 859, 672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers for each of anti-212 and syn-212) δ 5.65 (s, 2H, =CH), 4.37 (m, 0.065H, NCH), 4.30 (d, J = 7.5 Hz, 0.065H, NCH), 4.04 (d, J = 4.0 Hz, 0.435H, NCH), 3.92 (d, J = 6.5 Hz, 0.435H, NCH), 3.59 (dd, J = 10.0, 7.0 Hz, 0.5H, NCH), 3.49 (dd, J = 10.0, 6.0 Hz, 0.5H, NCH), 3.31 (dd, J = 10.0, 5.0 Hz, 0.5H, NCH), 3.21 (dd, J = 10.0, 8.0 Hz, NCH), 2.67-1.82 (m, 6H, CH), 1.48 (s, 4.5H, CMe₃), 1.41 (s, 4.5H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) for anti-212 (rotamers) δ 178.8 (C=O, CO₂H), 175.3 (C=O, CO₂H), 156.9 (C=O, Boc), 154.5 (C=O, Boc), 124.8 (=CH), 124.4 (=CH), 124.0 (=CH), 123.7 (=CH), 81.4 (CMe₃), 80.6 (CMe₃), 64.7 (NCH), 63.7 (NCH), 51.5 (NCH₂), 51.3 (NCH₂), 40.4 (CH), 37.6 (CH), 33.3 (CH), 32.7 (CH), 28.5 (CMe₃), 28.4 (CMe₃), 24.8 (CH₂), 24.7 (CH₂), 24.6 (CH₂), 24.2 (CH₂); HRMS (ESI) m/z calcd for C₁₄H₂₁NO₄ (M + Na)⁺ 290.1363, found 290.1348 (+4.6 ppm error). The stereochemistry of anti-212 and syn-212 has not been proven but is assumed from literature precedent.⁴

Lab Book Reference: AMI_12
Me$_3$Si-diazomethane (0.40 mL of a 2 M solution in hexanes, 2.0 eq.) was added to a stirred solution of an 87:13 mixture of carboxylic acids anti-212 and syn-212 (71 mg, 0.264 mmol, 1.0 eq.) in toluene (1.8 mL) and MeOH (1.2 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min and then warmed to rt over 30 min. AcOH (16 mg, 0.02 mL, 1.0 eq.) was added and then the solvent was evaporated under reduced pressure. The residue was partitioned between H$_2$O and Et$_2$O and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture (by $^1$H NMR spectroscopy) of methyl esters anti-219 and syn-219. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave an 87:13 mixture of methyl esters anti-219 and syn-219 (64 mg, 86%) as a colourless oil, $R_f$ (80:20 hexane-EtOAc) 0.18; IR 2979, 2927, 1750 (C=O), 1697 (C=O), 1391, 1365, 1252, 1162, 1126, 731, 665 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (60:40 mixture of rotamers for each of anti-219 and syn-219) δ 5.64 (s, 2H, =CH), 4.33 (d, $J = 7.0$ Hz, 0.05H, NCH), 4.27 (d, $J = 7.0$ Hz, 0.08H, NCH), 4.02 (d, $J = 4.5$ Hz, 0.35H, NCH), 3.90 (d, $J = 6.0$ Hz, 0.52H, NCH), 3.74 (s, 1.04H, OMe), 3.73 (s, 1.57H, OMe), 3.70 (s, 0.23H, OMe), 3.68 (s, 0.16H, OMe), 3.62-3.56 (m, 1H, NCH), 3.29 (dd, $J = 10.0$, 4.5 Hz, 0.6H, NCH), 3.18 (dd, $J = 10.0$, 7.0 Hz, 0.4H, NCH), 2.49-2.14 (m, 4H, CH), 1.98-1.91 (m, 1H, CH), 1.91-1.84 (m, 1H, CH), 1.45 (s, 3.6H, CMe$_3$), 1.40 (s, 5.4H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) for anti-219 (rotamers) δ 173.5 (C=O, COOMe), 173.1 (C=O, COOMe), 150.1 (C=O, Boc), 154.4 (C=O, Boc), 124.8 (=CH), 124.5 (=CH), 124.0 (=CH), 123.7 (=CH), 80.1 (CMe$_3$), 80.0 (CMe$_3$), 64.1 (NCH), 63.9 (NCH), 52.3 (OMe), 52.1 (OMe), 51.5 (NCH$_2$), 51.3 (NCH$_2$), 40.3 (CH), 39.0 (CH), 33.2 (CH), 32.6 (CH), 28.5 (CMe$_3$), 28.4 (CMe$_3$), 25.0 (CH$_2$), 24.7 (CH$_2$), 24.6 (CH$_2$), 24.4 (CH$_2$); HRMS (ESI) $m/z$ calcd for C$_{15}$H$_{23}$NO$_4$ (M + Na)$^+$ 304.1519, found 304.1515 (+0.8 ppm error).

Lab Book Reference AMI_20
(1R*,3aS*,7aR*) and (1S*,3aS*,7aR*)-tert-Butyl-1-[(S) and (R)-hydroxy(phenyl) methyl]-2,3a,4,7,7a-hexahydro-1H-isooindole-2-carboxylate anti-anti-214, anti-syn-214, syn-anti-214 and syn-syn-214

Using general procedure A, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.40 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (241 mg, 1.08 mmol, 1.0 eq.) and TMEDA (163 mg, 0.21 mL, 1.40 mmol, 1.3 eq.) in Et₂O (7 mL) and then PhCHO (229 mg, 0.22 mL, 2.16 mmol, 2.0 eq.) gave the crude product, which contained a 58:29:9:4 mixture (by 1H NMR spectroscopy) of anti-anti-214, anti-syn-214, syn-anti-214, syn-syn-214. Purification by flash column chromatography on silica using 99:1 CH₂Cl₂-acetone as eluent gave an 80:20 mixture of pyrrolidines anti-anti-214 and syn-syn-214 (164 mg, 46%) as a colourless oil, Rₓ (98:2 CH₂Cl₂-acetone) 0.16; IR (ATR) 3386 (OH), 2970, 2890, 1663 (C=O), 1404, 1367, 1159, 1126, 1051, 701 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.42-7.30 (m, 5H, Ph), 5.74 (d, J = 3.0 Hz, 0.8 H, OH), 5.56-5.49 (m, 2H, =CH), 4.70 (d, J = 5.0 Hz, 0.2H, PhCHO), 4.61 (dd, J = 9.0, 3.0 Hz, 0.8H, PhCHO), 4.11 (dd, J = 5.0, 4.0 Hz, 0.2H, NCH), 3.78 (d, J = 9.0 Hz, 0.8H, NCH), 3.64 (br s, 0.2H, NCH), 3.49 (dd, J = 10.5, 8.0 Hz, 0.8H, NCH), 3.21 (dd, J = 10.5, 10.5 Hz, 0.8H, NCH), 3.12 (dd, J = 10.5, 10.5 Hz, 0.2H, NCH), 2.54-1.64 (m, 6H, CH), 1.50 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.4 (C=O-syn-syn), 159.2 (C=O-anti-anti), 142.7 (ipso-Ph-anti-anti), 142.0 (ipso-Ph-syn-syn), 128.7 (Ph-syn-syn), 128.6 (Ph-anti-anti), 128.1 (Ph-anti-anti), 128.0 (Ph-syn-syn), 127.3 (Ph-anti-anti), 127.1 (Ph-syn-syn), 127.1 (=CH-syn-syn), 126.9 (=CH-syn-syn), 124.6 (=CH-anti-anti), 124.2 (=CH-anti-anti), 81.0 (CMe₃-anti-anti), 80.2 (CMe₃-syn-syn), 79.1 (PhCHO-anti-anti), 75.7 (PhCHO-syn-syn), 72.0 (NCH-syn-syn), 71.5 (NCH-anti-anti), 52.0 (NCH-anti-anti), 50.9 (NCH-anti-anti), 36.0 (CH-anti-anti), 33.8 (CH-syn-syn), 32.7 (CH-anti-anti), 29.8 (CH-syn-syn), 28.61 (CMe₃-syn-syn), 28.59 (CMe₃-anti-anti), 25.6 (CH₂-anti-anti), 24.0 (CH₂-anti-anti), 23.4 (CH₂-syn-syn), 21.67 (CH₂-syn-syn); HRMS (ESI) m/z calcd for C₂₀H₂₇NO₃ (M + Na)⁺ 352.1883, found 352.1880 (+0.9 ppm error), pyrrolidine anti-syn-214 (82 mg, 23%) as a colourless oil, Rₓ (98:2 CH₂Cl₂-acetone) 0.13; IR (ATR) 3407 (OH), 2974, 2927, 1666 (C=O), 1392, 1365, 1160, 1127, 702, 662 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.28 (m, 5H, Ph), 6.07 (d, J
$J = 7.5 \text{ Hz, 1H, OH}$, 5.61 (m, 2H, =CH), 4.83 (d, $J = 7.5 \text{ Hz, 1H, PhCHO}$), 3.97 (d, $J = 7.0 \text{ Hz, 1H, NCH}$), 3.13 (dd, $J = 10.5, 5.0 \text{ Hz, 1H, NCH}$), 2.75 (dd, $J = 10.5, 6.0 \text{ Hz, NCH}$), 2.45-1.94 (m, 5H, CH), 1.80-1.75 (m, 1H, CH), 1.51 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 158.2 (C=O), 141.3 (ipso-Ph), 128.1 (Ph), 127.5 (Ph), 127.1 (Ph), 124.9 (=CH), 124.1 (=CH), 80.7 (CMe$_3$), 76.3 (PCHO), 68.3 (NCH), 53.0 (NCH$_2$), 36.6 (CH), 31.9 (CH), 28.6 (CMe$_3$), 25.2 (CH$_2$), 24.7 (CH$_2$); HRMS (ESI) $m/z$ calcd for C$_{20}$H$_{27}$NO$_3$ (M + Na)$^+$ 352.1883, found 352.1881 (+0.4 ppm error) and pyrrolidine syn-anti-214 (11 mg, 3%) as a pale yellow solid, mp 124-126 °C, $R_F$ (98:2 CH$_2$Cl$_2$-acetone) 0.19; IR (ATR) 3295 (OH), 2933, 2876, 1668 (C=O), 1409, 1228, 1151, 1122. 762, 704, 681 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43-7.69 (m, 5H, Ph), 5.56-5.46 (m, 2H, =CH), 4.69 (dd, $J = 8.5, 2.0 \text{ Hz, 1H, PhCH}_2$), 4.19 (dd, $J = 8.5, 4.0, 1H, NCH$), 3.61 (dd, $J = 10.5, 8.0 \text{ Hz, 1H, NCH}$), 3.23 (dd, $J = 10.5, 10.5 \text{ Hz, NCH}$), 2.28-1.80 (m, 6H, CH), 1.50 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 158.6 (C=O), 142.7 (ipso-Ph), 128.5 (Ph), 127.95 (Ph), 127.93 (Ph), 124.8 (=CH), 123.6 (=CH), 81.0 (CMe$_3$), 75.7 (PCHO), 74.9 (NCH), 52.5 (NCH$_2$), 37.2 (CH), 33.7 (CH), 28.6 (CMe$_3$), 24.1 (CH$_2$), 20.7 (CH$_2$); HRMS (ESI) $m/z$ calcd for C$_{20}$H$_{27}$NO$_3$ (M + Na)$^+$ 352.1883, found 352.1881 (+0.4 ppm error).

Lab Book Reference: AMI_51

**1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 239**

![Image of 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 239](image)

2-Iodobenzoic acid (10.00 g, 40.32 mmol, 1.0 eq.) was added in one portion to a solution of Oxone (37.18 g, 129.96 mmol, 3.0 eq.) in deionised water (200 mL). The resulting mixture was warmed to 70 °C over 20 min and mechanically stirred at this temperature for 3 h. The resulting suspension was cooled to 0 °C and maintained at this temperature for 1.5 h with slow stirring. The mixture was filtered through a sintered glass funnel and the collected solids were washed with water (6 x 40 mL) and acetone (2 x 40 mL) and then dried by suction to give intermediate IBX (9.12 g, 80%) as a white solid.
Acetic acid (10.49 g, 174.69 mmol, 8.7 eq., 10 mL) and acetic anhydride (20.56 g, 201.37 mmol, 10.0 eq., 19 mL) were added to IBX (3.49 g, 20.16 mmol, 1.0 eq.). The resulting suspension was stirred under Ar and heated at 85 °C for 30 min until all of the solids had dissolved. Heating and stirring were discontinued and the solution was allowed to cool to rt over 24 h. The solution of excess reagents was removed from the solid precipitate by cannula transfer under Ar. Et$_2$O (20 mL) was then added and the solids were washed by swirling followed by removal of the solvent by cannula transfer under Ar. This process was repeated with Et$_2$O (3 x 20 mL). The resulting solid was dried in vacuo to give Dess-Martin periodinane 239 (3.62 g, 70%) as a white solid, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 (dd, $J = 7.5$, 1.5 Hz, 1H, Ar), 8.28 (d, $J = 7.5$ Hz, 1H, Ar), 8.07 (ddd, $J = 7.5$, 7.5, 1.5 Hz, 1H, Ar), 7.90 (dd, $J = 7.5$, 7.5 Hz, 1H, Ar), 2.32 (s, 1H, COCH$_3$), 1.99 (s, 6H, COCH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 175.9 (C=O, COCH$_3$), 174.2 (C=O, COCH$_3$), 166.3 (C=O, ArCO), 142.4 (Ar), 135.9 (Ar), 133.9 (Ar), 131.9 (Ar), 126.6 (Ar), 129.1 (Ar), 20.5 (COCH$_3$), 20.4 (COCH$_3$). Spectroscopic data consistent with those reported in the literature.

Lab Book Reference: AMI_104

**tert-Butyl-(1R*,3aS*,7aR*)-1-benzoyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate anti-213**

![Image of anti-213 structure]

Using general procedure D, 2,3,4-trisubstituted N-Boc pyrrolidine anti-syn-214 (82 mg, 0.248 mmol, 1.0 eq.) and DMP (116 mg, 0.272 mmol, 1.1 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave ketone anti-213 (63 mg, 77%) as a colourless oil, $R_F$ (98:2 CH$_2$Cl$_2$-acetone) 0.19; IR (ATR) 2975, 2930, 1686 (C=O), 1391, 1365, 1220, 1165, 1125, 1003, 696, 660 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (60:40 mixture of rotamers) $\delta$ 7.97-7.93 (m, 2H, Ph), 7.58-7.43 (m, 3H, Ph), 5.67 (m, 2H, =CH), 5.07 (d, $J = 2.5$ Hz, 0.4H, NCH), 4.89 (d, $J = 5.0$ Hz, 0.6H, NCH), 3.79 (dd, $J = 10.5$, 6.5 Hz, 0.6H, NCH), 3.74 (dd, $J = 10.5$, 7.5 Hz, 0.4H, NCH), 3.33 (dd, $J = 10.5$, 6.5 Hz, 0.6H, NCH), 3.22 (dd, $J = 10.5$, 6.5, 0.4H, NCH), 2.53-1.95 (m, 6H, CH), 1.46 (s, 3.6H, CMe$_3$), 1.22 (s, 5.4H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) (rotamers)
δ 198.9 (PhC=O), 197.9 (PhC=O), 155.1 (C=O, Boc), 154.4 (C=O, Boc), 135.9 (ipso-Ph), 135.6 (ipso-Ph), 133.38 (Ph), 133.35 (Ph), 128.9 (Ph), 128.8 (Ph), 128.5 (Ph), 128.3 (Ph), 125.2 (=CH), 124.8 (=CH), 124.0 (=CH), 123.6 (=CH), 80.1 (CMe₃), 79.9 (CMe₃), 67.5 (NCH), 66.8 (NCH), 51.1 (NCH₂), 50.7 (NCH₂), 40.0 (CH), 38.5 (CH), 32.7 (CH), 32.3 (CH), 28.6 (CMe₃), 28.3 (CMe₃), 25.5 (CH₂), 25.1 (CH₂), 24.6 (CH₂), 24.2 (CH₂); HRMS (ESI) m/z calcd for C₂₀H₂₅NO₃ (M + Na)⁺ 350.1727, found 350.1725 (+2.7 ppm error).

Lab Book Reference: AMI_55

**tert-Butyl-(1S*,3aS*,7aR*)-1-benzoyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate syn-213**

![Syn-213](image)

Using general procedure D, 2,3,4-trisubstituted N-Boc pyrrolidine *syn-anti*-214 (32 mg, 0.096 mmol, 1.0 eq.) and DMP (45 mg, 0.106 mmol, 1.1 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave ketone *syn-213* (19 mg, 60%) as a colourless oil, *Rf* (98:2 CH₂Cl₂-acetone) 0.19; IR (CHCl₃) 2991, 2931, 1697 (C=O), 1406, 1366, 1216, 1168, 1123, 921 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 8.00 (d, *J* = 7.0 Hz, 0.8H, Ph), 7.95 (d, *J* = 7.5 Hz, 1.2H, Ph), 7.57-7.41 (m, 3H, Ph), 5.60-5.47 (m, 2H, =CH), 5.39 (d, *J* = 6.5 Hz, 0.4H, NCH), 5.32 (d, *J* = 6.5 Hz, 0.6H, NCH), 3.76 (dd, *J* = 10.5, 7.5 Hz, 0.6H, NCH), 3.32-3.24 (m, 1H, NCH), 1.93 (m, 6H, CH), 1.46 (s, 3.6H, CMe₃), 1.22 (s, 3.6H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 196.3 (PhC=O), 171.4 (C=O, Boc), 136.9 (ipso-Ph), 133.2 (Ph), 128.8 (Ph), 128.3 (Ph), 127.9 (Ph), 124.6 (=CH), 124.3 (=CH), 124.1 (=CH), 123.9 (=CH), 80.1 (CMe₃), 79.9 (CMe₃), 66.4 (NCH), 66.2 (NCH), 50.7 (NCH₂), 50.2 (NCH₂), 38.0 (CH), 37.20 (CH), 35.6 (CH), 35.0 (CH), 26.3 (CMe₃), 24.22 (CH₂), 24.20 (CH₂), 21.5 (CH₂), 21.4 (CH₂); HRMS (ESI) m/z calcd for C₂₀H₂₅NO₃ (M + Na)⁺ 350.1727, found 350.1723 (+0.9 ppm error).

Lab Book Reference: AMI_53
**tert-Butyl-(1S*,3aS*,7aR*)-1-benzoyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate syn-213**

Crystal data and structure refinement for *syn-213*

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Final R indexes [$I \geq 2\sigma (I)$]  $R_1 = 0.0366$, $wR_2 = 0.0867$
Final R indexes [all data]  $R_1 = 0.0431$, $wR_2 = 0.0920$
Largest diff. peak/hole / e Å$^{-3}$  0.23/-0.22
Flack parameter  0.68(19)

**N-Methoxy-N-methylbenzamide 215**

![N-Methoxy-N-methylbenzamide](image)

Benzoyl chloride (5.0 g, 35.6 mmol, 1.0 eq.) was added to a stirred solution of $N,O$-dimethylhydroxylamine hydrochloride (3.47 g, 35.6 mmol, 1.0 eq.) and Et$_3$N (10.81 g, 107 mmol, 14.9 mL, 3.0 eq.) in CH$_2$Cl$_2$ (150 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. Then, saturated NH$_4$Cl$_{\text{aq}}$ (20 mL) and saturated NaHCO$_3$$_{\text{aq}}$ (20 mL) were added. The two layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave Weinreb amide 215 (5.79 g, 99\%) as a colourless oil, $R_F$ (4:1 hexane-EtOAc) 0.08; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69-7.66 (m, 2H, Ph), 7.48-7.37 (m, 3H, Ph), 3.56 (s, 3H, OMe), 3.36 (s, 3H, NMe); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 169.8 (C=O), 134.0 ($ipso$-Ph), 130.4 (Ph), 128.0 (Ph), 127.9 (Ph), 60.9 (OMe), 33.7 (NMe). Spectroscopic data consistent with those reported in the literature.\textsuperscript{156}

Lab Book Reference: AMI_268
(1S*,3aS*,7aR*) and (1R*,3aS*,7aR*)-tert-Butyl-1-benzoyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate *anti*-213 and *syn*-213

Using general procedure D, an 80:20 mixture of 2,3,4-trisubstituted *N*-Boc pyrrolidines *anti*-214 and *syn*-214 (164 mg, 0.498 mmol, 1.0 eq.) and DMP (232 mg, 0.548 mmol, 1.1 eq.) gave the crude product, which contained a 90:10 mixture of *anti*-213 and *syn*-213 (by $^1$H NMR spectroscopy of *anti*-213 and *syn*-213). Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave a 90:10 mixture of ketones *anti*-213 and *syn*-213 (117 mg, 72%) as a colourless oil.

Lab Book Reference: AMI_54

Using general procedure A, s-BuLi (0.90 mL of a 1.3 M solution in hexanes, 1.17 mmol, 1.3 eq.), *N*-Boc pyrrolidine 96 (201 mg, 0.90 mmol, 1.0 eq.) and TMEDA (136 mg, 1.17 mmol, 0.18 mL, 1.3 eq.) in Et$_2$O (7mL) for 10 min and then Weinreb amide 215 (297 mg, 1.80 mmol, 274 μL, 2.0 eq.) gave the crude product, which contained an 87:13 mixture (by $^1$H NMR spectroscopy) of ketones *anti*-213 and *syn*-213. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave ketone *anti*-213 (197 mg, 67%) as a colourless oil and ketone *syn*-213 (19 mg, 6%) as a pale yellow solid.

Lab Book Reference: AMI_270
Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, N-Boc pyrrolidine 96 (224 mg, 1.00 mmol, 1.0 eq.) was added followed by TMEDA (150 mg, 1.30 mmol, 1.3 eq., 0.20 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 10 min. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 15 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (840 mg, 1.98 mmol, 2.0 eq.) in CH₂Cl₂ (10 mL) gave the crude product, which contained an 87:13 mixture (by ¹H NMR spectroscopy) of ketones anti-213 and syn-213. Purification by flash column chromatography on silica using 98:2 CH₂Cl₂:acetone as eluent gave an 87:13 mixture (by ¹H NMR spectroscopy) of ketones anti-213 and syn-213 (254 mg, 78%) as a colourless oil.

For N-Boc pyrrolidine 96, a peak at 1702 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1651 cm⁻¹ was observed which was assigned to νC=O in the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed and complete trapping was observed after 1 min. When PhCHO was added (after a 10 min total lithiation time), the signal for the lithiated intermediate (νC=O = 1651 cm⁻¹) disappeared after 1 min, indicating complete trapping had occurred. During the trapping process, another peak appeared at 1709 cm⁻¹ which was assigned to the trapped adduct 214.

Lab Book Reference: AMI_95
(15S*,3aS*,7aR*)\text{-}\text{tert-Butyl 1\text{-}(trimethylsilyl)-3a,4,7,7a\text{-}tetrahydro\text{-}1H\text{-}isoindole\text{-}2(3H)\text{-}carboxylate }\text{ anti\text{-}99 \ and \ (15S*,3aS*,7aR*)\text{-}\text{tert-Butyl 1\text{-}benzoyl\text{-}3a,4,7,7a\text{-}tetrahydro\text{-}1H\text{-}isoindole\text{-}2(3H)\text{-}carboxylate }\text{ syn\text{-}213}

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, DiComp) at rt under Ar. After cooling to \(-78\ °C\), a solution of \text{-}N\text{-}Boc\ pyrrolidine \text{96} (231 mg, 1.04 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by TMEDA (156 mg, 1.35 mmol, 1.3 eq., 0.20 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR®). Then s\text{-}BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.35 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at \(-78\ °C\) for 10 min. Then, Me₃SiCl (225 mg, 2.07 mmol, 2.0 eq., 0.26 mL) was added and the solution was stirred at \(-78\ °C\) for 2.5 h. PhCHO (220 mg, 2.07 mmol, 2.0 eq., 0.21 mL) was also added and the solution was stirred for a further 10 min at \(-78\ °C\). Then, saturated NH₄Cl\text{(aq)} (10 mL) was added and the two layers were separated. The aqueous layers was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (484 mg, 1.08 mmol, 1.0 eq.) gave the crude product, which contained an 86:14 mixture (by \text{¹H NMR spectroscopy}) of \text{anti\text{-}99} and \text{syn\text{-}213}. Purification by flash column chromatography on silica using 90:10 hexane\text{-}EtOAc as eluent gave 2\text{-}silyl\ pyrrolidine \text{anti\text{-}99} (164 mg, 53%) as a colourless oil and ketone \text{syn\text{-}213} as a pale yellow solid (35 mg, 10%).

For \text{-}N\text{-}Boc\ pyrrolidine \text{96}, a peak at 1702 cm\(^{-1}\) was observed and assigned to \text{ν}_{\text{C}=\text{O}}. After addition of s\text{-}BuLi, a new peak at 1652 cm\(^{-1}\) was observed which was assigned to \text{ν}_{\text{C}=\text{O}} in the
lithiated intermediate. After a lithiation time of 4 min, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed. When Me₃SiCl was added (after a 10 min total lithiation time), the signal for the lithiated intermediate (υ_C=O = 1652 cm⁻¹) decreased slowly and then plateaued after 2.5 h. During this time, a signal for the Me₃SiCl-trapped adduct anti-99 (υ_C=O = 1693 cm⁻¹) appeared and increased in intensity over the 2.5 h then plateaued. When PhCHO was added (after the 2.5 h Me₃SiCl trapping), the signal for the lithiated intermediate (υ_C=O = 1652 cm⁻¹) disappeared after 1 min and a new peak for the PhCHO-trapped product anti-214 (υ_C=O = 1707 cm⁻¹) was observed, indicating that complete trapping had occurred.

Lab Book Reference: AMI_114

**tert-Butyl (1S*, 3aS*,7aR*)-1-(trimethylsilyl)-2,3,3a,4,7,7a-hexahydro-1H-isindole-2-carboxylate anti-99**

![Anti-99 structure](image)

Using general procedure B, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.43 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (246 mg, 1.10 mmol, 1.0 eq.) and TMEDA (166 mg, 1.43 mmol, 1.3 eq.) in Et₂O (7 mL) for 2 min and then Me₃SiCl (239 mg, 0.28 mL, 2.20 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave a single diastereomer of 2,3,4-trisubstituted pyrrolidine anti-99 (210 mg, 64%) as a colourless oil.

Lab Book Reference: AMI_59
Using general procedure B, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.35 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (232 mg, 1.04 mmol, 1.0 eq.) and TMEDA (157 mg, 1.35 mmol, 1.3 eq.) in Et₂O (7 mL) for 2 min and then Me₂SO₄ (261 mg, 0.20 mL, 2.07 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 70:30 mixture (by ¹H NMR spectroscopy of sulfonamides anti-218 and syn-218) of 2,3,4-trisubstituted pyrrolidines anti-211 and syn-211 (161 mg, 65%) as a colourless oil.

Lab Book Reference: AMI_61

TFA (469 mg, 0.32 mL, 4.12 mmol, 10 eq.) was added to a stirred solution of 2,3,4-trisubstituted pyrrolidine 211 (98 mg, 0.412 mmol, 1.0 eq.) in CH₂Cl₂ (7 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated NaHCO₃ (aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organics were dried (Na₂SO₄), filtered and evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ (4 mL) and Et₃N (51 mg, 0.494 mmol, 1.2 eq.) and p-TsCl (108 mg, 0.57 mmol, 1.2 eq.) were added. The resulting solution was stirred at rt for 16 h. Then, CH₂Cl₂ (10 mL) and 0.1 M HCl (aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x
10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product, which contained a 70:30 mixture (by $^1$H NMR spectroscopy) of *anti*-218 and *syn*-218. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 70:30 mixture of sulfonamides *anti*-218 and *syn*-218 (44 mg, 37%) as a white solid.

Lab Book Reference: AMI_62

(1R*,3aS*,7aR*) and (1S*,3aS*,7aR*)-tert-Butyl-1-[(S)- and (R)-hydroxy(phenyl)methyl]-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate *anti-anti*-214, *anti-syn*-214, *syn-anti*-214 and *syn-syn*-214

Using general procedure B, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (222 mg, 0.993 mmol, 1.0 eq.), TMEDA (150 mg, 0.19 mL, 1.29 mmol, 1.3 eq.) in Et₂O (7 mL) and then PhCHO (210 mg, 0.20 mL, 2.0 mmol, 2.0 eq.) gave the crude product, which contained a 25:25:25:25 mixture (by $^1$H NMR spectroscopy) of *anti-anti*-214, *anti-syn*-214, *syn-anti*-214, *syn-syn*-214. Purification by flash column chromatography on silica using 99:1 CH₂Cl₂-Acetone as eluent gave a 50:50 mixture of pyrrolidines *anti-anti*-214 and *syn-syn*-214 (88 mg, 27%) as a colourless oil, pyrrolidine *anti-syn*-214 (54 mg, 17%) as a colourless oil and pyrrolidine *syn-anti*-214 (74 mg, 23%) as a pale yellow solid.

Lab Book Reference: AMI_60
3,7-Bis(propan-2-yl)-3,7-diazabicyclo[3.3.1]nonan-9-one 225

![Chemical Structure](attachment:image.png)

$i$-PrNH$_2$ (6.1 mL, 71.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of $N$-$i$-Pr-4-piperidone (10.6 mL, 71.0 mmol, 1.0 eq.), paraformaldehyde (6.40 g, 213 mmol 3.0 eq.) and AcOH (4.23 mL, 75.3 mmol, 1.05 eq.) in MeOH (100 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% KOH(aq) (250 mL) and Et$_2$O (250 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 x 250 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave bispidone 225 (6.52 g, 41%) as a colourless oil, bp 116-130 °C/2.5 mmHg (lit.,$^{157}$ bp 110-120 °C/10$^{-5}$ mmHg); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 2.96 (dd, $J = 10.5, 3.0$ Hz, 4H, NCH), 2.81-2.73 (m, 6H, NCH), 2.48-2.41 (m, 2H, COCH), 0.95 (d, $J = 6.5$ Hz, 12H, NCHMe$_2$). Spectroscopic data consistent with those reported in the literature.$^{157}$

Lab Book Reference: AMI_26

3,7-Bis(propan-2-yl)-3,7-diazabicyclo[3.3.1]nonane 30

Hydrazine monohydrate (2.65 mL, 54.5 mmol, 5.6 eq.) was added dropwise to a stirred mixture of bispidone 225 (2.18 g, 9.74 mmol) and KOH (6.39 g, 113.4 mmol, 11.7 eq.) in diethylene glycol (60 mL) at rt under Ar. The resulting mixture was stirred and heated at 180 °C for 16 h. After cooling to 60 °C, the mixture was transferred to a separating funnel and H$_2$O (80 mL) was added. Then Et$_2$O (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et$_2$O (6 x 50 mL) and the combined organic layers were washed with NaOH(aq) (6 x 50 mL), dried (Na$_2$SO$_4$), filtered and evaporated under reduced
pressure to give the crude product. Purification by distillation gave di-\(i\)-Pr bispidine 30 (1.87 g, 91%) as a colourless oil, bp 120-130 °C/3.5 mmHg; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 2.62-2.54 (m, 2H, NCH), 2.49-2.41 (m, 8H, NCH), 1.94-1.86 (m, 2H, NCH\(_2\)CH\(_2\)), 1.41-1.35 (m, 2H, bridge CH\(_2\)), 0.93 (d, \(J = 6.5\) Hz, 12H, NCH\(_2\)Me\(_2\)). Spectroscopic data consistent with those reported in the literature.\(^{158}\)

Lab Book Reference: AMI_32

\[3,7\text{-Dipropyl-3,7-diazabicyclo[3.3.1]nonan-9-one 227}\]

\(n\)-PrNH\(_2\) (5.83 mL, 70.81 mmol, 1.0 eq.) was added dropwise to a stirred solution of \(N\)-\(n\)-Pr-4-piperidone (10.7 mL, 35.5 mmol), paraformaldehyde (6.38 g, 212.4 mmol, 3.0 eq.) and AcOH (4.2 mL, 73.8 mmol, 1.04 eq.) in MeOH (100 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% KOH\(_{aq}\) solution (250 mL) and Et\(_2\)O (250 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (2 x 250 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave bispidone 227 (6.04 g, 38%) as a colourless oil, bp 115-120 °C/1.0 mmHg; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 2.89 (dd, \(J = 11.0, 3.0\) Hz, 4H, NCH), 2.67 (dd, \(J = 11.0, 6.0\) Hz, 4H, NCH), 2.42 (br s, 2H, COCH), 2.24 (t, \(J = 7.0\) Hz, 4H, NCH\(_2\)CH\(_2\)), 1.41-1.32 (m, 4H, NCH\(_2\)CH\(_2\)), 0.82 (t, \(J = 7.5\) Hz, 6H, Me). Spectroscopic data consistent with those reported in the literature.\(^{138}\)

Lab Book Reference: AMI_33
Hydrazine monohydrate (4.2 mL, 86.15 mmol, 5.5 eq.) was added dropwise to a stirred mixture of bispidone 227 (3.51 g, 15.66 mmol) and KOH (10.11 g, 180.13 mmol, 11.5 eq.) in diethylene glycol (90 mL) at rt under Ar. The resulting mixture was stirred and heated at 180 ºC for 16 h. After cooling to 60 ºC, the mixture was transferred to a separating funnel and H₂O (80 mL) was added. Then Et₂O (80 mL) was added and the layers were separated. The aqueous layer was extracted with Et₂O (6 x 60 mL) and the combined organic layers were washed with 20% NaOH (aq) (6 x 90 mL), dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by distillation gave di-n-Pr bispidine 105 (3.51 g, 95%) as a colourless oil, bp 105-115 ºC/1.0 mmHg, \(^1\)H NMR (400 MHz, DMSO-d₆) δ 2.57 (br d, \(J = 10.5\) Hz, 4H, NCH), 2.19 (dd, \(J = 10.5, 4.5\) Hz, 4H, NCH), 2.09 (t, \(J = 7.0\) Hz, 4H, NCH₂CH₂), 1.84 (br s, 2H, NCH₂CH), 1.40-1.29 (m, 6H, NCH₂CH₂ + bridge CH₂), 0.81 (t, \(J = 7.5\) Hz, 6H, Me). Spectroscopic data consistent with those reported in the literature.\(^{138}\)

Lab Book Reference: AMI_37
(1R*,3aS*,7aR*) and (1S*,3aS*,7aR*) tert-Butyl-1-benzoyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole-2-carboxylate *anti*-213 and *syn*-213

\[
\text{Et}_2\text{O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR}^{\text{TM}} \text{ probe (iC 10, SiComp) at rt under Ar. After cooling to } -78 \degree \text{C, a solution of } N\text{-Boc pyrrolidine 96 (222 mg, 1.00 mmol, 1.0 eq.) in Et}_2\text{O (2 mL) was added followed by a solution of TMCDA trans-161 (186 mg, 1.29 mmol, 1.3 eq.) in Et}_2\text{O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR}^{\text{TM}} \text{). Then, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at } -78 \degree \text{C for 15 min. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at } -78 \degree \text{C for a further 15 min. Saturated NH}_4\text{Cl (aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et}_2\text{O (3 x 10 mL) and the combined organics were dried (MgSO}_4\text{), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (632 mg, 1.49 mmol, 1.5 eq.) in CH}_2\text{Cl}_2 (10 mL) gave the crude product, which contained an 87:13 mixture (by }^1\text{H NMR spectroscopy) of ketones } *anti*-213 \text{ and } *syn*-213 \text{. Purification by flash column chromatography on silica using 98:2 CH}_2\text{Cl}_2\text{-acetone as eluent gave an 87:13 mixture (by }^1\text{H NMR spectroscopy) of ketones } *anti*-213 \text{ and } *syn*-213 \text{ (246 mg, 76%) as a colourless oil.}

\[
\text{For } N\text{-Boc pyrrolidine 96, a peak at 1701 cm}^{-1} \text{ was observed and assigned to } \nu_{\text{C=O}} \text{. After addition of s-BuLi, a new peak at 1678 cm}^{-1} \text{ was observed which was assigned to } \nu_{\text{C=O}} \text{ in the prelithiation complex. A new peak at 1645 cm}^{-1} \text{ was also observed and this was assigned to}
\]
the lithiated intermediate. After a lithiation time of 4 min, complete lithiation of $N$-Boc pyrrolidine 96 to give the lithiated intermediate was observed. The PhCHO trapping was not monitored by ReactIR$^\text{TM}$.

Lab Book Reference: AMI_73 + AMI_75

Et$_2$O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR$^\text{TM}$ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, $N$-Boc pyrrolidine 96 (224 mg, 1.00 mmol, 1.0 eq.) was added followed by TMPDA 179 (170 mg, 0.22 mL, 1.30 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^\text{TM}$). Then, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 12 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 15 min. Saturated NH$_4$Cl$_\text{(aq)}$ (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (848 mg, 2.0 mmol, 2.0 eq.) in CH$_2$Cl$_2$ (10 mL) gave the crude product, which contained an 80:20 mixture (by $^1$H NMR spectroscopy) of ketones anti-213 and syn-213. Purification by flash column chromatography on silica using 98:2 CH$_2$Cl$_2$-acetone as eluent gave an 80:20 mixture (by $^1$H NMR spectroscopy) of ketones anti-213 and syn-213 (221 mg, 67%) as a colourless oil.

For $N$-Boc pyrrolidine 96, a peak at 1702 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1644 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 9 h, complete lithiation of $N$-Boc pyrrolidine
to give the lithiated intermediate was observed. The PhCHO trapping was not monitored by ReactIR™.

Lab Book Reference: AMI_97 + AMI_99

Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, DiComp) at rt under Ar. After cooling to −78 °C, a solution of N-Boc pyrrolidine 96 (225 mg, 1.01 mmol, 1.0 eq.) in Et₂O (2 mL) was added followed by a solution DPE 177 (221 mg, 1.31 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.) was added. The resulting solution was stirred at −78 °C for 1 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for a further 10 min. Saturated NH₄Cl(aq) (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (857 mg, 2.02 mmol, 2.0 eq.) in CH₂Cl₂ (10 mL) gave the crude product, which contained a 92:8 mixture (by ¹H NMR spectroscopy) of ketones anti-213 and syn-213. Purification by flash column chromatography on silica using 98:2 CH₂Cl₂-acetone as eluent gave a 92:8 mixture (by ¹H NMR spectroscopy) of ketones anti-213 and syn-213 (286 mg, 86%) as a colourless oil.

For N-Boc pyrrolidine 96, a peak at 1702 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1643 cm⁻¹ was observed which was assigned to νC=O in the lithiated intermediate. After a lithiation time of 50 min, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed. When PhCHO was added
(after a 65 min total lithiation time), the signal for the lithiated intermediate ($\nu_{C=O} = 1643 \text{ cm}^{-1}$) disappeared after 1 min, indicating complete trapping had occurred.

Lab Book Reference: AMI_101 + AMI_102

Et$_2$O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR$^\text{TM}$ probe (ReactIR$^\text{TM}$ 15, DiComp) at rt under Ar. After cooling to $-78 \degree C$, a solution of N-Boc pyrrolidine \textbf{96} (234 mg, 1.05 mmol, 1.0 eq.) in Et$_2$O (2 mL) was added followed by a solution tetra-isopropyl diamine \textbf{178} (311 mg, 1.36 mmol, 1.3 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR$^\text{TM}$). Then, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.36 mmol, 1.3 eq.) was added. The resulting solution was stirred at $-78 \degree C$ for 16 h. Then, PhCHO (211 mg, 0.20 mL, 2.00 mmol, 2.0 eq.) was added and the solution was stirred at $-78 \degree C$ for a further 15 min. Saturated NH$_4$Cl$_{aq}$ (10 mL) was added and the solution was then allowed to warm to rt over 30 min and the two layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organics were dried (MgSO$_4$), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (891 mg, 2.10 mmol, 2.0 eq.) in CH$_2$Cl$_2$ (10 mL) gave the crude product, which contained a $>$95:5 mixture (by $^1$H NMR spectroscopy) of ketones \textit{anti}-\textbf{213} and \textit{syn}-\textbf{213}. Purification by flash column chromatography on silica using 98:2 CH$_2$Cl$_2$-acetone as eluent gave a $>$95:5 mixture (by $^1$H NMR spectroscopy) of ketones \textit{anti}-\textbf{213} and \textit{syn}-\textbf{213} (54 mg, 16%) as a colourless oil and recovered starting material \textbf{96} (146 mg, 62%).

For N-Boc pyrrolidine \textbf{96}, a peak at 1702 cm$^{-1}$ was observed and assigned to $\nu_{C=O}$. After addition of s-BuLi, a new peak at 1648 cm$^{-1}$ was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 6.5 h, the ReactIR$^\text{TM}$ apparatus encountered
an error and data collection was stopped so a lithiation time could not be determined. The PhCHO trapping was not monitored by ReactIR™.

Lab Book Reference: AMI_164 + AMI_165

\( s\)-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of \(N\)-Boc pyrrolidine 96 (237 mg, 1.06 mmol, 1.0 eq.) in THF (7 mL) at \(-78 \degree C\) under Ar. The resulting solution was stirred at \(-78 \degree C\) for 4.5 h. Then, PhCHO (225 mg, 2.12 mmol, 2.0 eq., 0.22 mL) was added and the resulting solution was stirred at \(-78 \degree C\) for 10 min and then allowed to warm to rt. Saturated NH\(_4\)Cl\(_\text{(aq)}\) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et\(_2\)O (3 x 10 mL) and the combined organics were dried (MgSO\(_4\)), filtered and evaporated under reduced pressure to give the crude product. Using general procedure D, the crude product and DMP (898 mg, 2.12 mmol, 2.0 eq.) in CH\(_2\)Cl\(_2\) (10 mL) gave the crude product, which contained a 93:7 mixture (by \(^1\)H NMR spectroscopy) of ketones anti-213 and syn-213. Purification by flash column chromatography on silica using 98:2 CH\(_2\)Cl\(_2\)-acetone as eluent gave a 93:7 mixture (by \(^1\)H NMR spectroscopy) of ketones anti-213 and syn-213 (239 mg, 69%) as a colourless oil.

Lab Book Reference: AMI_74 + AMI_76

**ReactIR™ spectroscopic monitoring of the lithiation of \(N\)-Boc pyrrolidine 96 using \(s\)-BuLi/di-\(i\)-Pr bispidine 30**

\( s\)-BuLi/di-\(i\)-Pr bispidine 30

Et\(_2\)O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, SiComp) at rt under Ar. After cooling to \(-78 \degree C\), a solution of di-\(i\)-Pr bispidine 30 (302 mg, 1.4 mmol, 1.3 eq.) in Et\(_2\)O (2 mL) was added followed by a solution of \(N\)-Boc pyrrolidine
96 (245 mg, 1.1 mmol, 1.0 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol, 1.3 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 5.5 h.

For N-Boc pyrrolidine 96, a peak at 1701 cm⁻¹ was observed and assigned to ν₁C=O. After addition of s-BuLi, a new peak at 1647 cm⁻¹ was observed which was assigned to ν₁C=O in the lithiated intermediate. After a lithiation time of 5 h, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed.

Using general procedure A, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.39 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (239 mg, 1.07 mmol, 1.0 eq.) and di-i-Pr bispidine 30 (292 mg, 1.39 mmol, 1.3 eq.) in Et₂O (7 mL) for 5 h and then Me₃SiCl (232 mg, 0.27 mL, 2.14 mmol, 2.0 eq.) gave the crude product, which contained only starting material 96 (by ¹H NMR spectroscopy).

Using general procedure A, s-BuLi (1.00 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (223 mg, 1.00 mmol, 1.0 eq.) and di-i-Pr bispidine 30 (273 mg,
1.3 mmol, 1.3 eq.) in Et₂O (7 mL) for 5 h and then Me₂SO₄ (252 mg, 0.19 mL, 2.00 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave starting material pyrrolidine 96 (75 mg, 34%) as a colourless oil and a 90:10 mixture (by ¹H NMR spectroscopy of sulfonamides anti-218 and syn-218) of 2,3,4-trisubstituted pyrrolidines anti-211 and syn-211 (89 mg, 38%) as a colourless oil.

Lab Book Reference: AMI_36

(1S*,3aS*,7aR*) and (1R*,3aS*,7aR*)-1-Methyl-2-(4-methylbenzenesulfonyl)-2,3,3a,4,7,7a-hexahydro-1H-isoindole anti-218 and syn-218

![anti-218](image)

![syn-218](image)

TFA (427 mg, 0.29 mL, 3.75 mmol, 10 eq.) was added to a stirred solution of 2,3,4-trisubstituted pyrrolidine 211 (89 mg, 0.375 mmol, 1.0 eq.) in CH₂Cl₂ (7 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated NaHCO₃(aq) (20 mL) was added with vigorous stirring until gas evolution ceased. The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organics were dried (Na₂SO₄), filtered and evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ (4 mL) and Et₃N (46 mg, 0.06 mL, 0.45 mmol, 1.2 eq.) and p-TsCl (86 mg, 0.45 mmol, 1.2 eq.) were added. The resulting solution was stirred at rt for 16 h. Then, CH₂Cl₂ (10 mL) and 0.1 M HCl(aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product, which contained a 90:10 mixture (by ¹H NMR spectroscopy) of sulfonamides anti-218 and syn-218.

Lab Book Reference: AMI_42
(1R*,3aS*,7aR*) and (1S*,3aS*,7aR*)-2-[(tert-Butoxy)carbonyl]-2,3,3a,4,7,7a-hexahydro-1H-isooindole-1-carboxylic acid *anti*-212 and *syn*-212 and 2-methylbutanoic acid 240

Using general procedure C, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.04 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (232 mg, 1.04 mmol, 1.0 eq.) and di-*i*-Pr bispidine 30 (284 mg, 1.35 mmol, 1.3 eq.) in Et₂O (7 mL) for 5 h and then dry CO₂ was bubbled through for 30 min to give the crude product. Purification by flash column chromatography on silica using 50:49.5:0.5 EtOAc-hexane-AcOH as eluent gave a 90:10 mixture of carboxylic acids *anti*-212 and *syn*-212 (141 mg, 51%) as a white solid and an inseparable 60:40 mixture (by ¹H NMR spectroscopy) of carboxylic acid 240 and recovered starting material 96 (171 mg, i.e. 109 mg (47%) of starting material 96). Diagnostic signals for acid 240: ¹H NMR (400 MHz, CDCl₃) δ 1.16 (d, J = 7.0 Hz, 3H, CH₃), 0.93 (t, J = 7.5 Hz, 3H, CH₂Me).

Lab Book Reference: AMI_48

*tert-Butyl (1S*, 3aS*,7aR*)-1-(trimethylsilyl)-2,3,3a,4,7,7a-hexahydro-1H-isooindole-2-carboxylate *anti*-99

Et₂O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe (iC 10, SiComp) at rt under Ar. After cooling to −78 °C, a solution of di-*n*-Pr bispidine 105 (302
mg, 1.4 mmol, 1.3 eq.) in Et₂O (2 mL) was added followed by a solution of N-Boc pyrrolidine 96 (245 mg, 1.1 mmol, 1.0 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.4 mmol, 1.3 eq.) was added dropwise and the resulting solution was stirred at −78 °C for 1 h. Then, Me₃SiCl (0.27 mL, 2.16 mmol, 2.0 eq.) was added and the solution was stirred at −78 °C for 2 h. ReactIR™ monitoring indicated trapping was incomplete so the solution was warmed to rt over 30 min allowing complete trapping to occur. Saturated NH₄Cl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave a single diastereomer of 2,3,4-trisubstituted pyrrolidine anti-99 (207 mg, 64%) as a colourless oil.

For N-Boc pyrrolidine 96, a peak at 1701 cm⁻¹ was observed and assigned to νC=O. After addition of s-BuLi, a new peak at 1682 cm⁻¹ was observed which was assigned to νC=O in the prelithiation complex. A new peak at 1630 cm⁻¹ was also observed and this was assigned to the lithiated intermediate. After a lithiation time of 40 min, complete lithiation of N-Boc pyrrolidine 96 to give the lithiated intermediate was observed. When Me₃SiCl was added (after 1 h total lithiation time), the signal for the lithiated intermediate (νC=O = 1630 cm⁻¹) decreased extremely slowly during the 2 h incubation at −78 °C. Whilst the reaction was warming from −78 °C to rt the signal for the lithiated intermediate disappeared, indicating complete trapping of N-Boc pyrrolidine 96 had occurred.

Lab Book Reference: AMI_39
(15R*,3aS*,7aR*) and (1R*,3aS*,7aR*)-\( \text{tert-Butyl-1-methyl-2,3,3a,4,7,7a-hexahydro-1H-isooindole-2-carboxylate} \) \( \text{anti-211} \) and \( \text{syn-211} \)

Using general procedure A, \( \text{s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.42 mmol, 1.3 eq.)} \), \( \text{N-Boc pyrrolidine 96 (244 mg, 1.09 mmol, 1.0 eq.)} \) and \( \text{di-\( \text{n-Pr bispidine 105 (298 mg, 1.42 mmol, 1.3 eq.) in Et}_2\text{O (7 mL)} \) for 1 h and then Me}_2\text{SO}_4 (275 mg, 0.21 mL, 2.18 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 85:15 \text{hexane-EtOAc as eluent gave a 90:10 mixture (by } \text{H NMR spectroscopy of sulfonamides } \text{anti-218 and syn-218) of 2,3,4-trisubstituted pyrrolidines } \text{anti-211 and syn-211 (200 mg, 77%) as a colourless oil.}\)

\( \text{Lab Book Reference: AMI_40} \)

(15R*,3aS*,7aR*) and (1R*,3aS*,7aR*)-1-Methyl-2-(4-methylbenzenesulfonyl)-2,3,3a,4,7,7a-hexahydro-1H-isooindole \( \text{anti-218} \) and \( \text{syn-218} \)

\( \text{TFA (442 mg, 0.30 mL, 3.88 mmol, 10 eq.) was added to a stirred solution of 2,3,4-trisubstituted pyrrolidine 211 (92 mg, 0.388 mmol, 1.0 eq.) in CH}_2\text{Cl}_2 (7 mL) \) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated NaHCO\(_3\text{(aq)} \) (20 mL) was added with vigorous stirring until gas evolution ceased. The mixture was extracted with CH\(_2\text{Cl}_2 \) (3 x 10 mL) and the combined organics were dried (Na\(_2\text{SO}_4\)), filtered and evaporated under reduced pressure. The residue was dissolved in CH\(_2\text{Cl}_2 \) (4 mL) and Et\(_3\text{N} \) (47 mg, 0.06 mL, 0.466 mmol, 1.2 eq.) and \( p\text{-TsCl (89 mg, 0.466 mmol, 1.2 eq.) were added. The resulting solution was stirred at rt for 16 h. Then, CH\(_2\text{Cl}_2 \) (10 mL) and 0.1 M HCl\(_\text{(aq)} \) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH\(_2\text{Cl}_2 \) (3 x
10 mL) and the combined organics were dried (MgSO₄), filtered and evaporated under reduced pressure to give the crude product, which contained a 90:10 mixture (by ¹H NMR spectroscopy) of sulfonamides *anti*-218 and *syn*-218.

Lab Book Reference: AMI_45

\[(1R^*,3aS^*,7aR^*)\text{ and } (1S^*,3aS^*,7aR^*)-2-[(\text{tert-Butoxy})\text{carbonyl}]-2,3,3a,4,7,7a\text{-hexahydro-1H-isoindole-1-carboxylic acid} \text{ anti-}212 \text{ and } \text{ syn-}212\]

Using general procedure C, s-BuLi (1.1 mL of a 1.3 M solution in hexanes, 1.41 mmol, 1.3 eq.), N-Boc pyrrolidine 96 (242 mg, 1.08 mmol, 1.0 eq.) and di-*n*-Pr bispidine 105 (296 mg, 1.41 mmol, 1.3 eq.) in Et₂O (7 mL) for 1 h and then dry CO₂ was bubbled through for 30 min to give the crude product. Purification by flash column chromatography on silica using 50:49.5:0.5 EtOAc-hexane-AcOH as eluent gave a 94:6 mixture of carboxylic acids *anti*-212 and *syn*-212 (253 mg, 87%) as a white solid.

Lab Book Reference: AMI_41
Abbreviations

AcOH  Acetic Acid
aq.    Aqueous
Ar     Aryl
Bn     Benzyl
Boc    tert-Butyloxycarbonyl
bp     Boiling Point
br     Broad
Bu     Butyl
cm⁻¹   Wavenumber
Cy     Cyclohexyl
d      Doublet
dba    Dibenzylideneacetone
DEPT   Distortionless Enhancement by Polarisation Transfer
DFT    Density Functional Theory
DIPEA  N,N-diisopropylamine
DKR    Dynamic kinetic resolution
DMF    Dimethylformamide
DMP    Dess-Martin Periodinane
DMSO   Dimethylsulfoxide
dr     Diastereomeric Ratio
E⁺     Electrophile
eq.    Equivalent(s)
er     Enantiomeric Ratio
ESI    Electrospray Ionisation
Et₂O   Diethyl Ether
EtOAc  Ethyl Acetate
FT     Fourier Transform
g      Gram(s)
G      Gibbs Free Energy
ΔG‡    Gibbs Free Energy of activation
H      Enthalpy
ΔH‡    Enthalpy of activation
h      Hour(s)
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<th><strong>Abbreviation</strong></th>
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<td>$O$-$\text{7-azabenzotriazol-1-yl})-N,N,N',N'$-tetramethyluronium hexafluorophosphate</td>
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<td>HRMS</td>
<td>High resolution mass spectrometry</td>
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<td>Hertz</td>
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<tr>
<td>$i$-$\text{Pr}$</td>
<td>Isopropyl</td>
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<tr>
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rate_{init} \quad \text{Initial Rate}

\text{RHF} \quad \text{Restricted Hartree Fock}

\text{R_F} \quad \text{Retention Factor}

\text{rt} \quad \text{Room Temperature}

\text{s} \quad \text{Singlet}

\text{s-BuLi} \quad \text{sec-Butyllithium}

\text{t} \quad \text{Triplet}

\text{THF} \quad \text{Tetrahydrofuran}

\text{TFA} \quad \text{Trifluoroacetic acid}

\text{TLC} \quad \text{Thin Layer Chromatography}

\text{TMEDA} \quad \text{N,N,N',N'-Tetramethylethlenediamine}

\text{Trisyl} \quad \text{2,4,6-triisopropylbenzenesulfonyl}

\text{Ts} \quad \text{p-Toluenesulfonyl}

\text{TS} \quad \text{Transition State}

\text{UV} \quad \text{Ultraviolet}

\delta \quad \text{Chemical Shift}

\nu_{C=O} \quad \text{Carbonyl IR stretching frequency}
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