Lithiation/Trapping of *N*-Boc Piperazines and Synthesis of the (–)-Sparteine Surrogate

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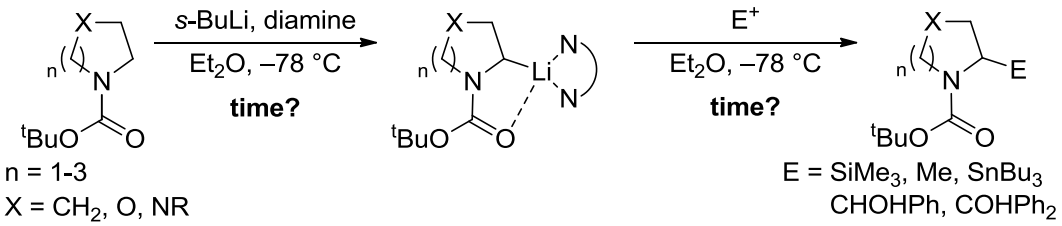
March 2014

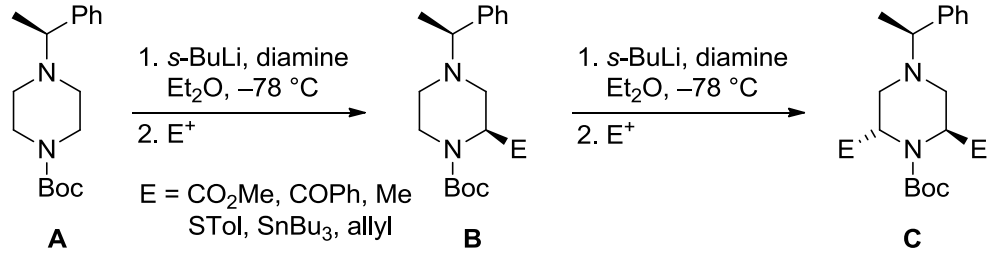
Abstract

This thesis describes some novel aspects of the *s*-BuLi mediated lithiation/trapping of *N*-Boc heterocycles, including a systematic investigation into the lithiation/trapping of *N*-Boc piperazines.

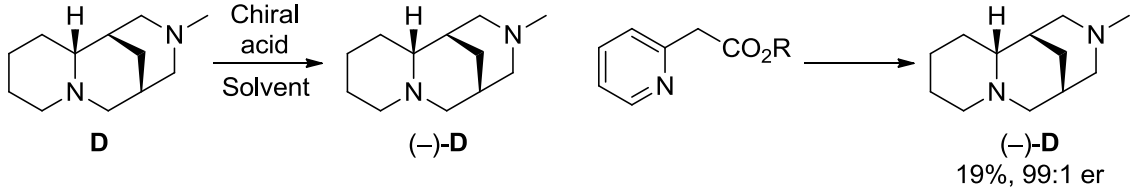
Chapter 2 details an *in situ* ReactIR™ investigation into the time required for both the lithiation and trapping events of some commonly used *N*-Boc heterocycles. The remarkable difference in the time taken for trapping with some electrophiles is of particular note.



The information garnered in this investigation was used to direct the racemic and asymmetric lithiation of *N*-Boc piperazines, as described in Chapters 3 and 4. A series of complications were encountered and overcome. The methodology culminated in the synthesis of enantiopure mono- and disubstituted *N*-Boc piperazines **B** and **C** through asymmetric lithiation/trapping of piperazine **A**.



In Chapter 5, an investigation into the synthesis of the (–)-sparteine surrogate (–)-**D** is reported. Two strategies are described: the synthesis and classic resolution of **D** and the synthesis of enantiopure (–)-**D** from commercially available precursors.



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Dedicated to the memory of Sue Firth

Acknowledgements

I would like to thank Professor Peter O'Brien for his encouragement, attention to detail and direction. Without his input and help, this research would have not been possible. I would also like to thank Professor Ian Fairlamb for his assistance and guidance as my independent panel member.

Next, I would like to thank the past and present members of the POB group who have made my time at York so enjoyable, as well as contributed to many helpful discussions. In no particular order, Graeme, Giorgio, Peter, Xiao, Dave, Giacomo, Nah, Mary, Sarah, Alice, Adam and Mickey. Thanks also to Parsons group members, Peter and Joe for the endless supply of glass and good humour. Additional thanks to the Taylor and Fairlamb groups for advice and loans of chemicals.

For the considerable support they have provided, I would like to thank Mike and Steve in stores, Heather for running the NMR service, Karl for mass spectrometry and to Graeme McAllister for making sure things worked properly.

I owe a debt of gratitude to several people at AstraZeneca who have helped me immensely. First, I would like to thank Leigh Ferris for his support and encouragement as my industrial supervisor. Thanks also to Karen Rome and Katy Hobday for help with GC and to Keith Mulholland for help with enzymatic resolutions.

I would like to thank my family for their love and support over the last four years. Finally, I would like to especially thank Helen for being by my side throughout, sharing the successes with me and for love and encouragement in the face of the endless failed reactions.

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.

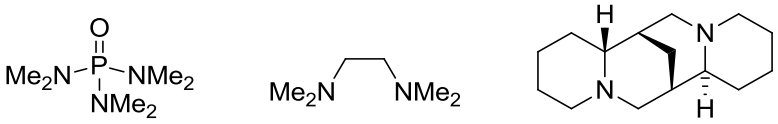
James Firth

Chapter One: Introduction

Organolithium reagents are of utmost importance to the modern synthetic chemist and since their discovery by William Schlenk in 1917,[1] they have become ubiquitous in organic synthesis. Modern organolithium chemistry was pioneered by Ziegler who, in 1930, showed that organolithium reagents could be formed from the reaction of lithium metal and alkyl or aryl halides; thus *n*-BuLi was born.[2] Further revolutionary work on the structure and reactivity of organolithiums was conducted by Ziegler, Wittig and in particular, Gilman.[3] Gilman showed that THF could be used to enhance the reactivity of *n*-BuLi and additionally, determined the temperatures and times for which many organolithiums are stable. This allowed the development of many of the common synthetic transformations used by organic chemists today, several of which have been used in the work presented in this thesis.[3]

Due to the significant covalent character of organolithiums, many alkyl and aryl lithium reagents are highly soluble in hydrocarbon solvents and are available commercially as solutions; these are often the starting point for the formation of organolithium reagents. A single carbon substituent does not provide sufficient stabilisation for the electron deficient lithium atom. Therefore, simple organolithium reagents in hydrocarbon solvents are founds as aggregates, often as hexamers, tetramers or dimers with the aggregation state governed by steric hindrance. For example, *n*-BuLi exists as a hexamer with the octahedral arrangement of the lithium atoms bridged by *n*-butyl ligands, whereas the more bulky *t*-BuLi exists as a tetramer.[4]

Coordinating ligands or solvents (such as Et_2O and THF) provide a source of electron density for the electron deficient lithium atoms. These ligands allow the formation of lower aggregates and hence greater reactivity, as originally observed by Gilman.[3] The modulation of the reactivity of organolithiums using ligands has become a cornerstone of synthetic organic chemistry, with ethereal solvents being used in almost all organolithium reactions. Importantly, the use of stoichiometric quantities of amine-containing ligands greatly enhances the reactivity of organolithiums.[4] Three commonly used amine ligands are shown in Figure 1.1.

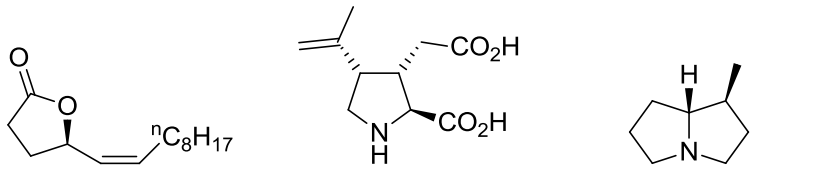


HMPA TMEDA (–)-sparteine

Figure 1.1

Many bioactive natural products and drug molecules exist as single stereoisomers due to the ability of natural systems to discriminate between the enantiomers of a compound. This proclivity of the natural world is both a blessing and a burden for the synthetic chemist, requiring the continued development of novel methods for the synthesis of complex enantioenriched organic compounds. This fundamental work allows us, as a community, to generate complex biologically active molecules with a view to improving the health and well-being of humanity.

Organolithium-based methodology has played a significant role in the advancement of the types molecules that can be predictably synthesised. A whole host of biologically active molecules have been synthesised using functionalised organolithium reagents.[5] A few of the many examples include the beetle pheromone (–)-japonilure,[6] (–)-kainic acid[7] and the alkaloid (+)-pseudoheliotridane[8] (Figure 1.2).

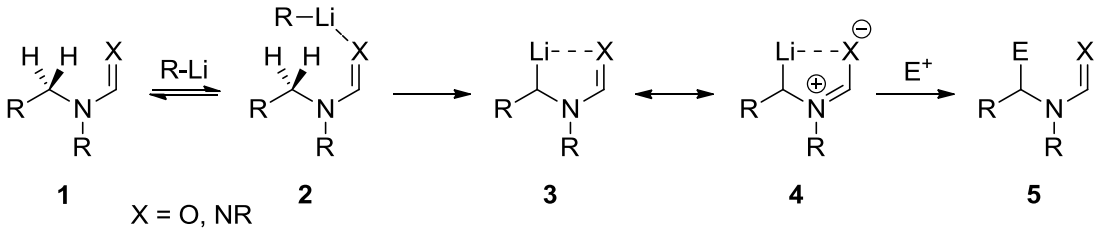


(–)-japonilure (–)-kainic acid (+)-pseudoheliotridane

Figure 1.2

1.1 Directed Deprotonation by Organolithium Reagents: The Complex Induced Proximity Effect

Directed deprotonation to generate dipole-stabilised carbanions *α* to heteroatoms is an important area of organolithium chemistry and has been widely investigated over the past few decades. This synthetic strategy has been used extensively for the incorporation of electrophilic partners, generating a new stereocentre. Typically, a directing group is appended to a heteroatom, for example nitrogen, which then allows lithiation *α* to the heteroatom substituent. The Lewis basic directing group of **1** facilitates coordination of an organolithium species resulting in the reversible formation of complex **2** prior to the lithiation event (Scheme 1.1). This effect was termed the "complex induced proximity effect" (CIPE) by Beak and Meyers in 1986.[9] Subsequent deprotonation *α* to the heteroatom results in generation of an organolithium species **3**, which can be stabilised by an adjacent positive charge on the heteroatom as in **4**, this is known as a dipole-stabilised carbanion.[10] Electrophilic trapping then releases the *α*-functionalised substrate **5**.

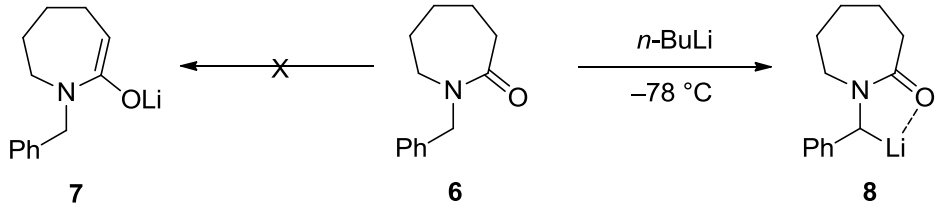


Scheme 1.1 Mechanism of directed deprotonation

Complex **2** is referred to as the pre-lithiation complex[11] and its formation results in an increased reactivity of the substrate towards deprotonation by holding the alkyllithium reagent in close proximity to the acidic proton. Several reviews of the use of directed deprotonation and the complex induced proximity effect have been published by Beak.[12-14] Strong experimental evidence for the existence of the CIPE in systems such as that depicted in Scheme 1.1 has been presented.[14]

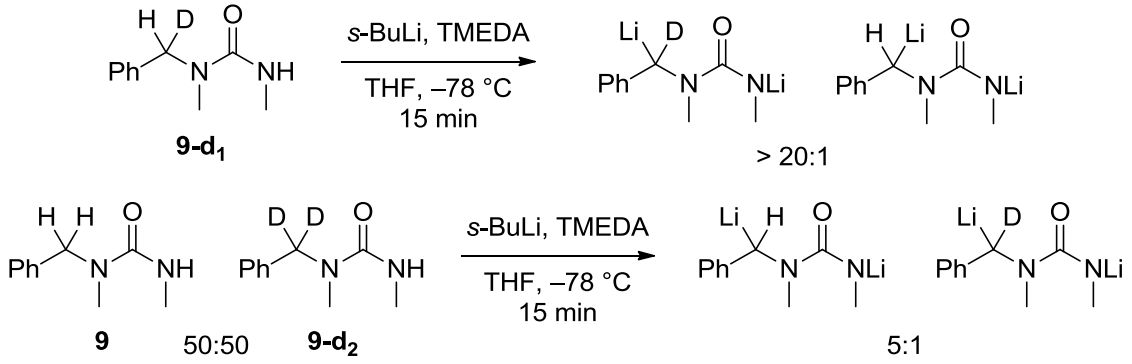
The complex induced proximity effect can control the regioselectivity of the lithiation of suitably configured substrates, for example benzyl carprolactam **6**. The thermodynamically favoured reaction would be removal of the methylene proton to

generate amide enolate **7**. In fact, kinetic deprotonation at the benzyl position occurs, directed by the CIPE, to give **8** (Scheme 1.2).[9]



Scheme 1.2

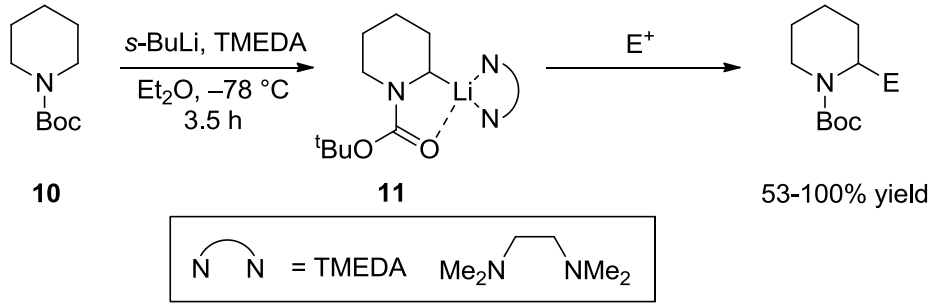
Although the CIPE model explains both the ability to effect *α*-deprotonation of relatively unreactive substrates and the prevalence for the formation of kinetic products, there was debate over the existence of a discrete pre-lithiation species. An alternative proposed by Beak was termed the "kinetically enhanced metalation" model where the directing group kinetically accelerates the proton transfer to the base by binding in the transition state for the deprotonation.[15] In other words, deprotonation is a single step process accelerated by the directing group, rather than a two step process as required by the CIPE. To distinguish between the two possibilities Beak performed an elegant set of deprotonation experiments using a urea substrate and assessed the kinetic isotope effects (Scheme 1.3). Lithiation of mono-deuterated urea **9-$\mathbf{d_1}$** with *s*-BuLi/TMEDA at –78 °C resulted in a >20:1 preference for removal of the proton over the deuterium. This was expected due to the kinetic isotope effect. Lithiation of a 50:50 mixture of undeuterated **9** and bis-deuterated **9-$\mathbf{d_2}$** resulted in a 5:1 mixture of lithiated products. This implies that deprotonation of urea **9** proceeds, at least in part, *via* a two step process. The first step was thought to be a slow, rate determining formation of a pre-lithiation complex followed by rapid removal of the benzylic proton in the second step. If lithiation was to proceed *via* a one-step kinetically enhanced metalation process then a >20:1 kinetic isotope effect would be observed. The same kinetic isotope ratio would also have been detected if deprotonation was the rate determining step within the two step sequence.



Scheme 1.3 Kinetic isotope effect in the lithiation of **9**

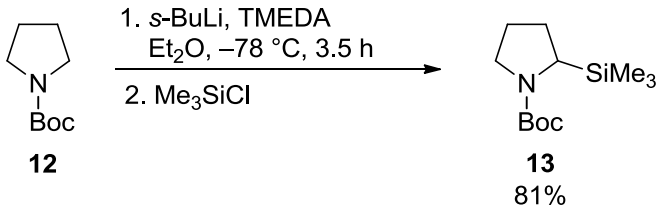
Additional evidence for the existence of the pre-lithiation complex and CIPE arises from studies into the kinetics of the asymmetric deprotonation of nitrogen heterocycles (see Scheme 1.11). Furthermore, direct observation of such complexes with *in situ* ReactIR™ spectroscopy has been performed and will be discussed in detail in Chapter 2.

Beak, Seebach and Meyers pioneered the development of CIPE lithiation techniques for lithiation adjacent to nitrogen, introducing a range of directing groups including amides,[10,16-22] nitrosamines[23,24] and formamidines[25-28] amongst others.[12] More recent examples from the groups of Metallinos[29,30] and Hodgson[31-33] include the use of ureas and thioamides as directing groups respectively. The requirements for a synthetically useful directing group are an ability to coordinate to the organolithium species (Lewis basicity), low reactivity towards nucleophilic attack and facile methods for incorporation into, and removal from, the substrate. A breakthrough came in 1989 when Beak introduced the use of a Boc group as a directing group for the *α*-lithiation of *N*-Boc heterocycles.[34] Deprotonation of *N*-Boc piperidine **10** was accomplished using *s*-BuLi and TMEDA in Et_2O at –78 °C for 3.5 h to give lithiated intermediate **11** (Scheme 1.4). Subsequent trapping with electrophiles gave *α*-substituted piperidines in 53-100% yield. Electrophiles used included Me_3SiCl, Bu_3SnCl, dimethyl sulfate, diphenyl disulfide and benzaldehyde.



Scheme 1.4

In the pioneering investigation a range of *N*-Boc heterocycles were investigated, including *N*-Boc pyrrolidine **12**. Lithiation of **12** followed by trapping with Me_3SiCl resulted in *α*-silyl pyrrolidine **13** in 81% yield (Scheme 1.5).



Scheme 1.5

The use of the Boc group to direct the lithiation of nitrogen heterocycles was quickly adopted by the synthetic community. As well as being effective in facilitating *α*-lithiation, the Boc group is highly resistant to nucleophilic attack. The Boc group is simple to introduce, usually with di-*tert*-butyl dicarbonate, and simple to remove under a range of conditions, usually with TFA or HCl.[35]

1.2 Lithiation/Trapping of *N*-Boc Heterocycles

Over the past 25 years, directed lithiation, and in particular, asymmetric directed lithiation has developed into a powerful method for the generation of *α*-substituted *N*-Boc heterocycles and a review of this work has recently been published.[36] Generally, enantioselective lithiation has been performed using a strong organolithium base, such as *s*-BuLi, in the presence of a chiral ligand. Historically, (–)-sparteine, a naturally occurring lupin alkaloid, has been the most important chiral ligand for asymmetric deprotonation chemistry (Figure 1.3).[4] It was first used by Nozaki and Noyori for the synthesis of cyclic allenes and in the asymmetric addition of organolithium or Grignard reagents to unsymmetrical ketones. However, these transformations proceeded with poor levels of enantioselectivity.[37-39] (–)-Sparteine is extracted from scotch broom and has, until recently, been cheap and commercially available. Its enantiomer, (+)-sparteine, although being a natural product was, until recently, unavailable from commercial suppliers (Figure 1.3).

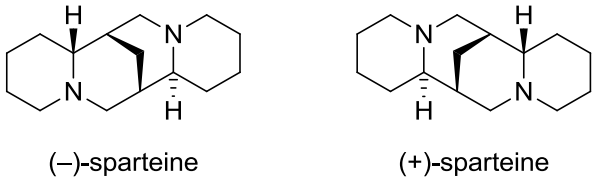
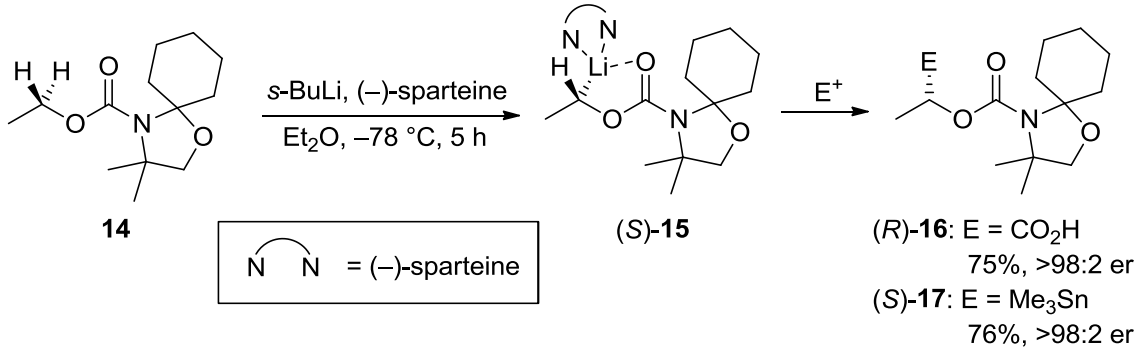


Figure 1.3

The use of (–)-sparteine in asymmetric deprotonation chemistry was first reported by Hoppe in 1989 for the lithiation of prochiral alkenyl carbamates. Lithiation, followed by selective crystallisation of one diastereomer of the lithiated intermediate, subsequent transmetalation to titanium and treatment with aldehydes led to homo-aldol products with good levels of enantioselectivity.[40]

More importantly, Hoppe published a pioneering report on the first enantioselective lithiation/trapping reaction in 1990.[41] Treatment of *O*-alkyl carbamate **14** with *s*-BuLi/(–)-sparteine at –78 °C in Et_2O for 5 h effected asymmetric deprotonation *via* the CIPE to give lithiated intermediate (*S*)-**15**. Trapping with CO_2 or Me_3SnCl proceeded with good yields and levels of enantioselectivity, giving both (*R*)-**16** and (*S*)-**17** in >98:2 er and in 75% and 76% yields respectively (Scheme 1.6).

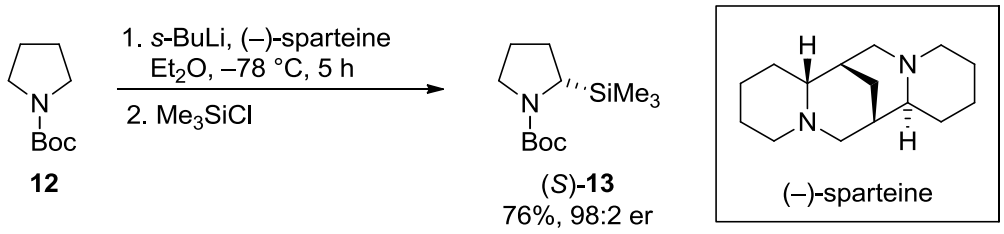


Scheme 1.6

The absolute stereochemistry was ascertained by comparison of the optical rotation of (*R*)-**16** with a sample synthesised from (*R*)-lactic acid. Hoppe postulated that the organolithium intermediate (*S*)-**15** was configurationally stable and that trapping occurred with retention of configuration.

1.2.1 Asymmetric Lithiation/Trapping of *N*-Boc Pyrrolidine

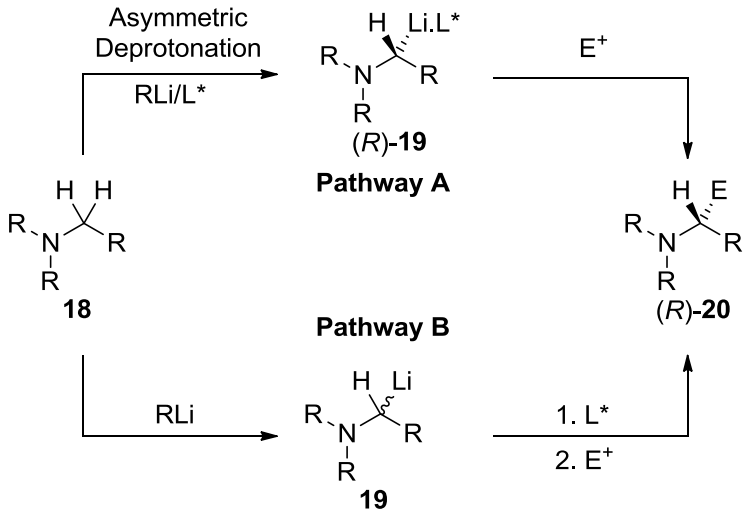
In 1991, a seminal report by Beak and Kerrick applied Hoppe's enantioselective deprotonation methodology to *N*-Boc pyrrolidine **12**.[42] Asymmetric deprotonation of **12** was accomplished using *s*-BuLi/(–)-sparteine at –78 °C in Et_2O for 4-6 h. Subsequent trapping with electrophiles gave *α*-substituted pyrrolidines in good yield (55-76%) and excellent levels of enantioselectivity (94:6-98:2 er). In one example, the use of Me_3SiCl as the electrophile gave *α*-silyl pyrrolidine (*S*)-**13** in 76% yield and 98:2 er (Scheme 1.7). The absolute configuration of the products was confirmed by comparison with products derived from (*S*)-proline.



Scheme 1.7

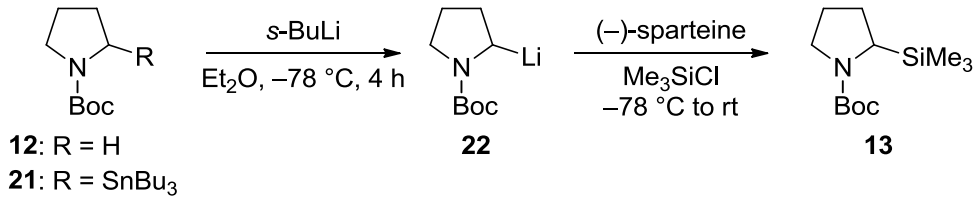
Asymmetry in chiral ligand mediated lithiation/trapping reactions requires diastereomeric interactions within the sequence, which is provided by the chiral diamine coordinating to the organolithium reagent. Two mechanisms for the observed

stereoselectivity in the lithiation/trapping of **18** were feasible (Scheme 1.8). First (Pathway A), it was proposed that the enantiodetermining step was an asymmetric deprotonation, where the organolithium/diamine complex acted as a strong chiral base resulting in a diastereoenriched, configurationally stable organolithium complex (*R*)-**19**. This then reacted stereospecifically with an electrophile to give the enantioenriched *α*-substituted product (*R*)-**20**. Alternatively (Pathway B), a post-deprotonation asymmetric substitution could occur. Deprotonation with the strong base would give racemic lithiated species **19**. Enantioenriched products (*R*)-**20** could be obtained from **19** under the influence of the chiral ligand by different pathways depending upon the rate of epimerisation of **19** relative to the rate of electrophile trapping.



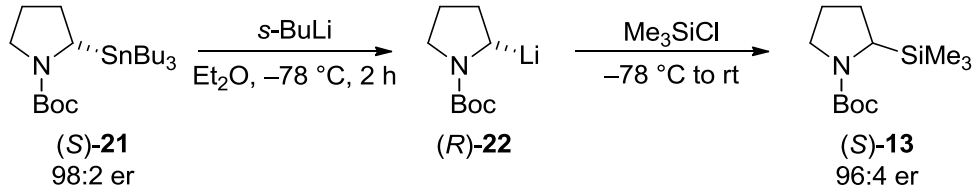
Scheme 1.8 Postulated mechanisms for enantioenrichment in lithiation/trapping reactions

To probe the mechanism by which enantioenrichment was induced, Beak performed a series of elegant experiments.[13] First, (–)-sparteine and Me_3SiCl were added to a sample of racemic 2-lithio-*N*-Boc pyrrolidine **22**, generated either by deprotonation of *N*-Boc pyrrolidine **12** or Sn/Li exchange of stannane **21** using *s*-BuLi (Scheme 1.9). The *α*-substituted pyrrolidine **13** isolated was essentially racemic and thus ruled out a post-deprotonation enantiodetermining step.



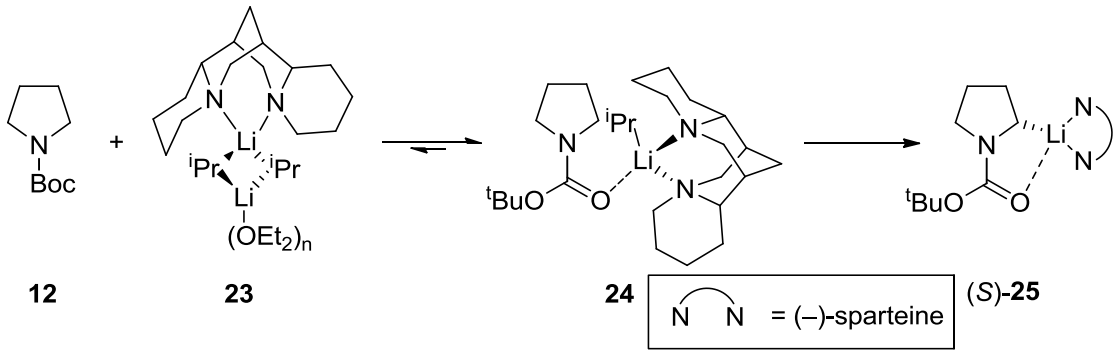
Scheme 1.9

Next, enantioenriched stannane (*S*)-**21** (98:2 er) was treated with *s*-BuLi to induce Sn/Li exchange, giving lithiated intermediate (*R*)-**22**. Trapping with Me_3SiCl then gave (*S*)-**13** with 96:4 er (Scheme 1.10). This shows conclusively that 2-lithio pyrrolidine (*R*)-**22** was configurationally stable at –78 °C for at least the time required for electrophilic trapping to occur and that asymmetric deprotonation was the enantiodetermining step (see Scheme 1.8, Pathway A).



Scheme 1.10

An investigation into the kinetics of the deprotonation of *N*-Boc pyrrolidine **12** with *i*-PrLi/(–)-sparteine complex **23** was performed by Beak with a view to elucidating the mechanism of deprotonation (Scheme 1.11).[11] It was found that the reaction was zero-order with respect to organolithium/diamine complex **23**. This observation rules out a single step deprotonation event from *N*-Boc pyrrolidine **12**. A mechanism that can account for the observed non-dependence of organolithium concentration on reaction rate is the rapid formation of a pre-lithiation complex **24** followed by rate-determining deprotonation to give lithiated intermediate (*S*)-**25**. Beak proposed complex **24** as the pre-lithiation complex, amongst several possible complexes, due to the close proximity of the chiral diamine to the reaction centre.



12 **23** **24** (*S*)-**25**

Scheme 1.11 Mechanism of CIPE asymmetric deprotonation

Computational studies into the deprotonation of **12** using an *i*-PrLi/(–)-sparteine complex were reported by Wiberg and Bailey.[43] It was shown that the *pro*-S proton was removed favourably due to a steric phenomenon. The transition state for removal of the *pro*-R proton was 3.2 kcal mol^{-1} higher in energy than the corresponding *pro*-S transition state due to the former being more sterically congested.

Although enantioselective deprotonation of *N*-Boc pyrrolidine **12** using *s*-BuLi/(–)-sparteine is highly successful giving rise to a range of enantioenriched products, the system suffers from one major intrinsic limitation. The natural alkaloid (–)-sparteine was, until recently, only available in bulk as one enantiomer. This considerable drawback precludes the synthesis of the opposite enantiomeric series of products. The total synthesis of (+)-sparteine and a synthesis of (–)-sparteine that would be applicable to the synthesis its enantiomer has been achieved by Aubé and O'Brien respectively.[44,45] However, these syntheses are not practical for the synthesis of (+)-sparteine on a multi-gram scale. Initial attempts to find other ligands that would induce comparable levels of enantioselectivity were moderately successful.[46,47]

In 2002, the O'Brien group published the first practical (+)-sparteine surrogate (+)-**26**.[48] It was designed to mimic (+)-sparteine, but it lacked the D ring as well as one of the stereogenic centres (Figure 1.4).[49] Structural comparisons of (+)-sparteine and diamine (+)-**26** complexed to lithium, as well as the calculated transition state for the deprotonation reaction suggested that the D ring was not essential for enantioinduction.[50] Synthesis of (+)-sparteine surrogate (+)-**26** was accomplished in three steps from (–)-cytisine (see Scheme 5.1 for details).[51]

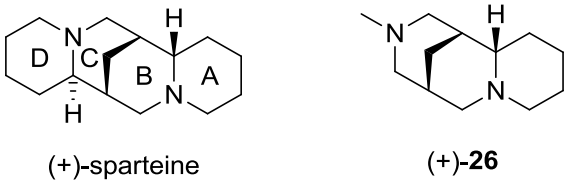
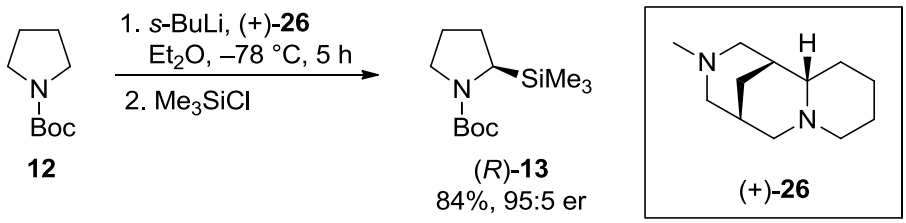


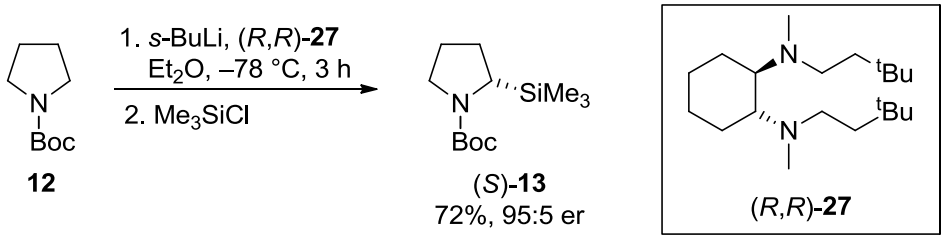
Figure 1.4 Design of the (+)-sparteine surrogate (+)-**26**

It was shown that (+)-sparteine surrogate (+)-**26** was comparable to (–)-sparteine for the lithiation/trapping of *N*-Boc pyrroline **12** in terms of yield and enantioselectivity. Lithiation of **12** with *s*-BuLi/(+)-**26** at –78 °C in Et_2O for 5 h and subsequent trapping with Me_3SiCl gave *α*-silyl pyrrolidine (*R*)-**13** in 84% yield and 95:5 er (Scheme 1.12).



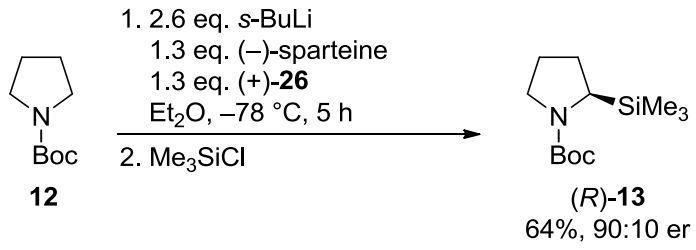
Scheme 1.12

O'Brien and co-workers later reported the use of the Alexakis diamine[52] (*R*,*R*)-**27** as a ligand for the enantioselective *s*-BuLi mediated lithiation/trapping of *N*-Boc pyrrolidine **12** (Scheme 1.13). Synthesis of *α*-silyl pyrrolidine (*S*)-**13** was accomplished in 72% yield and 95:5 er after lithiation of *N*-Boc pyrrolidine **12** using *s*-BuLi/(*R*,*R*)-**27** at –78 °C in Et_2O for 3 h before trapping with Me_3SiCl. The yield and enantioselectivity were comparable with those obtained in the same reaction with (–)-sparteine and (+)-sparteine surrogate (+)-**26**. Importantly, the synthesis of the Alexakis diamine **27** begins with resolution of cyclohexane-1,2-diamine with tartaric acid allowing both enantiomers to be synthesised.



Scheme 1.13

Understandably, the suitability of a diamine for asymmetric lithiation chemistry has been assessed by evaluation of the level of enantioselectivity of products obtained. Although this method is useful for identifying excellent ligands in terms of enantioinduction, it gives no information about the reactivity of a particular *s*-BuLi/diamine complex. Thus, O'Brien and co-workers performed competition experiments to determine a relative reactivity series for some commonly used chiral and achiral diamines.[53] Lithiation of *N*-Boc pyrrolidine **12** in the presence of 2.6 eq. of *s*-BuLi, 1.3 eq. of (–)-sparteine and 1.3 eq. of (+)-sparteine surrogate (+)-**26**, followed by trapping with Me_3SiCl led to a surprising result (Scheme 1.14). Silyl pyrrolidine (*R*)-**13** was isolated in 64% yield with a 90:10 er, i.e. the same sense of enantioinduction as seen with (+)-sparteine surrogate (+)-**26**. This showed that *s*-BuLi/(+)-**26** was much more reactive than *s*-BuLi/(–)-sparteine for the lithiation of *N*-Boc pyrrolidine **12**. A range of such competition experiments was performed with diamines and (–)-sparteine and the relative reactivity series of a selection of diamines is shown in Figure 1.5.



Scheme 1.14

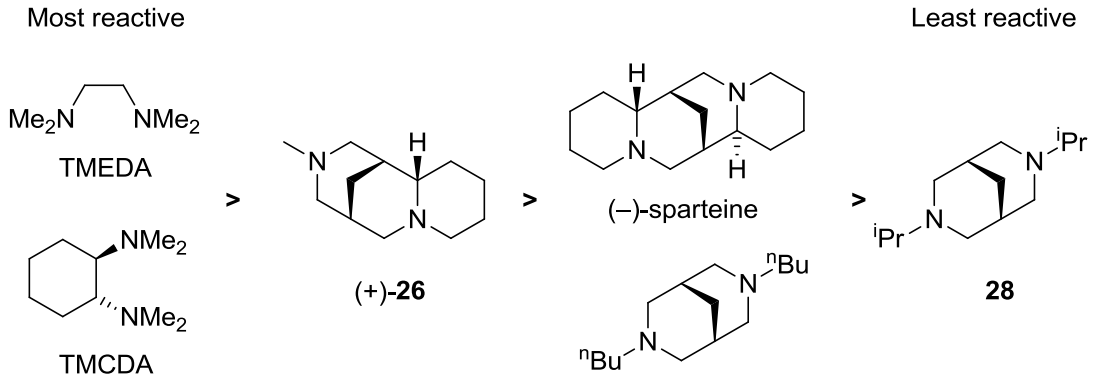


Figure 1.5 Reactivity series of a selection of diamines

In contrast to asymmetric lithiations in Et_2O, it has been observed that lithiation of substrates using *s*-BuLi/(–)-sparteine in THF proceed with negligible levels of enantioselectivity.[54,55] This has been attributed to the THF complexing preferentially to

the organolithium.[56] As part of a detailed study, O'Brien and co-workers have shown that this was not the case when using *s*-BuLi/(+)-sparteine surrogate (+)-**26** in THF. This observation was guided by investigating the solution structure of *i*-PrLi/chiral diamine complexes in Et_2O-d_{10} and THF-d_8 at –78 °C using ^{6}Li and ^{13}C NMR spectroscopy experiments.[57] Beak showed, through analogous NMR spectroscopic experiments, that a complex of *i*-PrLi (an achiral model for *s*-BuLi) and (–)-sparteine in Et_2O existed as heterodimer **23** (Figure 1.6).[58] O'Brien found that a complex of *i*-PrLi and (+)-sparteine surrogate (+)-**26** in Et_2O existed as a homodimer **29**. The sterically less hindered (+)-**26** presumably allowed homodimer formation. When analogous experiments were conducted in THF-d_8, it was found that (–)-sparteine did not displace THF from the organolithium complex until 3.0 eq. of (–)-sparteine (relative to *i*-PrLi) were added. In contrast, addition of 1.0 eq. of (+)-**26** resulted in the formation of a monomeric complex **30** of *i*-PrLi and (+)-**26**.

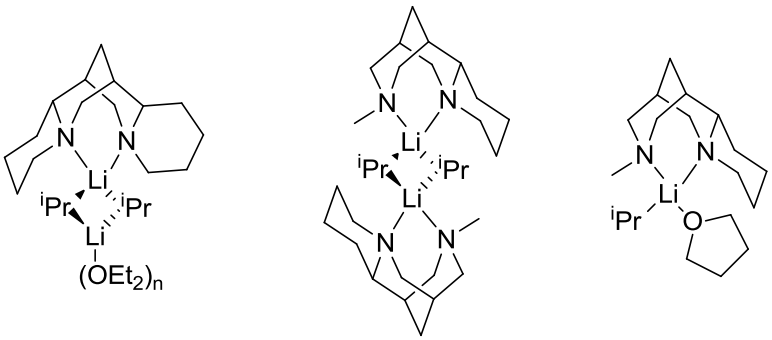
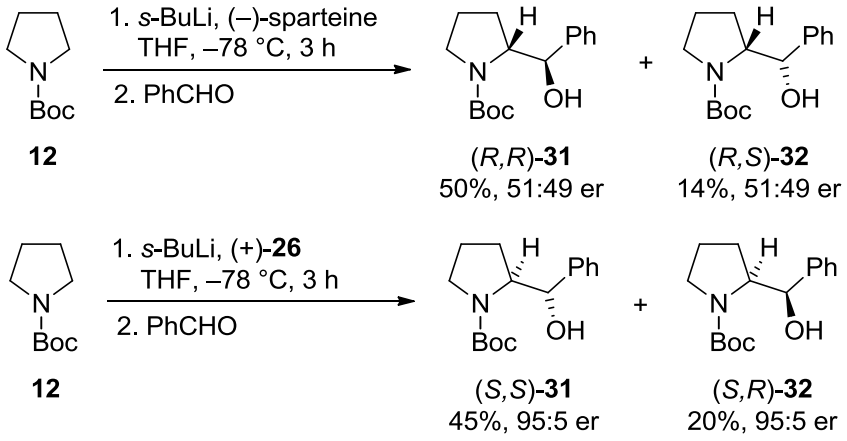


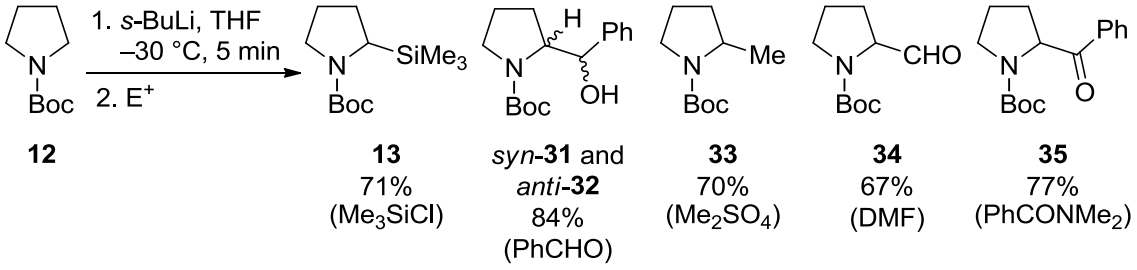
Figure 1.6 Solution structures of *i*-PrLi and (–)-sparteine or (+)-**26**

Whereas (–)-sparteine does not form chiral organolithium complexes in THF, the (+)-sparteine surrogate (+)-**26** does. This result has far reaching consequences for organolithium chemistry; asymmetric lithiation adjacent to heteroatoms in THF is possible with the (+)-sparteine surrogate (+)-**26** but not with (–)-sparteine. For example, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine in THF at –78 °C for 5 h, followed by trapping with benzaldehyde gave (*R*,*R*)-**31** in 50% yield and (*R*,*S*)-**32** in 14% yield and both diastereomers had enantiomeric ratios of 51:49 er (Scheme 1.15). This was indicative of lithiation proceeding *via* a *s*-BuLi/THF complex, as indicated by the NMR spectroscopic experiments. Conversely, a comparable reaction with (+)-**26** resulted in (*S*,*S*)-**31** being isolated in 45% yield and (*S*,*R*)-**32** in 20% yield, both with high levels of enantioselectivity (95:5 er).



Scheme 1.15 *s*-BuLi/chiral diamine mediated lithiation/trapping of **12** in THF

The observation that (–)-sparteine does not form complexes with *s*-BuLi in THF, but lithiation/trapping still occurs to give racemic products, was turned into an advantage by O'Brien; racemic lithiation/trapping could be performed without a the use of a diamine. Building upon this observation, an operationally simple, fast, diamine-free racemic lithiation/trapping of *N*-Boc heterocycles in THF at –30 °C was developed.[59] Racemic *α*-substituted *N*-Boc pyrrolidines were obtained through lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi in THF at –30 °C for 5 min followed by trapping. A wide range of electrophiles were tolerated, giving racemic *α*-substituted pyrrolidines **13**, **31**-**35** in 67-84% yield (Scheme 1.16). This chemistry was also applied to the synthesis of *α*-functionalised *N*-Boc imidazolidine and *N*-Boc piperazine products.

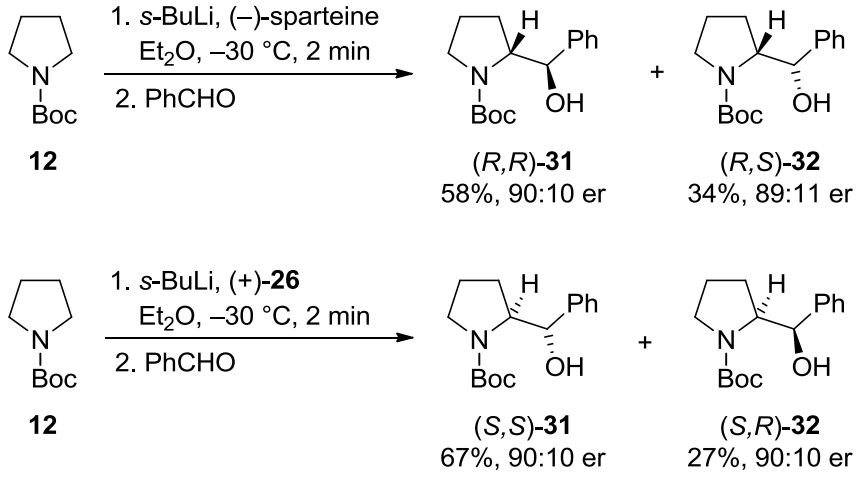


Scheme 1.16 Racemic Lithiation/Trapping of **12** in THF

With the success of the 'high temperature' racemic lithiation of *N*-Boc heterocycles, Gelardi and O'Brien set about an investigation of the asymmetric high temperature lithiation of *N*-Boc pyrrolidine **12** in order to develop a more efficient, sustainable procedure.[60] Raising the temperature above –78 °C was envisaged to require substantial reaction optimisation. The following salient points were identified: (i) lithiation at

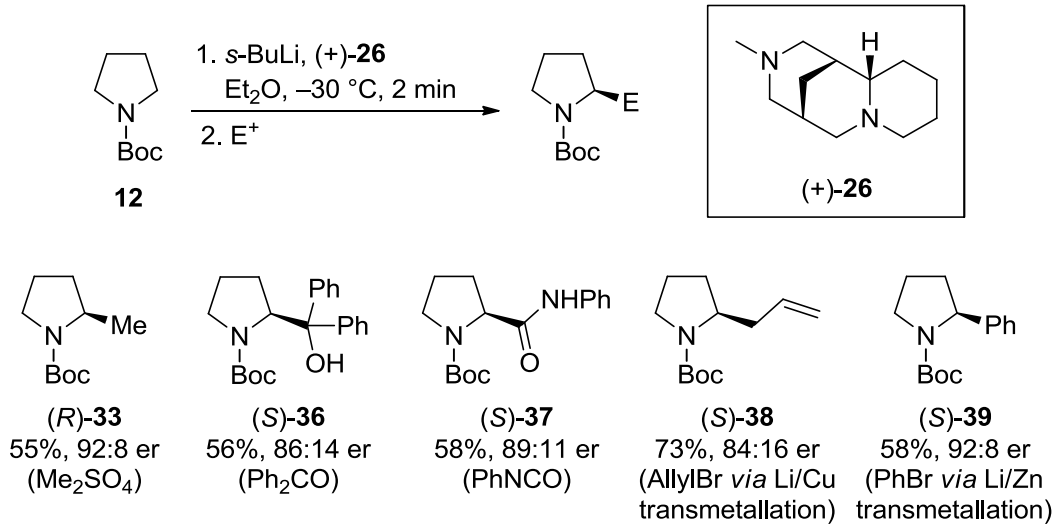
higher temperatures would take a shorter time to reach completion; (ii) the chemical stability of the lithiated *N*-Boc heterocycles may be compromised at higher temperatures; (iii) the enantioselectivity (i.e., the kinetic selectivity due to the interaction of the *s*-BuLi/diamine complex with the *N*-Boc heterocycle) would be a function of temperature; and, (iv) the configurational stability of the lithiated intermediate would be compromised at high temperatures.[61]

Significant experimentation led to the development of optimised conditions. Lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi and either (–)-sparteine or (+)-sparteine surrogate (+)-**26** in Et_2O at –30 °C for 2 min was followed by trapping. Employment of (–)-sparteine and trapping with benzaldehyde gave (*R*,*R*)-**31** in 58% yield and 90:10 er and (*R*,*S*)-**32** in 34% yield and 89:11 er (Scheme 1.17). Access to antipodes (*S*,*S*)-**31** and (*S*,*R*)-**32** in 67% yield (90:10 er) and 27% (90:10 er) respectively was accomplished using (+)-sparteine surrogate (+)-**26**. A small reduction in enantiomeric ratio occurs in comparison with reactions at –78 °C (see Scheme 1.13). This was probably due to a reduction in the kinetic selectivity of the deprotonation.



Scheme 1.17 'High temperature' asymmetric lithiation/trapping of **12**

The electrophile scope was investigated with *s*-BuLi/(+)-sparteine surrogate (+)-**26** using the optimised conditions. A further five *α*-substituted *N*-Boc pyrrolidines **33, 36-39** were synthesised in 55-73% yield and 84:16-92:8 er (Scheme 1.18).



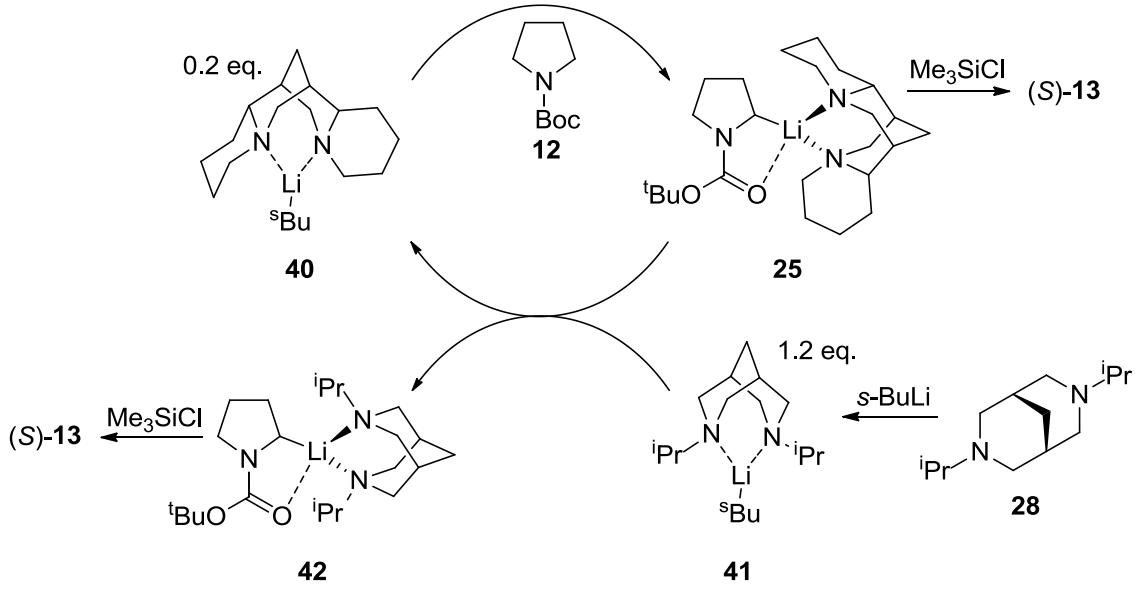
Scheme 1.18 Asymmetric Lithiation/Trapping of **12** with *s*-BuLi/(+)-**26**

2-Allyl pyrrolidine (*S*)-**38** was accessed through a Li/Cu transmetallation before trapping, whereas 2-phenyl pyrrolidine (*S*)-**39** was available through a Li/Zn transmetalation then Negishi coupling (see Section 1.3 for discussion of these methodologies). This high temperature asymmetric lithiation methodology was also applied to *N*-Boc piperidine **10** and *N*-Boc piperazine systems with slightly modified reaction conditions.

The requirement for stoichiometric amounts of the chiral diamines is a drawback of the asymmetric lithiation methodology. Initial attempts at using a substoichiometric amount of (–)-sparteine resulted in products being isolated in poor yield and er due to lack of catalytic turnover, as the diamine does not easily dissociate from the lithiated intermediate.[62]

To provide a solution to this problem, the O'Brien group developed a catalytic asymmetric lithiation protocol using a ligand exchange approach.[63] This process allows a chiral diamine to be recycled by exchange with a stoichiometric amount of a second ligand. Scheme 1.19 details the proposed catalytic cycle for the catalytic lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi, (–)-sparteine and achiral bispidine **28**. *N*-Boc pyrrolidine **12** underwent lithiation with a complex of *s*-BuLi/(–)-sparteine **40** (present in a substoichiometric quantity, 0.2 eq.) to give lithiated complex **25**. Then, ligand exchange occurred between the *s*-BuLi/achiral bispidine complex **41** and the *N*-Boc pyrrolidine/(–)-sparteine complex **25**. This regenerated the reactive *s*-BuLi/(–)-sparteine complex **40** and allowed catalytic turnover. Finally electrophilic trapping of **25** or **42**

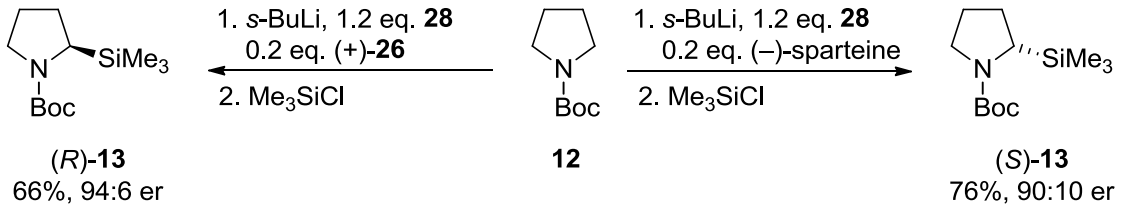
with, for example Me_3SiCl, then formed the desired *α*-substituted *N*-Boc pyrrolidine (*S*)-**13**.



Scheme 1.19 Mechanism of the catalytic asymmetric lithiation of **12**

There are three requirements that must be met for this approach to succeed. First, ligand exchange must be able to occur. Secondly, organolithium species **25** and **42** must be configurationally stable and finally, deprotonation by the *s*-BuLi/(–)-sparteine complex **40** must be significantly faster than by the achiral *s*-BuLi/bispidine complex **41**.

When lithiation of *N*-Boc pyrrolidine **12** was performed with *s*-BuLi, 0.2 eq. of (–)-sparteine and 1.2 eq. of bispidine **28**, followed by trapping with Me_3SiCl, *α*-silyl pyrrolidine (*S*)-**13** was isolated in 76% yield and 90:10 er (Scheme 1.20). An analogous catalytic lithiation in the presence 0.2 eq. of (+)-sparteine surrogate (+)-**26** and 1.2 eq. of **28** gave (*R*)-**13** in 66% yield and 94:6 er.

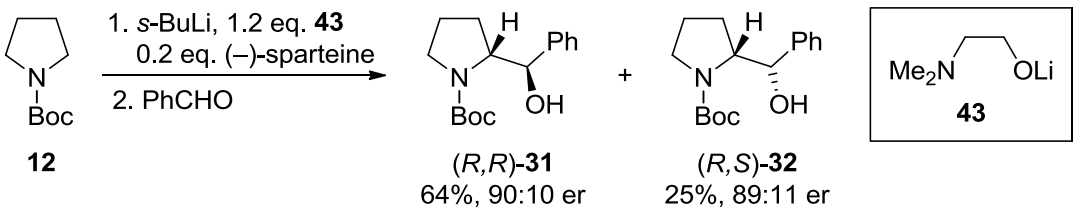


Scheme 1.20

Only a small decrease in enantiomeric ratio was seen, compared to the stoichiometric method (see Scheme 1.13). This was due to the significantly lower reactivity of the *s*-BuLi/bispidine **28** complex **41** relative to the *s*-BuLi/(–)-sparteine complex **40**. The use of (+)-**26** resulted in a better enantiomeric ratio than with (–)-sparteine due to the increased reactivity of the *s*-BuLi/(+)-**26** system.

One major drawback of this system was that the achiral bispidine **28** was not commercially available and had to be synthesised. However, its synthesis was accomplished in two steps with a good yield.[64,65] Further work led to the development of other stoichiometric diamines suitable for the two-ligand catalysis methodology, although they also required synthesis.[53,66] Another problem encountered was that the stoichiometric diamines could not be separated from the chiral diamines (–)-sparteine or (+)-**26**, precluding the recovery and re-use of the valuable chiral ligands.

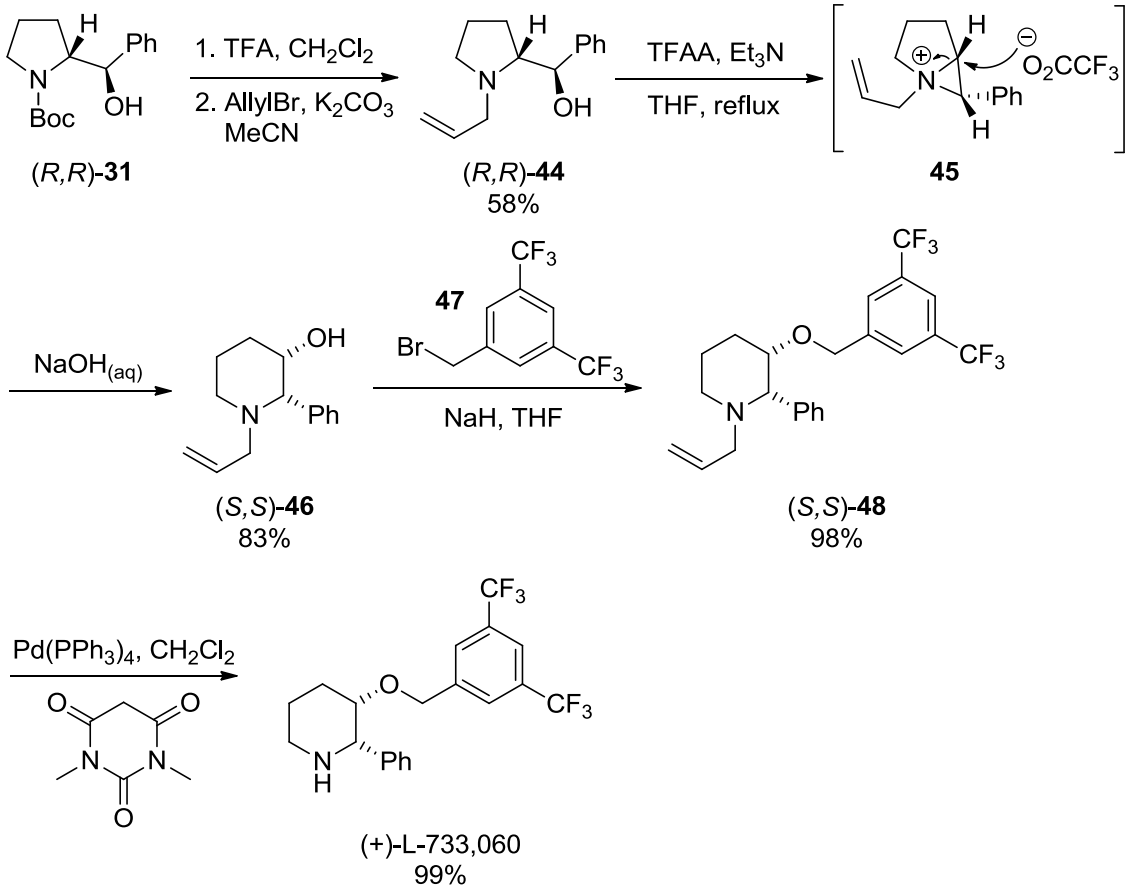
To overcome this limitation, O'Brien and co-workers developed the use of commercially available lithiated dimethylaminoethanol (LiDMAE) **43** as a stoichiometric ligand.[67] Importantly, this ligand could be separated from (–)-sparteine through a simple acid/base work-up protocol. Lithiation of *N*-Boc pyrrolidine **12** using *s*-BuLi with a substoichiometric amount of (–)-sparteine and stoichiometric LiDMAE **43**, followed by trapping with benzaldehyde, gave substituted pyrrolidines (*R*,*R*)-**31** in 64% yield and 90:10 er and (*R*,*S*)-**32** in 25% yield and 89:11 er (Scheme 1.21).



Scheme 1.21

To showcase the synthetic utility of the two-ligand catalysis methodology, the synthesis of (+)-L-733,060, a neuronkinin-1 receptor antagonist, was accomplished starting from (*R*,*R*)-**31** (Scheme 1.22). Boc removal with TFA followed by allylation gave allyl pyrrolidine (*R*,*R*)-**44** in 58% yield. Next, ring expansion to hydroxyl piperidine (*S*,*S*)-**46** was accomplished in 83% yield by treatment of (*R*,*R*)-**44** with TFAA and Et_3N. Ring expansion occurred *via* formation and opening of intermediate aziridinium ion **45** and was followed by base-mediated ester hydrolysis. The final two steps proceeded without

issue. Firstly *O*-alkylation of (*S*,*S*)-**46** was accomplished with NaH and benzyl bromide **47** giving benzyl ether (*S*,*S*)-**48** in 98% yield. *N*-Deallylation was performed using Pd(0) and *N*,*N*′-dimethylbarbituric acid to give (+)-L-733,060 in 99% yield.

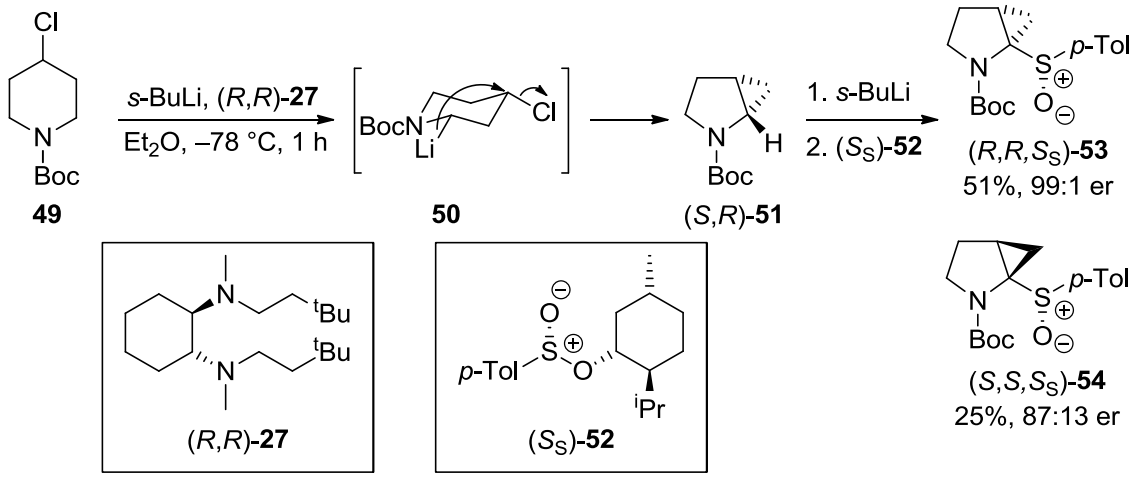


Scheme 1.22 Synthesis of (+)-L-733,060 from (*R*,*R*)-**31**

The enantioselectivity of asymmetric deprotonation reactions is generally excellent (90:10-95:5 er). However, synthesis of enantiopure substituted *N*-Boc heterocycles is not usually possible using asymmetric deprotonation chemistry. An ingenious method to circumvent this issue has been developed by Rayner and O'Brien.[68] It was envisaged that asymmetric lithiation followed by trapping with an enantiomerically pure sulfinate would lead to the generation of enantiomerically pure *α*-sulfoxide *N*-Boc heterocycles. Subsequent sulfoxide/Mg exchange would generate configurationally stable heterocyclic Grignard reagents, which could undergo electrophilic trapping.

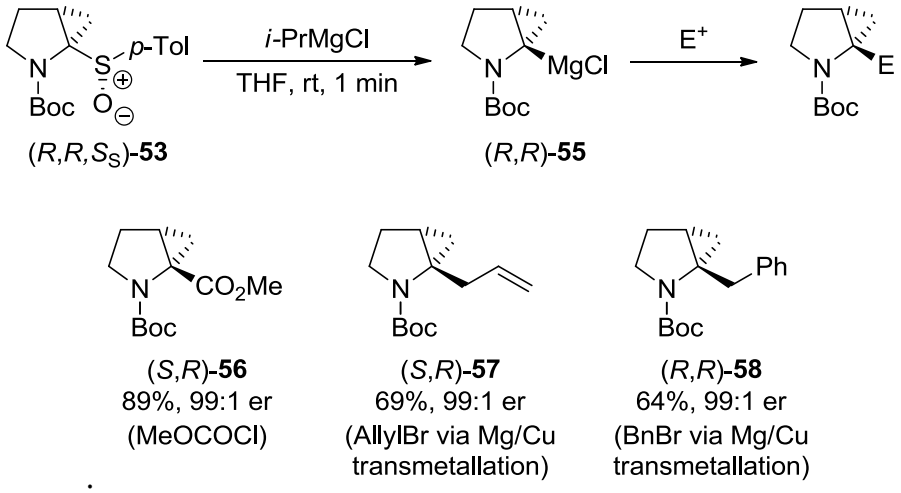
As a demonstration of this strategy, lithiation of 4-chloro-*N*-Boc piperidine **49** (first reported by Beak with (–)-sparteine[69]) with *s*-BuLi and the Alexakis diamine (*R*,*R*)-**27** in Et_2O at –78 °C followed by trapping with enantiomerically pure Andersen's sulfinate

(S_S)-**52** gave sulfoxides (*R*,*R*,S_S)-**53** in 51% yield and 99:1 er and (*S*,*S*,S_S)-**54** in 25% yield and 87:13 er (Scheme 1.23). Mechanistically, piperidine **49** underwent α-lithiation to give **50**, which cyclised to give cyclopropane (*S*,*R*)-**51**, which then underwent a second lithiation.



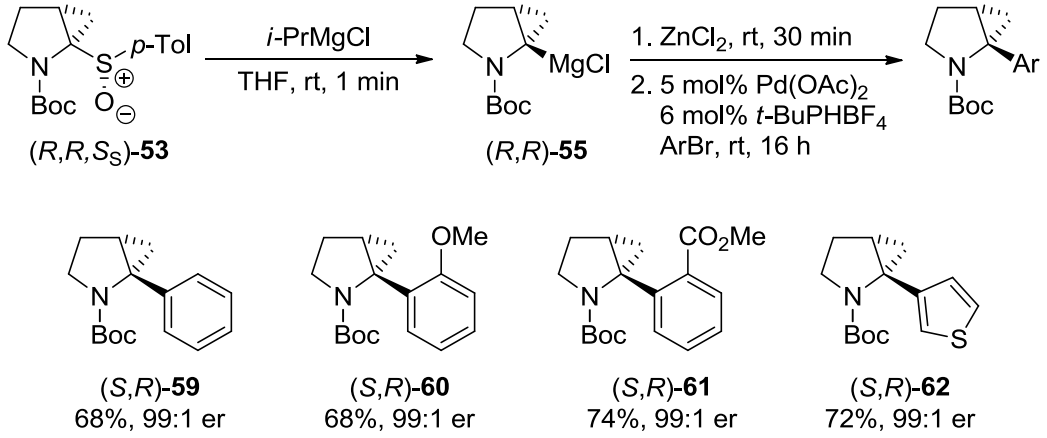
Scheme 1.23 Synthesis of enantiopure sulfoxide (*R*,*R*,S_S)-**53**

Sulfoxide/Mg exchange was accomplished rapidly at room temperature by treatment of (*R*,*R*,S_S)-**53** with *i*-PrMgCl to give enantiopure Grignard reagent (*R*,*R*)-**55** (Scheme 1.24). Electrophilic trapping delivered **56**-**58** in 64-89% yield and in 99:1 er. Importantly, the Grignard reagent **55** was configurationally stable at room temperature for the duration of the reaction.



Scheme 1.24 Sulfoxide/Mg exchange/trapping approach to enantiopure *N*-Boc heterocycles

Additionally, Mg/Zn transmetallation and subsequent Negishi coupling delivered 2-aryl heterocycles **59**-**62** in 68-74% yield, with 99:1 er (Scheme 1.25).



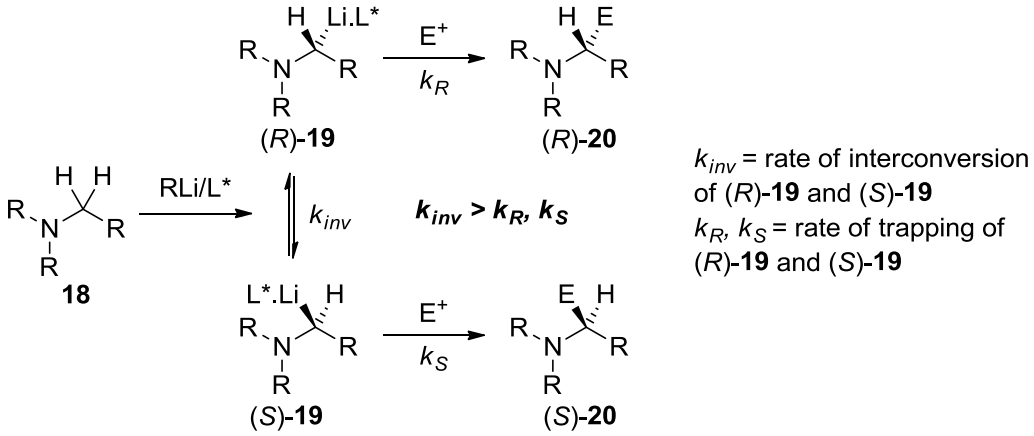
Scheme 1.25 Sulfoxide/Mg exchange/trapping approach to enantiopure 2-aryl *N*-Boc heterocycles

The beauty of this sulfoxide methodology is that it allows the synthesis of a range of enantiopure substituted *N*-Boc heterocycles from a bench stable common intermediate, (*R*,*R*,S_S)-**53**. Unfortunately, trapping of *N*-Boc pyrrolidine **12** with Anderson's sulfinate (S_S)-**52** was unsuccessful. This may be due to the instability of the *N*-Boc pyrrolidine sulfoxide.[70]

1.2.2 Dynamic Kinetic Resolution of *N*-Boc Pyrrolidine

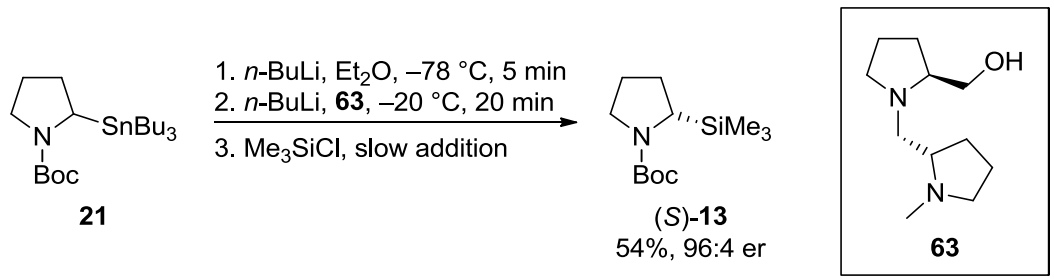
An alternative method to generate enantioenriched *α*-substituted *N*-Boc heterocycles through lithiation/trapping is dynamic kinetic resolution. If the intermediate organolithium species is configurationally unstable in the presence of a chiral ligand, at a particular temperature, then the degree of enantioselectivity can be controlled by the relative rates of electrophilic trapping of the diastereomeric lithiated intermediate/ligand complexes. A general reaction mechanism is shown in Scheme 1.26.[4,13] First, deprotonation of substrate **18** with an organolithium reagent (RLi) and a chiral ligand (L^*) results in a mixture of diastereomeric organolithium complexes, (*R*)-**19** and (*S*)-**19**. These two diastereomeric intermediates can undergo relatively rapid interconversion through configurational instability at the rate k_{inv}. These species react at different rates (k_R or k_S) with an electrophile resulting in products (*R*)-**20** and (*S*)-**20**. For this process

to be successful, the rate of interconversion of diastereomeric complexes (k_{inv}) must be faster than the rate of electrophilic trapping (k_R and k_S). The degree of enantioselectivity is governed by the energy difference between the energies of the trapping transition states.[13]



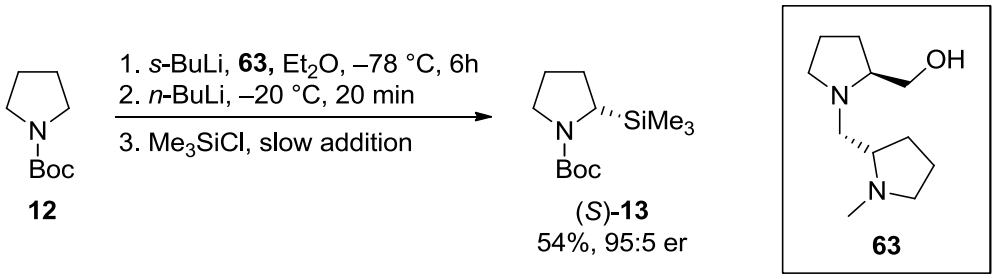
Scheme 1.26 Mechanism of dynamic kinetic resolution

In 2005, Coldham and co-workers published a dynamic kinetic resolution of 2-lithio-*N*-Boc pyrrolidine.[71] Treatment of stannane **21** with *n*-BuLi gave 2-lithio-*N*-Boc pyrrolidine. Addition of lithiated ligand **63** generated diastereomeric lithiated intermediates and subsequent warming to –20 °C facilitated interconversion of these intermediates. Trapping with Me_3SiCl gave *α*-silyl pyrrolidine (*S*)-**13** in 54% yield and 96:4 er (Scheme 1.27).



Scheme 1.27

A dynamic kinetic resolution *via* deprotonation of *N*-Boc pyrrolidine **12** with *s*-BuLi was also demonstrated. Silyl pyrrolidine (*S*)-**13** was isolated in 54% yield and 95:5 er (Scheme 1.28).

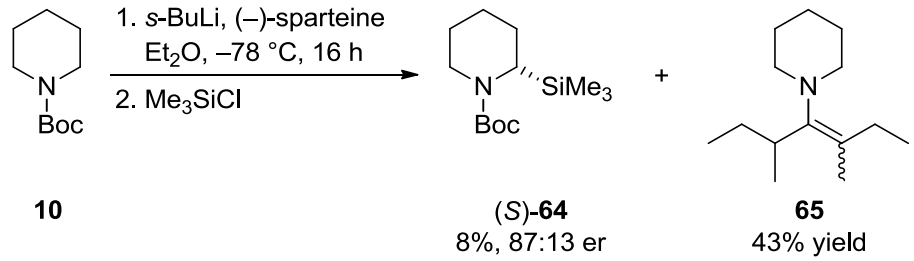


Scheme 1.28

Critically, a large excess of *n*-BuLi (>10 eq.) and slow addition of the electrophile were required for high levels of enantioselectivity. Additionally, the DKR process was highly electrophile dependent. High enantiomeric ratios were only obtained with Me_3SiCl.

1.2.3 Asymmetric Lithiation/Trapping of *N*-Boc Piperidine

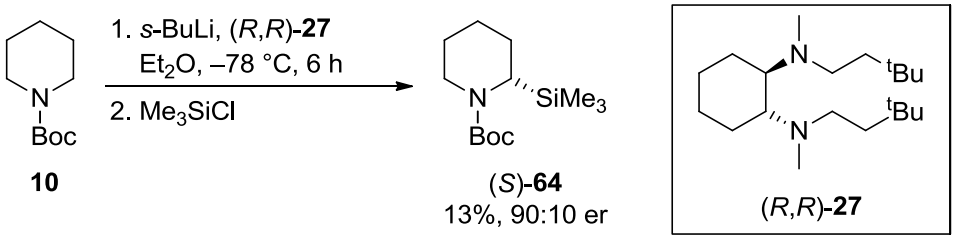
With the great degree of success seen with the asymmetric lithiation of *N*-Boc pyrrolidine **12**, it is perhaps surprising that asymmetric lithiation of *N*-Boc piperidine **10** was much more problematic. Although racemic lithiation with *s*-BuLi/TMEDA proceeds smoothly[34] the asymmetric variant originally met with failure. Beak investigated the *s*-BuLi/(–)-sparteine mediated lithiation/trapping of *N*-Boc piperidine **10**.[72] Lithiation in Et_2O at –78 °C for 16 h, followed by trapping with Me_3SiCl generated (*S*)-**64** in only 8% yield and 87:13 er (Scheme 1.29). The major product was a mixture of isomeric enamines **65** obtained in 43% yield. The very slow rate of lithiation of *N*-Boc piperidine **10** using *s*-BuLi/(–)-sparteine allowed nucleophilic attack of *s*-BuLi on the Boc group to become competitive. Nevertheless, the absolute sense of chiral induction was confirmed by X-ray crystallography of a derivative of (*S*)-**64**. The *s*-BuLi/(–)-sparteine complex **40** favours removal of the *pro*-S proton of both *N*-Boc piperidine **10** and *N*-Boc pyrrolidine **12**.



Scheme 1.29

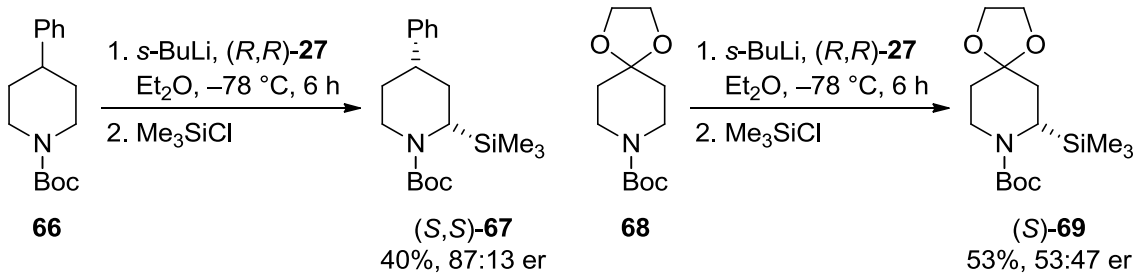
Computational studies performed on *N*-Boc piperidine **10** suggested that the *α*-proton is much less acidic than the corresponding *α*-proton of *N*-Boc pyrrolidine **12**. The activation energy for removal of a proton from *N*-Boc piperidine **10** is 2-3 kcal mol^{-1} higher than with the five-membered analogue, thus explaining the relatively slow rate of lithiation of the former.

In an attempt to develop a high yielding asymmetric lithiation/trapping of *N*-Boc piperidine **10**, Coldham and O'Brien explored 14 different diamines.[73] The investigation generated modest results with the use of Alexakis diamine (*R*,*R*)-**27** being slightly more successful than (–)-sparteine. Lithiation of **10** for 6 h at –78 °C before trapping gave (*S*)-**64** in 13% yield and 90:10 er (Scheme 1.30).



Scheme 1.30

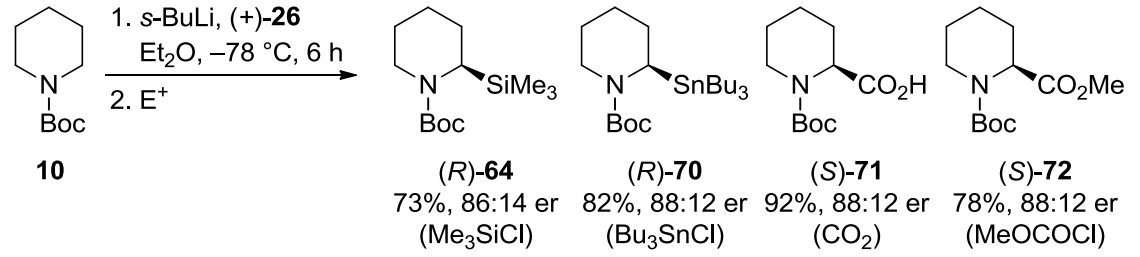
It was shown that 4-substitited piperidines undergo asymmetric lithiation more readily than *N*-Boc piperidine **10**. For example, lithiation of 4-phenyl piperidine **66** with *s*-BuLi/(*R*,*R*)-**27** followed by trapping with Me_3SiCl gave (*S*,*S*)-**67** as a single diastereomer[74] in 40% yield and 87:13 er (Scheme 1.31). For explanation of the diastereoselectivity, see Scheme 1.42. Additionally, lithiation of acetal **68** and trapping with Me_3SiCl gave (*S*)-**69** in 53% yield and 53:47 er.



Scheme 1.31

The increased yields of (*S,S*)-**67** and (*S*)-**69** showed that lithiation of these 4-subsitiuted piperidines was easier than *N*-Boc piperidine **10** under the same reaction conditions. In fact, Beak had previously shown through competition experiments that lithiation of 4-phenyl *N*-Boc piperidine **66** was easier than the lithiation of *N*-Boc piperidine **10** using *s*-BuLi/TMEDA.[75]

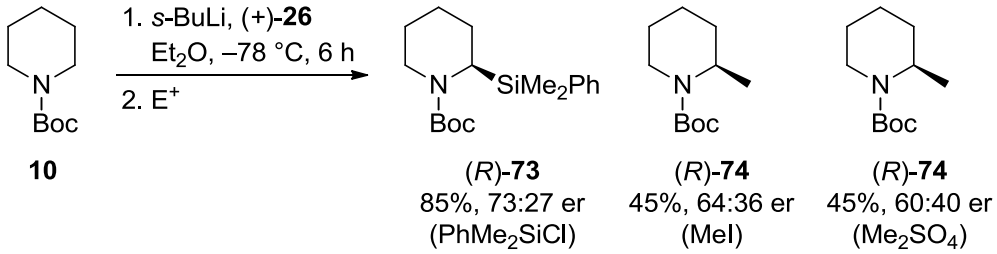
Work within the O'Brien group showed that lithiation with *s*-BuLi/(+)-sparteine surrogate (+)-**26** was more rapid than with *s*-BuLi/(–)-sparteine (see Scheme 1.14).[53] Thus, it was hypothesised that (+)-**26** would be more successful in the lithiation of *N*-Boc piperidine **10**. This was the case, lithiation for 6 h at –78 °C followed by addition of a selection of electrophiles gave *α*-substituted piperidines (*R*)-**64**, **70-72** in 73-92% yield and 86:14-88:12 er (Scheme 1.32). Trapping with Me_3SiCl resulted in (*R*)-**64** being obtained in a much improved 73% yield and 86:14 er.



Scheme 1.32 Asymmetric lithiation/trapping of **10** with *s*-BuLi/(+)-**26**

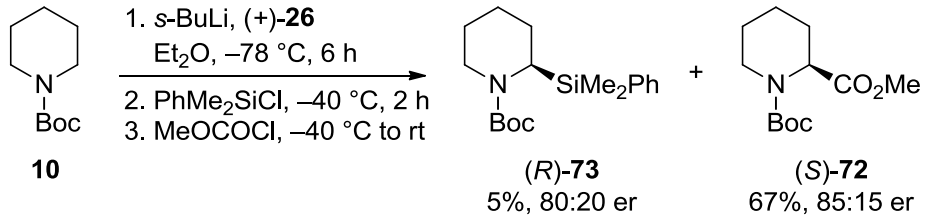
Other electrophiles were investigated by O'Brien and co-workers, but they gave lower enantiomeric ratios of products (Scheme 1.33). Lithiation of *N*-Boc piperidine **10** followed by trapping with bulky silyl reagent $PhMe_2SiCl$ gave (*R*)-**73** in 85% yield and 73:27 er. Trapping with methylating agents, such as methyl iodide and dimethyl sulfate, gave 2-methyl piperidine (*R*)-**74** in 45% yield in both cases, and 64:36 er and 60:40 er respectively. It was suggested that in these cases, trapping at –78 °C did not occur readily due to the steric bulk of the diamine. On warming the reaction from –78 °C

towards room temperature, the higher temperatures allowed trapping to occur. It was suggested that as the reactions warmed up, the lithiated intermediates became configurationally unstable, leading to the observed reduction in enantioselectivity.[61]



Scheme 1.33 Asymmetric lithiation/trapping of **10** with *s*-BuLi/(+)-**26**

Interestingly, an electrophile competition experiment proved that $PhMe_2SiCl$ trapped out the lithiated intermediate slowly, even at –40 °C. Lithiation of **10** using *s*-BuLi/(+)-**26** was performed at –78 °C for 6 h, then the temperature was raised to –40 °C and $PhMe_2SiCl$ was added. After 2 h at –40 °C, a fast trapping electrophile, methyl chloroformate, was added. Silyl piperidine (*R*)-**73** was isolated in 5% yield and 80:20 er and ester (*S*)-**72** was isolated in 67% yield and 85:15 er (Scheme 1.34). This conclusively proved that $PhMe_2SiCl$ trapped lithiated *N*-Boc piperidine slowly even at –40 °C in the presence of the (+)-sparteine surrogate (+)-**26**. The reduction in enantiomeric ratio of the two products can be attributed to partial configurational instability of the lithiated intermediate at –40 °C.

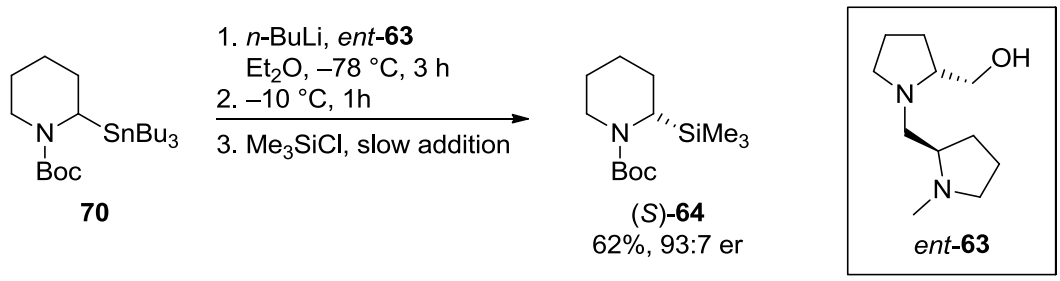


Scheme 1.34 Electrophile competition experiment in the lithiation/trapping of **10**

Earlier work by Coldham and O'Brien also showed slower trapping of lithiated *N*-Boc piperidine **10** by $PhMe_2SiCl$ than with Me_3SiCl by examination of enantiomeric ratios of the corresponding products.[73]

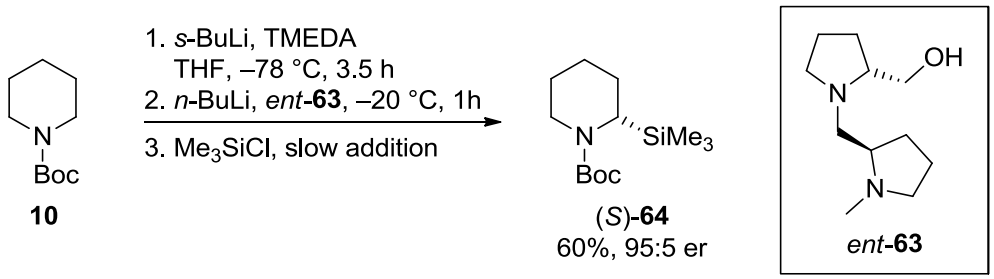
1.2.4 Dynamic Kinetic and Thermodynamic Resolution of *N*-Boc Piperidine

Coldham applied a dynamic kinetic resolution (DKR) approach to the synthesis of substituted *N*-Boc piperidines.[76] Treatment of stannane **70** with *n*-BuLi and ligand *ent*-**63** in Et_2O at –10 °C effected Sn/Li exchange generating diastereomeric lithiated intermediates that readily interconverted. After an hour at –10 °C, Me_3SiCl was added slowly over 4.5 h. Silyl piperidine (*S*)-**64** was isolated in 62% yield and 93:7 er (Scheme 1.35).



Scheme 1.35

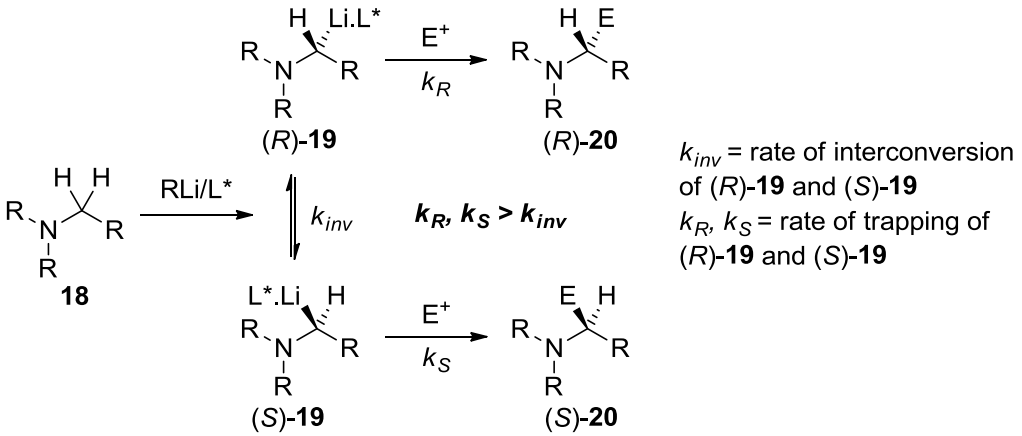
A dynamic kinetic resolution *via* deprotonation of *N*-Boc piperidine **10** with *s*-BuLi was also demonstrated (Scheme 1.36). Racemic lithiation was accomplished using *s*-BuLi/TMEDA in THF at –78 °C for 3.5 h. Subsequent warming to –20 °C before addition of *n*-BuLi and *ent*-**63** and then Me_3SiCl gave silyl piperidine (*S*)-**64** in 60% yield and 95:5 er.



Scheme 1.36

The electrophile scope of this reaction was poor. Quenching the diastereomeric intermediates with dimethyl sulfate, DMF, Bu_3SnCl or allyl bromide resulted in products with little or no enantioselectivity. This was attributed to more reactive electrophiles being unable to discriminate efficiently between the diastereomeric organolithium complexes.

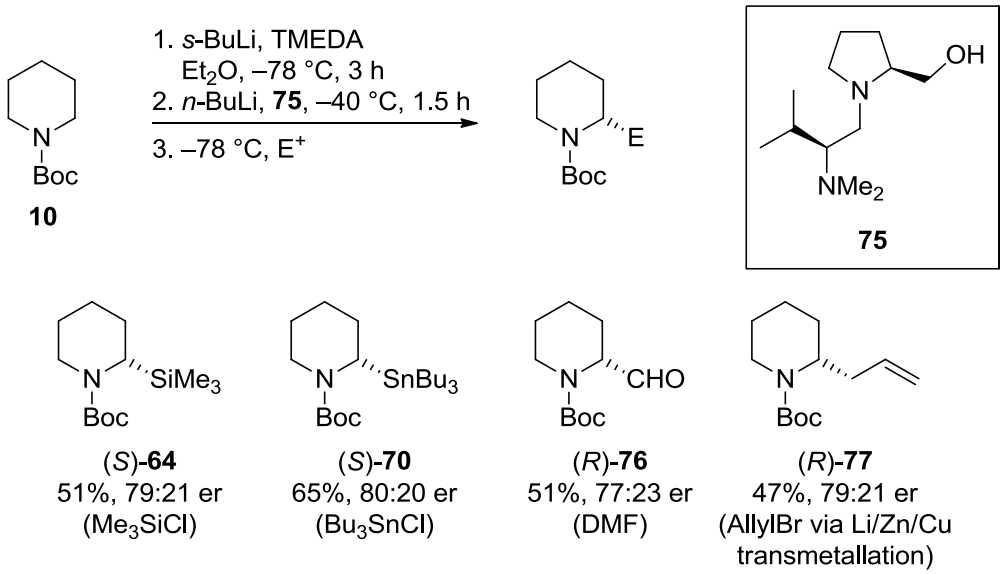
As well as asymmetric deprotonation and DKR, a third mechanism by which enantioenriched substituted *N*-Boc heterocycles can be accessed is dynamic thermodynamic resolution (DTR).[77] If the intermediate organolithium species is configurationally unstable in the presence of a chiral ligand, but the diastereomeric organolithium complexes do not interconvert on the timescale of the electrophilic trapping then the ratio of enantiomeric final products is dependent upon the ratio of the diastereomeric organolithiums. A general reaction mechanism is shown in Scheme 1.37.[4,13] First, deprotonation of substrate **18** with an organolithium (RLi) and a chiral ligand (L*) results in a mixture of diastereomeric organolithium complexes, (*R*)-**19** and (*S*)-**19**. These two diastereomeric organolithiums can undergo interconversion through configurational instability at the rate, k_{inv}, at a given temperature, to give a thermodynamic ratio of (*R*)-**19** and (*S*)-**19**. These two diastereomeric complexes react with electrophiles (k_R and k_S), resulting in products (*R*)-**20** and (*S*)-**20**. Because k_R and k_S are greater than the rate of interconversion of (*R*)-**19** and (*S*)-**19** (k_{inv}), the thermodynamic ratio of diastereomeric organolithiums is effectively frozen. The enantioselectivity of a DTR process will directly reflect the thermodynamic ratio of diastereomeric organolithium species (*R*)-**19** and (*S*)-**19**, which is governed by the energy difference between the two lithiated intermediates. In practice, the thermodynamic diastereomeric ratio of (*R*)-**19** and (*S*)-**19** is often formed at an elevated temperature (>–78 °C) and then the mixture is cooled to –78 °C to prevent further interconversion before an electrophile is added.



Scheme 1.37 Mechanism of dynamic thermodynamic resolution

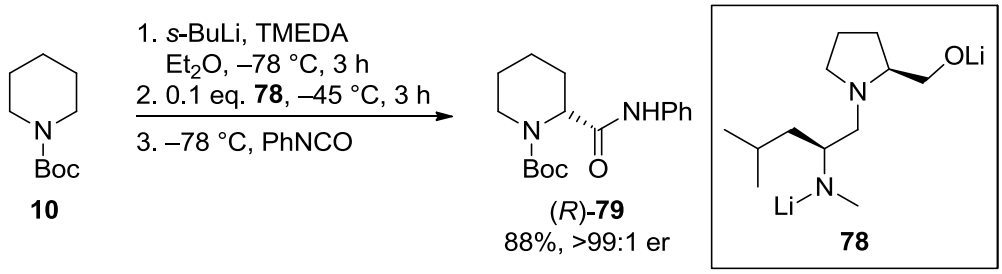
An initial attempt at a DTR process applied to *N*-Boc piperidine **10** using *ent*-**63** as a ligand resulted in a poor degree of enantioselectivity.[76] However, a screen of 24 ligands

by Coldham and co-workers led to the development of a modestly successful method.[78] Lithiation of *N*-Boc piperidine **10** was performed at –78 °C with *s*-BuLi/TMEDA in Et_2O. Then, the lithiated ligand **75** was added and the reaction warmed to –40 °C before ageing for 1.5 h to establish the thermodynamic ratio of diastereomeric organolithium complexes. Next, the reaction was cooled to –78 °C to prevent further interconversion of organolithiums, prior to addition of the electrophile. In this way, *α*-substituted piperidines (*S*)-**64**, (*S*)-**70**, (*R*)-**76**-**77** were isolated in 47-65% yield and 77:23-80:20 er (Scheme 1.38). Allyl piperidine (*R*)-**77** was formed through a Li/Zn/Cu transmetallation prior to electrophilic trapping.



Scheme 1.38 Dynamic thermodynamic resolution of **10**

In 2010 Beng and Gawley reported a highly successful catalytic DTR approach for the formation of substituted *N*-Boc piperidines.[79] Lithiation of **10** using *s*-BuLi/TMEDA was performed before addition of a substoichiometric amount (0.1 eq.) of lithiated ligand **78** and warming to –45 °C for 3 h. Following cooling to –78 °C, electrophile trapping gave a range of product in excellent yield and er. In one example, trapping with phenyl isocyanate gave (*R*)-**79** in 68% yield and >99:1 er (Scheme 1.39).



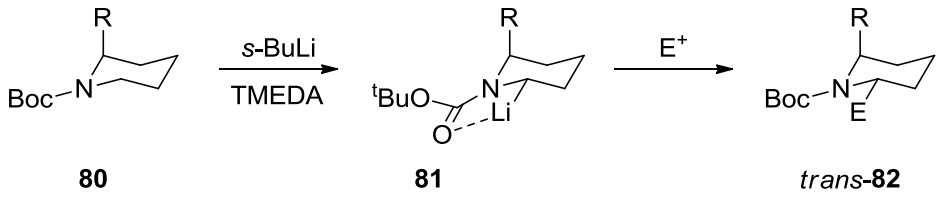
Scheme 1.39

For this procedure to be effective the asymmetric ligand-complexed lithiated intermediates must be configurationally labile at the reaction temperature and the TMEDA-complexed lithiated intermediates must be configurationally stable. Investigations showed that this was the case at temperatures below –27 °C. A full mechanistic study into the catalytic dynamic resolution of *N*-Boc piperidine **10** was reported.[80]

1.2.5 Synthesis of Disubstituted *N*-Boc Piperidines

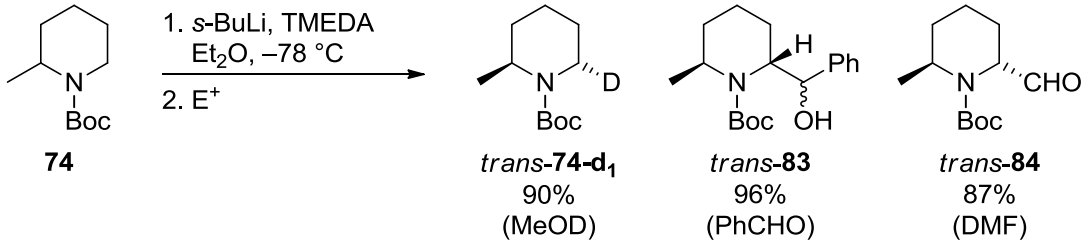
In order to increase the complexity of substituted piperidine products, Beak investigated the regioselective and diastereoselective lithiation of racemic monosubstituted *N*-Boc piperidines.[74,75] The regioselectivity and diastereoselectivity observed can be rationalised by the mechanism shown in Scheme 1.40.

The substituent of *N*-Boc piperidine **80** adopts an axial orientation to avoid the unfavourable $A^{1,3}$-type strain between the Boc group and the substituent.[81] Lithiation of monosubstituted *N*-Boc piperidine **80** gives rise to the equatorially lithiated species **81**. Equatorial lithiation is favoured because of the complex induced proximity effect and the fact that it avoids the repulsive interactions between the carbanionic lone pair in a p-orbital and the amide π bond.[13] Trapping with retention occurs to give equatorially substituted piperidine *trans*-**82**. Regioselectivity in the deprotonation event is due to lithiation occurring at the least sterically hindered position.



Scheme 1.40 Rationale for *trans* selectivity in the lithiation/trapping of **80**

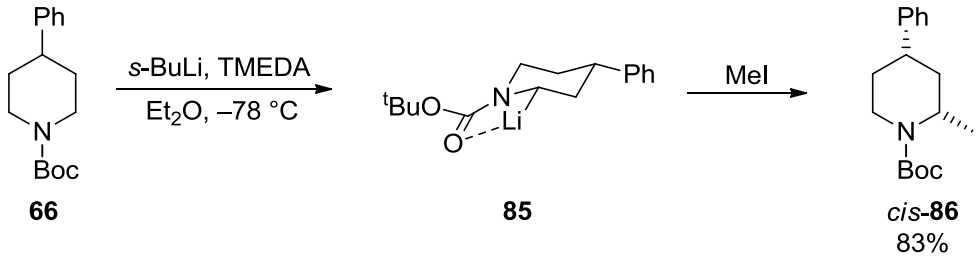
Lithiation of 2-methyl-*N*-Boc piperidine **74** with *s*-BuLi/TMEDA followed by trapping gave disubstituted piperidines as single regioisomers and diastereomers.[75] A set of representative examples, *trans*-**74-d$_1$**, *trans*-**83** and *trans*-**84** are shown in Scheme 1.41.



Scheme 1.41 Synthesis of 2,6-*trans*-disubstitited piperidines from **74**

This methodology has been recently applied to the synthesis of 2,6-dialkyl piperidine natural products by Beak,[82] Beng and Gawley[83] and Ferringa.[84]

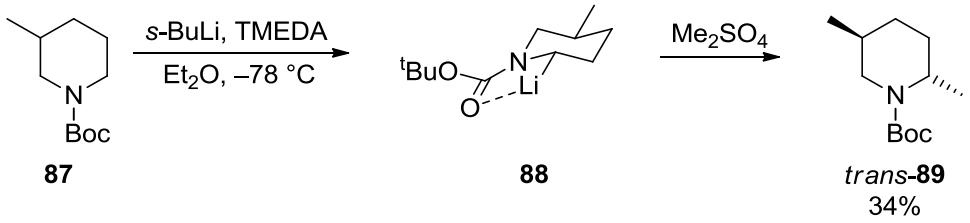
The synthesis of 2,4-disubsbtitiuted piperidines has been investigated by Beak.[74] For example, lithiation of 4-phenyl *N*-Boc piperidine **66** with *s*-BuLi/TMEDA followed by trapping with methyl iodide gave *cis*-2,4-disubsitiuted piperazine *cis*-**86** in 83% yield as a single diastereomer (Scheme 1.42). The diastereoselectivity can be rationalised through the phenyl ring of **66** adopting an equatorial orientation and the reaction proceeding through equatorial lithiation to lithiated species **85**.



Scheme 1.42 Synthesis of 2,4-*cis*-disubstitited piperidine *cis*-**86**

Lithiation/trapping of 3-substituted piperidine **87** with *s*-BuLi/TMEDA and dimethyl sulfate resulted in the formation of *trans*-2,5-dimethyl piperidine *trans*-**89** in 34% as a

single diastereomer (Scheme 1.43).[75] The methyl substituent of **87** adopted an equatorial orientation and equatorial lithiation resulted in the formation of lithiated species **88**.

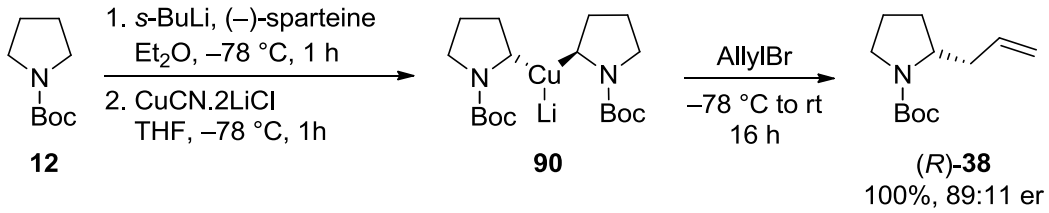


87 **88** *trans*-**89** 34%

Scheme 1.43 Synthesis of 2,5-*trans*-disubstitited piperidine *trans*-**89**

1.3 Expanding the Electrophile Scope *via* Transmetallation.

The asymmetric lithiation/trapping methodology of *N*-Boc heterocycles described thus far has been essentially limited to trapping with electrophiles that contain a carbonyl functionality or can undergo S_N2 reactions. Addition of, for example, allyl halides generally resulted in low yields of 2-allyl cyclic amines.[85] The enantiomeric ratios can also be lower than expected due to competing single electron transfer processes.[86] To address these limitations, Dieter developed the transmetallation of racemic lithiated species derived from *N*-Boc pyrrolidine **12** and *N*-Boc piperidine **10** with CuCN.2LiCl and subsequent trapping with a wide range of electrophiles such as vinyl halides, allyl halides, propargyl bromides and Michael acceptors.[87-92] Dieter also showed that lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine followed by transmetallation with 0.5 eq. of CuCN.2LiCl resulted in formation of dialkyl cuprate **90**. Subsequent trapping with allyl bromide gave 2-allyl *N*-Boc pyrrolidine (*R*)-**38** in 100% yield and 89:11 er (Scheme 1.44).[93] There was only a slight loss of enantioenrichment from the lithiated intermediate, which is typically generated with ~95:5 er.

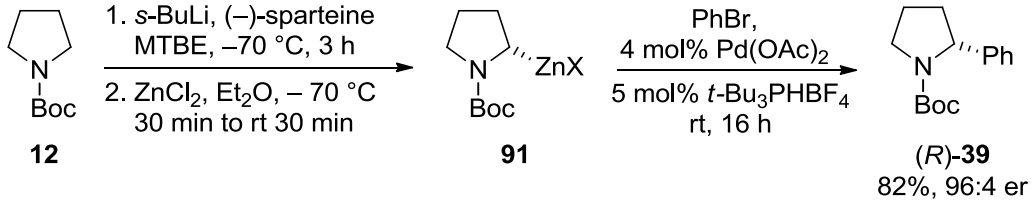


Scheme 1.44 Asymmetric lithiation/transmetallation/trapping of **12**

Transmetalation of enantioenriched lithiated species using CuCN.2LiCl followed by trapping with allyl bromide has been widely accepted by the synthetic community. It has been used with *N*-Boc pyrrolidine based systems,[60,68,94] and with *N*-Boc piperidines through DTR[78,85] or asymmetric deprotonation.[95] The general transmetallation to copper strategy has also been used in the synthesis of a range of naturally occurring alkaloids by Dieter,[96] O'Brien,[94] Coldham[85] and Gawley[83].

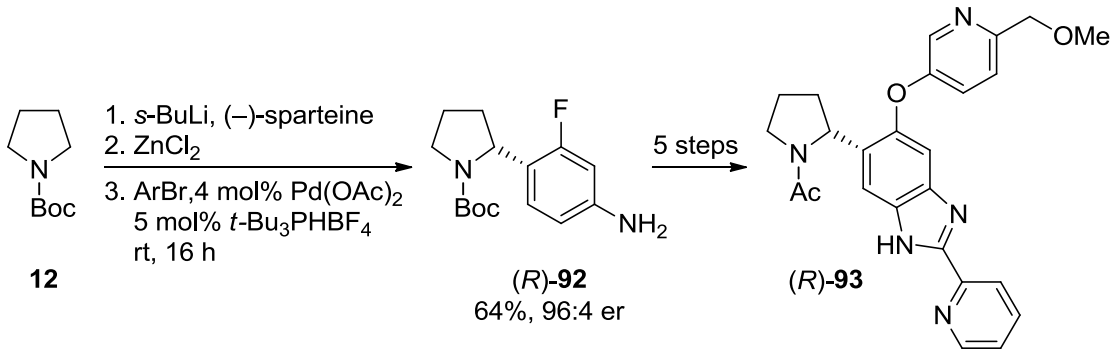
In 2006, Campos published a pioneering report on the enantioselective α-arylation of *N*-Boc pyrrolidine **12**.[97] Lithiation of **12** was followed by transmetallation to form configurationally stable alkyl zinc species **91** (Scheme 1.45). Palladium catalysed Negishi coupling using palladium(II) acetate and *t*-Bu_3PHBF_4 gave a range of 2-aryl

pyrrolidines in good yield and excellent enantioselectivity (96:4 er). As a typical example, 2-phenyl pyrrolidine (*R*)-**39** was obtained in 82% yield and 96:4 er.



Scheme 1.45 Asymmetric lithiation/Negishi coupling of **12**

Campos and co-workers applied the lithiation-arylation protocol to the synthesis of glucokinase activator (*R*)-**93** on a large scale *via* synthesis of (*R*)-**92** (Scheme 1.46).[98] In a testament to both the asymmetric lithiation and Negishi methodology, (*R*)-**92** was isolated in 64% yield with 96:4 er on a 6.0 mol scale. In total, 2.13 kg of (*R*)-**92** was synthesised over two batches *via* this approach.



Scheme 1.46

The diamine-free high temperature lithiation methodology developed by O'Brien (see Scheme 1.16) has been applied to the *α*-arylation of *N*-Boc pyrrolidine **12** and *N*-Boc imidazolidine.[59] Additionally, in 2011, O'Brien and Campos published a comprehensive study into the enantioselective lithiation/arylation of *N*-Boc pyrrolidine **12**.[99] The use of alternative diamines, namely the (+)-sparteine surrogate (+)-**26** and the Alexakis diamine (*R*,*R*)-**27**, was investigated, as was the aryl halide scope and a two-ligand catalytic system. Vinyl halides were also successfully coupled. The application of the developed methodology to the synthesis of several natural products and drug molecules was undertaken: (*S*)-nicotine, (*S*)-SIB-1508Y, (*R*)-crispine A and (*R*)-maackiamine were all synthesised in a short number of synthetic steps (Figure 1.7)

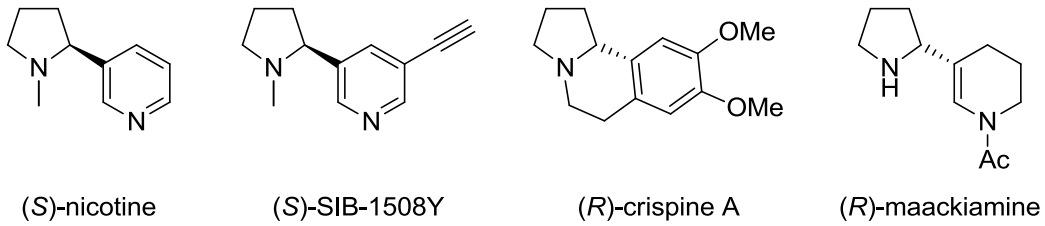
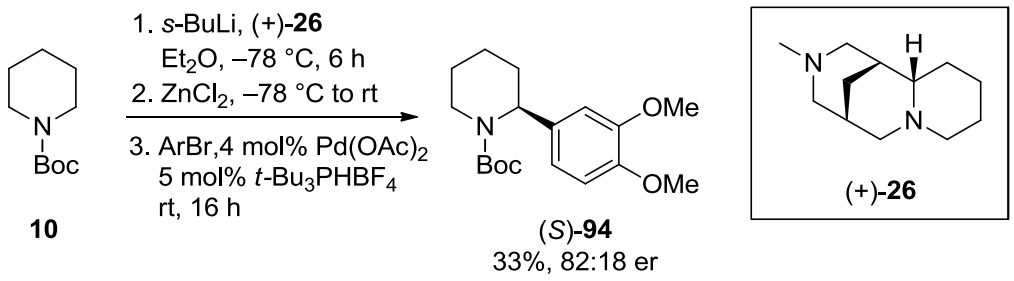


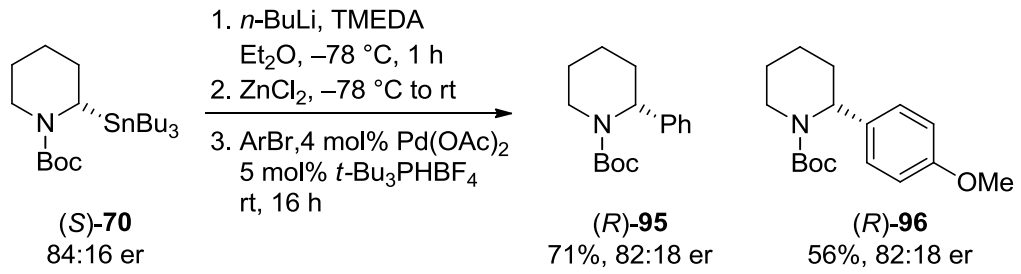
Figure 1.7

The lithiation/arylation methodology has been successfully applied to other heterocycles. Coldham reported the racemic lithiation/Negishi coupling of *N*-Boc piperidine **10**[100] and the O'Brien group reported an isolated asymmetric example.[95] The asymmetric lithiation of the relatively unreactive *N*-Boc piperidine **10** with *s*-BuLi and the (+)-sparteine surrogate (+)-**26** preceded transmetallation and Negishi coupling with 4-bromoveratrole, to give aryl piperidine (*S*)-**94** in a modest 33% yield and 82:18 er (Scheme 1.47).



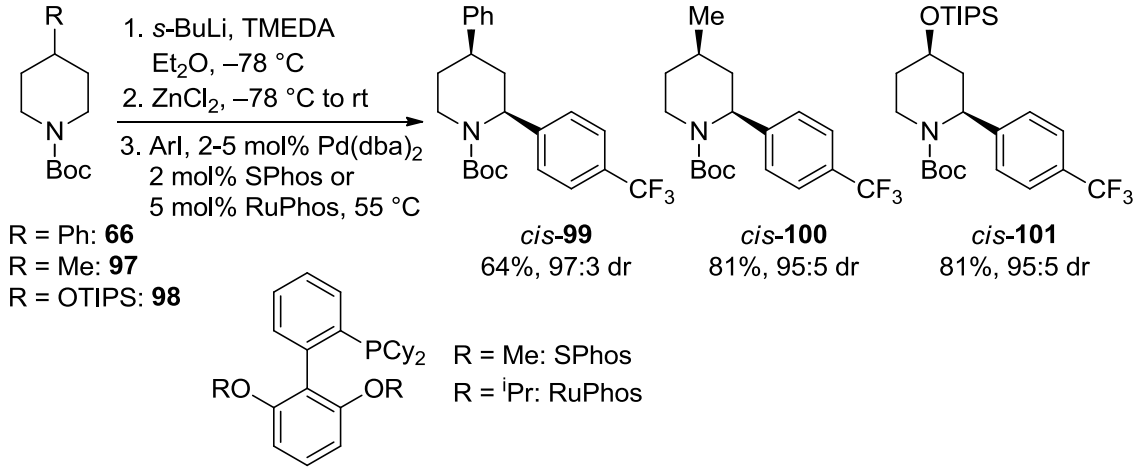
Scheme 1.47

Coldham attempted to use a DTR lithiation approach to form 2-aryl piperidines.[101] However, it was found that zinc to palladium transmetallation did not occur, possibly due to coordination of the bulky DTR ligands to the zinc. To circumvent this problem, Sn/Li exchange of enantioenriched stannane (*S*)-**70** (itself synthesised *via* a DTR protocol) and then Negishi coupling give 2-aryl piperidines with modest levels of enantioselectivity, (*R*)-**95** and (*R*)-**96** were obtained in 71% and 56% yields respectively and in 82:18 er (Scheme 1.48). Subsequently, Gawley reported a catalytic dynamic resolution method for the α-arylation and vinylation of *N*-Boc piperidine **10** in 2010.[102]



Scheme 1.48 DTR lithiation/Negishi coupling of (*S*)-**70**

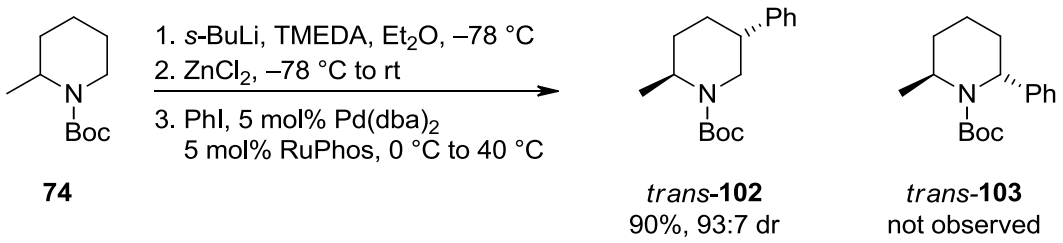
Knochel and co-workers applied the racemic lithiation/arylation methodology to the synthesis of di- and trisubstituted piperidines.[103] Lithiation of 4-substitiuted piperidines followed by Negishi coupling gave rise to *cis*-2,4-disubstitiuted piperidines in good diastereomeric ratios and the rationale for the *cis*-diastereoselectivity is shown in Scheme 1.42. Lithiation/arylation of 4-substituted piperidines **66**, **97** and **98** using 4-iodobenzotrifluoride, $Pd(dba)_2$ and either SPhos or RuPhos gave 2-aryl piperidines *cis*-**99**, *cis*-**100** and *cis*-**101** in 64% yield (97:3 dr), 81% yield (95:5 dr) and 81% yield (95:5 dr) respectively (Scheme 1.49).



Scheme 1.49 Racemic lithiation/Negishi coupling of racemic *N*-Boc piperidines

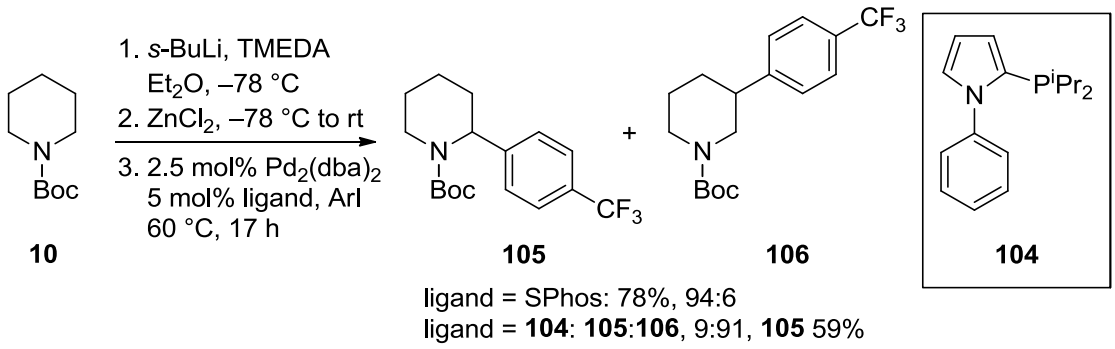
Interestingly, lithiation of 2-methyl *N*-Boc piperidine **74** followed by transmetallation and Negishi coupling gave *trans*-2,5-substituted *N*-Boc piperidine *trans*-**102** in 90% yield and 93:7 dr. None of the expected *trans*-2,6-substituted *N*-Boc piperidine *trans*-**103** was observed (Scheme 1.50). Knochel proposed that formation of *trans*-**102** can be accounted for by *β*-hydride elimination of the palladium intermediate. The resulting "$PhPdL_2H$" complex can then undergo *syn*-addition to the tetrahydropyridinyl ring, placing the palladium in the least sterically hindered 3-position. Reductive elimination then gave the 2,5-substitited product *trans*-**102**. The high level of diastereoselectivity

was accounted for by the "$PhPdL_2H$" complex remaining coordinated to the bottom face of the ring after *β*-hydride elimination.



Scheme 1.50 Unexpected synthesis of *trans*-2,5-substituted *N*-Boc piperidine *trans*-**102**

Baudoin capitalised on Knochel's observation and recently developed a *β*-selective arylation of *N*-Boc piperidines through a regioselective ligand controlled lithiation/arylation procedure.[104] Lithiation of *N*-Boc piperidine **10** under standard racemic conditions (*s*-BuLi/TMEDA in Et_2O at –78 °C) was followed by transmetalation and arylation using 4-bromobenzotrifluoride, $Pd_2(dba)_3$ and Buchwald ligands to give a mixture of *α*- and *β*-arylated piperidines **105** and **106** (Scheme 1.51). When using similar conditions to those employed by Knochel, namely using SPhos as a ligand, **105** and **106** were isolated in a combined 78% yield in a 94:6 ratio. Interestingly, use of pyrrole derived phosphine ligand **104** gave a 91:9 mixture of **106** and **105**, with the former being isolated in 59% yield after flash column chromatography.

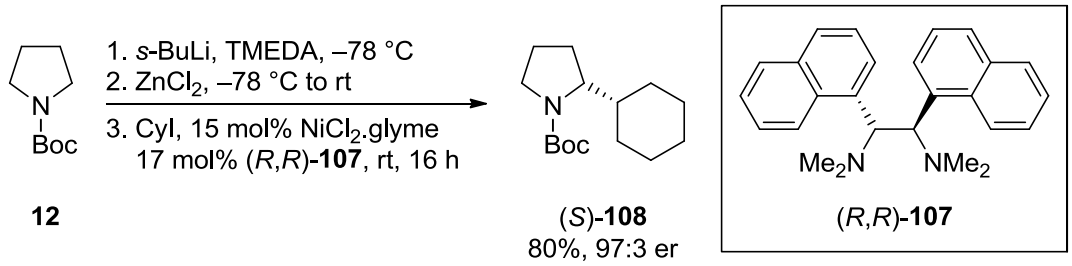


Scheme 1.51 Ligand controlled regioselective lithiation/arylation of **10**

The use of phosphine ligand **104** resulted in good regioselectivity for the *β*-arylated products for a wide range of aryl iodides. Computational studies showed that reductive elimination to form the C-Ar bond was the rate-determining step, with the transition state for the formation of *β*-arylated product **106** being 1.4 kcal mol^{-1} lower in energy than the corresponding transition state for formation of *α*-arylated product **105** (when

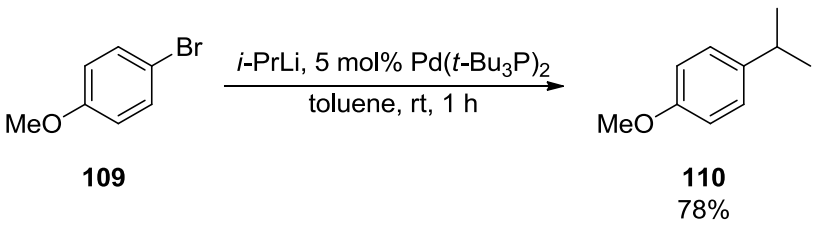
104 was used as a ligand). Application of the same reaction conditions to analogous 5, 7 and 8- membered rings resulted in the preferential formation of α-arylated products.

Recently, Fu and co-workers have reported an enantioselective nickel catalysed alkyl-alkyl cross coupling between *N*-Boc pyrrolidine **12** and secondary alkyl halides.[105] Racemic lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/TMEDA followed by transmetalation using $ZnCl_2$ was performed. Coupling in the presence of a nickel catalyst and chiral diamine (*R*,*R*)-**107** was successful with a range of secondary alkyl iodides and bromides to give 2-alkyl pyrrolidines in excellent yield and er. In one example, coupling with cyclohexyl iodide gave (*S*)-**108** in 80% yield and 97:3 er (Scheme 1.52). Experiments using an enantioenriched organozinc species showed ligand controlled stereoselectivity regardless of the original enantioenrichment. The origin of enantioselectivity is not known, but kinetic resolution has been ruled out.



Scheme 1.52

In a ground-breaking recent publication, Feringa disclosed the direct palladium-catalysed cross coupling of alkyl and aryl bromides with alkyl and aryl lithium reagents at room temperature.[106] A wide range of examples was given, but the coupling of secondary alkyl lithiums and aryl bromides was probably of most interest. In one example, coupling between *i*-PrLi and 4-bromoanisole **109** using Pd(*t*-$Bu_3P)_2$ in toluene at room temperature gave **110** in 78% yield (Scheme 1.53). It is possible that this methodology could be applied to the racemic synthesis of 2-aryl *N*-Boc heterocycles.

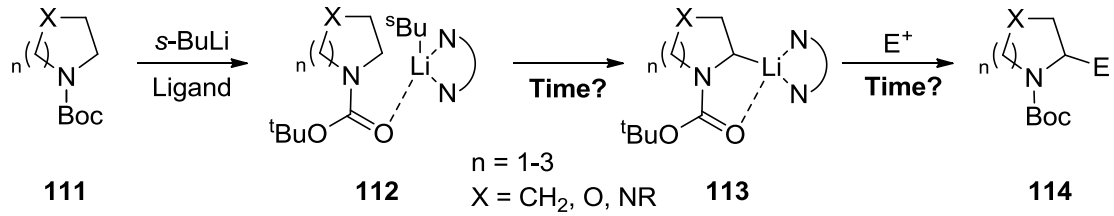


Scheme 1.53

1.4 Project Outline

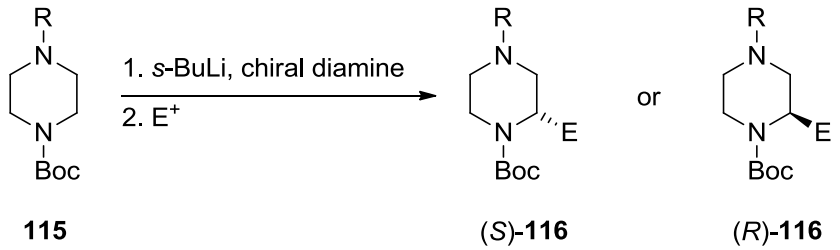
The research described within this thesis covers a number of issues relating to the lithiation/trapping of *N*-Boc heterocycles.

Since Beak's original report of the Boc directed lithiation of nitrogen heterocycles, considerable advances have been made. However, the time taken for the lithiation and trapping events has never been systematically studied. Building on previous work within the O'Brien group, the use of *in situ* ReactIR™ spectroscopy to build-up a full picture of the time taken for lithiation and trapping events will be detailed. This should lead to an improved understanding of the processes involved and aid reaction optimisation. Monitoring changes in the carbamate $\nu_{C=O}$ allows progress of the reaction to be observed, from **111** through the pre-lithiation complex **112**, lithiated intermediate **113** and finally the α-substituted *N*-Boc heterocycle **114** (represented in generic form in Scheme 1.54). This investigation is presented in Chapter 2.



Scheme 1.54

The lithiation of *N*-Boc pyrrolidine **12** and *N*-Boc piperidine **10** has been extensively studied by Beak, O'Brien and others. However, very little work has been performed on *N*-Boc piperazine systems, even though piperazines are very common within medicinal compounds.[107] Although a few reports of racemic lithiation/trapping exist, there has only been one isolated example of the asymmetric lithiation/trapping of *N*-Boc piperazines.[108] A general, asymmetric lithiation/trapping of *N*-Boc piperazines **115** will be detailed, with a full exploration of the scope and limitations of the methodology (Scheme 1.55).

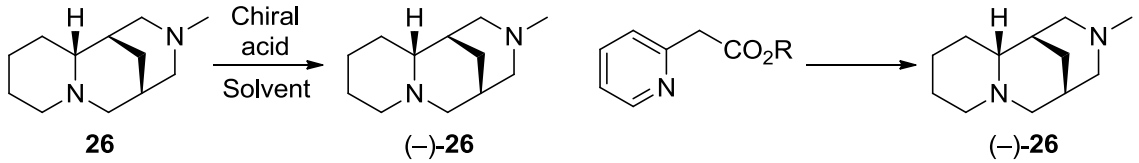


115 (*S*)-**116** (*R*)-**116**

Scheme 1.55

In situ ReactIR™ spectroscopy will be used to determine the time taken for the lithiation and trapping events. Additionally, transmetallation to zinc and subsequent Negishi coupling to give *α*-aryl piperazines will be explored. Both the racemic and asymmetric lithiation/trapping investigations will be reported (Chapters 3 and 4).

The major problem faced by the modern asymmetric lithiation chemist is the lack of a reliable supply of (–)-sparteine. Although the (+)-sparteine surrogate (+)-**26** is in many ways superior to (–)-sparteine for asymmetric deprotonation chemistry, the antipode (–)-**26** is not readily available. Chapter 5 will detail investigations into the synthesis of a direct (–)-sparteine replacement, the (–)-sparteine surrogate (–)-**26**. Firstly, an attempt at the classical resolution of racemic surrogate **26** will be explored. Secondly, a synthesis of enantiopure (–)-**26** from commercially available precursors, building on work previously reported within the O'Brien group, will be described (Scheme 1.56).



26 (–)-**26** (–)-**26**

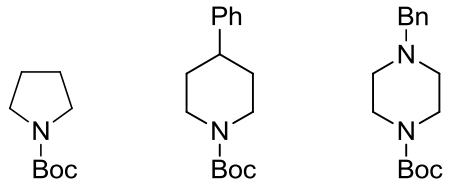
Scheme 1.56

Chapter Two: *In situ* IR Monitoring of the Lithiation/Trapping of *N*-Boc Heterocycles

The lithiation of *N*-Boc heterocycles using *s*-BuLi and diamines has traditionally been performed at –78 °C for between three and six hours before addition of the electrophile. However, there is little evidence to suggest that these lengthy reaction times are required apart from with the most unreactive substrates. It was envisaged that a comprehensive *in situ* ReactIR™ spectroscopic investigation involving monitoring of the lithiation of *N*-Boc heterocycles with a range of diamines would provide definitive lithiation times for each *N*-Boc heterocycle. This would be of much use in the optimisation of lithiation methodology as well as providing a handy guide for the application of this methodology to new substrates.

This chapter details an investigation into the *in situ* ReactIR™ monitoring of the lithiation times of commonly used *N*-Boc heterocycles to build up a relative reactivity series. Heterocycles that have been regularly investigated by the synthetic community have been used in conjunction with diamines, such as TMEDA, (–)-sparteine and the (+)-sparteine surrogate (+)-**26**.

The use of *in situ* ReactIR™ spectroscopy has been recently adopted by several groups for the monitoring of lithiation reactions. However, very few examples of the use of this technique for the monitoring of the electrophilic trapping step have been performed. The second part of this chapter will look at the time taken for electrophile trapping using *N*-Boc pyrrolidine **12**, 4-phenyl *N*-Boc piperidine **66** and *N*-Boc-*N′*-benzyl piperazine **117** as representative substrates (Figure 2.1). The effect of the substrates, the nature of electrophiles and of the diamines will be presented.

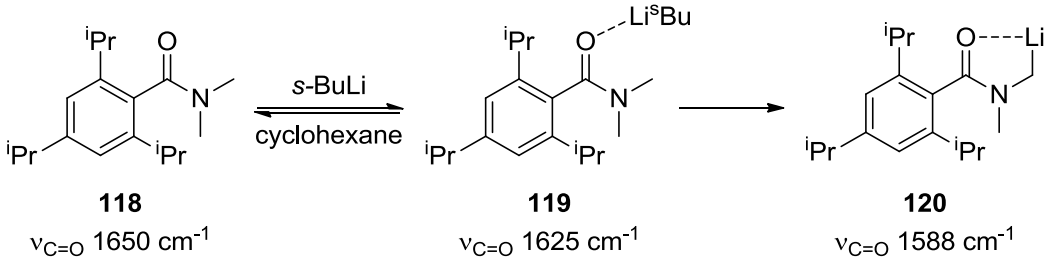


12 **66** **117**

Figure 2.1 *N*-Boc heterocycles used for the *in situ* ReactIR™ spectroscopic study of trapping times

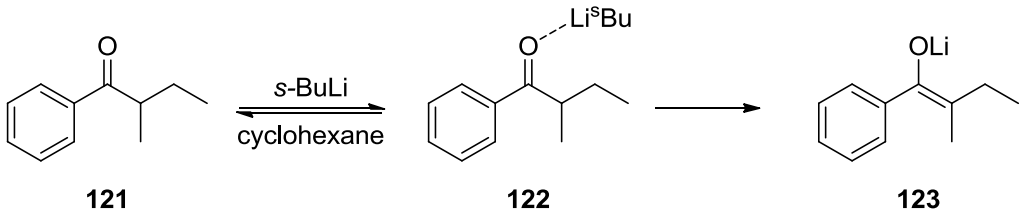
2.1 Previous Use of the *in situ* IR Monitoring of Lithiation Reactions

Directed lithiation adjacent to heteroatoms has previously been studied using *in situ* IR spectroscopy. Beak and Smith reported the first use of such a technique in 1983 when they observed the existence of a pre-lithiation complex directly, using stopped flow *in situ* IR and observing shifts in the carbonyl region of the spectrum.[18] Addition of *s*-BuLi to hindered amide **118** ($\nu_{C=O}$ 1650 cm^{-1}) in cyclohexane at 25 °C led to the rapid formation of pre-lithiation complex **119** ($\nu_{C=O}$ 1625 cm^{-1}). Lithiation then occurred to give lithiated species **120** ($\nu_{C=O}$ 1588 cm^{-1}) (Scheme 2.1). The use of a non-coordinating solvent ensured lithiation proceeded through *s*-BuLi tetramers. An investigation into the kinetics of the lithiation of **118** with *s*-BuLi/TMEDA showed a rate enhancement. This was speculatively attributed not to be due to de-aggregation of the *s*-BuLi tetramers, but to the fact that TMEDA activates the coordinating organolithium agregate.[20]



Scheme 2.1

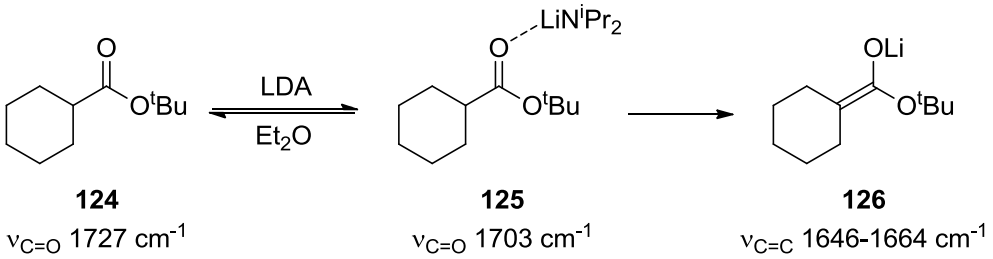
In 1984, An investigation into the enolisation of ketones with *n*-BuLi and *s*-BuLi in cyclohexane was reported by Smith.[109] Using stopped-flow *in situ* IR it was shown that the organolithium reagents reacted as aggregates, reversibly forming a pre-lithiation complex **122** from ketone **121**, before lithiation to give the enolate **123** (Scheme 2.2).



Scheme 2.2

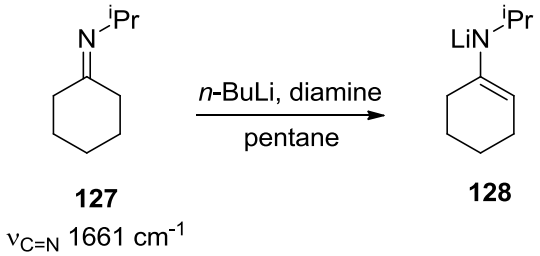
Smith went on to investigate the nucleophilic addition of *s*-BuLi to esters and pre-lithiation complexes were similarly observed.[110]

Collum probed the mechanism of enolisation of esters using LDA in ethereal solvents.[111] In Et_2O, addition of LDA to ester **124** ($\nu_{C=O}$ 1727 cm^{-1}) resulted in the formation of pre-lithiation complex **125** ($\nu_{C=O}$ 1703 cm^{-1}) before formation of lithium enolate **126** ($\nu_{C=C}$ 1646-1664 cm^{-1}) (Scheme 2.3). Interestingly, the pre-lithiation complex was not observed for enolisation in THF. Kinetic studies indicated that enolisation was effected by the LDA/THF monomer after pre-equilibration from the dimer. Further studies into the role of solvents and additives and the resulting LDA aggregation states were conducted.[112]



Scheme 2.3

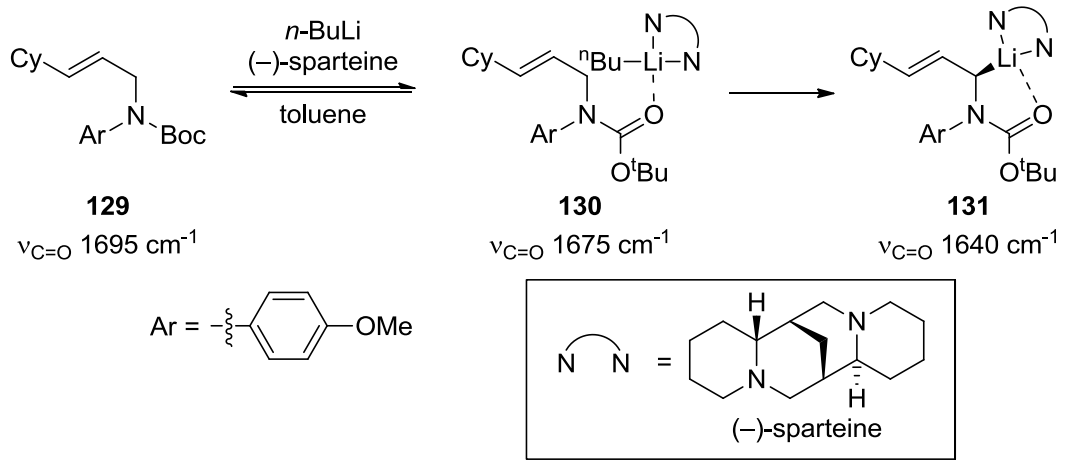
Collum and co-workers also reported the monitoring of the α-lithiation of imine **127** by *in situ* ReactIR™ spectroscopy.[113] Deprotonation of imine **127** with *n*-BuLi in pentane with a range of diamines to give **128** was followed by monitoring the disappearance of the band for the starting material ($\nu_{C=N}$ 1661 cm^{-1}) (Scheme 2.4). ReactIR™ spectroscopy was also used to determine the relative rates of α-deprotonation and 1,2-addition to a different imine through kinetic studies.



Scheme 2.4

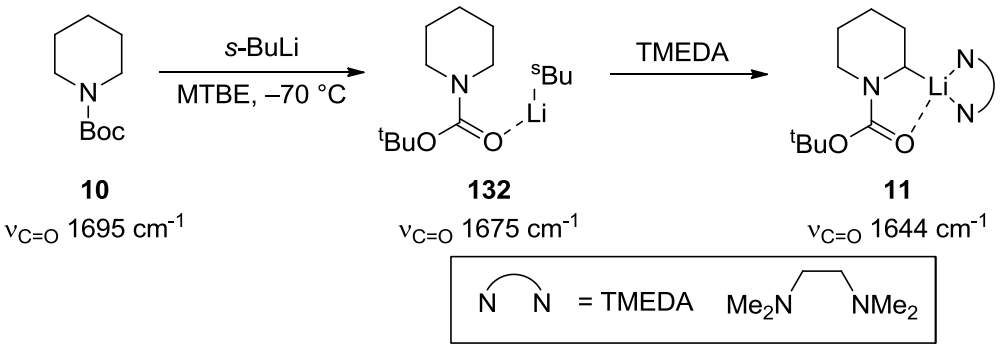
In 2001, Beak reported the first use of *in situ* ReactIR™ spectroscopy to monitor a Boc-directed α-lithiation process.[114] Addition of *n*-BuLi to a mixture of allylamine derivative **129** ($\nu_{C=O}$ 1695 cm^{-1}) and (–)-sparteine led to consumption of **129** and rapid formation of pre-lithiation complex **130** ($\nu_{C=O}$ 1675 cm^{-1}) before slow formation of lithiated intermediate **131** ($\nu_{C=O}$ 1640 cm^{-1}) (Scheme 2.5). Investigation into the kinetics of

deprotonation showed that the reaction rate exhibited a zero-order dependence on the concentration of *n*-BuLi/(–)-sparteine. This gave credence to the assumption that the signal at $\nu_{C=O}$ 1675 cm^{-1} was indeed due to pre-lithiation complex **130**.



Scheme 2.5

More recently, O'Brien and Campos used *in situ* ReactIR™ spectroscopy to determine the time taken for the lithiation of *N*-Boc piperidine **10** using *s*-BuLi and TMEDA, (–)-sparteine or (+)-sparteine surrogate (+)-**26** at –70 °C.[95] Addition of *s*-BuLi to **10** ($\nu_{C=O}$ 1695 cm^{-1}) in MTBE led to the formation of pre-lithiation complex **132** ($\nu_{C=O}$ 1675 cm^{-1}). Then, addition of TMEDA resulted in deprotonation and lithiated intermediate **11** ($\nu_{C=O}$ 1644 cm^{-1}) was observed (Scheme 2.6). Lithiation was found to be complete within 1 hour at –70 °C. This was the first direct observation of a pre-lithiation complex for an *N*-Boc heterocycle.

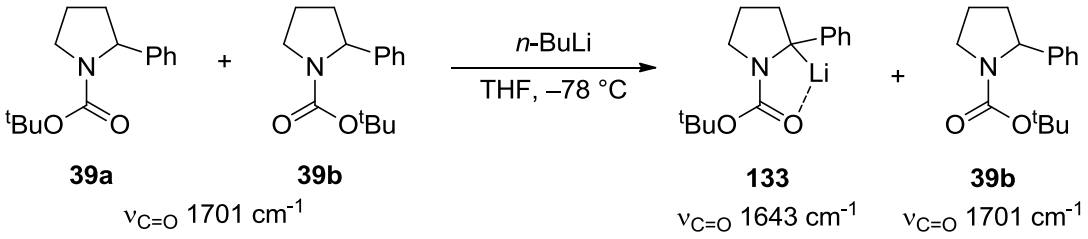


Scheme 2.6

Lithiation in the presence of (–)-sparteine was considerably slower. Lithiated intermediate **11** was found to be only a minor component (~10%) after 6 hours.

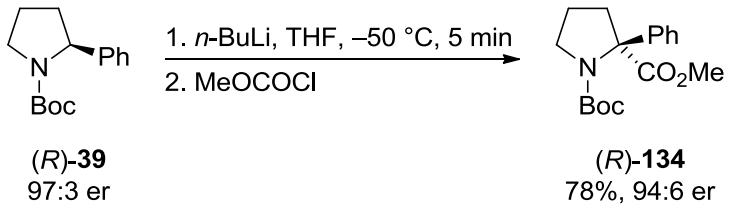
Conversely, lithiation of *N*-Boc piperidine **10** using *s*-BuLi/(+)-sparteine surrogate (+)-**26** led to rapid formation of lithiated species **11**, with lithiation reaching completion within 3 hours. The reactivity series of the *s*-BuLi/diamine complexes observed in this study corroborated the reactivity series determined by competition experiments in the lithiation of *N*-Boc pyrroline **12** (see Scheme 1.14).[53]

In situ ReactIR™ spectroscopy is a powerful tool for detecting reactive intermediates and for elucidating reaction times and kinetics. Additionally, it can be used to probe the subtleties of reaction mechanisms. In 2012, O'Brien and Coldham reported the benzylic lithiation of 2-phenyl *N*-Boc pyrrolidine **39**, with the methodology development assisted by the use of *in situ* ReactIR™ spectroscopy.[115] Lithiation of 2-phenyl *N*-Boc pyrrolidine **39** ($\nu_{C=O}$ 1701 cm^{-1}) with *n*-BuLi in THF at –78 °C was monitored by *in situ* ReactIR™ spectroscopy. It was found that fast initial lithiation to give lithiated species **133** ($\nu_{C=O}$ 1643 cm^{-1}) occurred within 2 min (Scheme 2.7). However, the reaction only reached partial completion. This was attributed to the fact that *N*-Boc rotamers **39a** and **39b** do not readily interconvert at –78 °C. Only **39a** can undergo benzylic lithiation due to the alignment of the Boc group. α-Lithiation of **39b** does not occur as *n*-BuLi is not basic enough to cause the transformation.



Scheme 2.7 Partial lithiation of 2-phenyl *N*-Boc pyrrolidine **39**

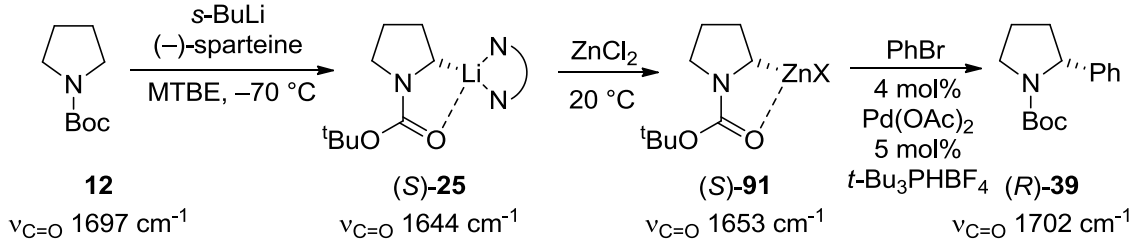
ReactIR™ spectroscopy was used to find a temperature at which *N*-Boc rotamers **39a** and **39b** could interconvert without significant loss of enantioenrichment, due to configurational instability of the intermediate organolithium.[61] The optimised conditions of –50 °C for 5 min before electrophile addition led to a range of products in good yield and er. In one example, 2-phenyl *N*-Boc pyrrolidine (*R*)-**39** (97:3 er) was converted into ester (*R*)-**134** in 78% yield and 94:6 er (Scheme 2.8).



Scheme 2.8

Interestingly, ReactIR™ spectroscopy showed that the rotamers of the six-membered analogue, 2-phenyl *N*-Boc piperidine **95** interconverted rapidly at –78 °C. A pre-lithiation complex was not observed in these cases, possibly due to the use of THF as a solvent, as observed by Collum in the enolisation of esters with LDA.[112]

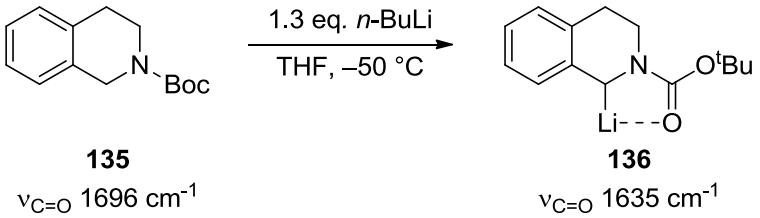
In situ ReactIR™ spectroscopy has not only been used to monitor the lithiation of *N*-Boc heterocycles. O'Brien and Campos showed that it was possible to monitor the entirety of a lithiation/transmetallation/Negishi coupling sequence with *N*-Boc pyrrolidine **12**.[99] Lithiation of **12** ($\nu_{C=O}$ 1697 cm^{-1}) using *s*-BuLi/(–)-sparteine proceeded *via* a pre-lithiation complex (not shown) to give 2-lithio-*N*-Boc pyrrolidine (*S*)-**25** ($\nu_{C=O}$ 1644 cm^{-1}) within 1 h (Scheme 2.9). Subsequent addition of $ZnCl_2$ caused no change in the IR spectrum at –70 °C. However, transmetallation was observed upon warming to 20 °C to give an organozinc species (*S*)-**91** ($\nu_{C=O}$ 1653 cm^{-1}). Finally, Negishi coupling was observed upon addition of bromobenzene, palladium(II) acetate and *t*-Bu_3PHBF_4 to give (*R*)-**39** ($\nu_{C=O}$ 1702 cm^{-1}).



Scheme 2.9

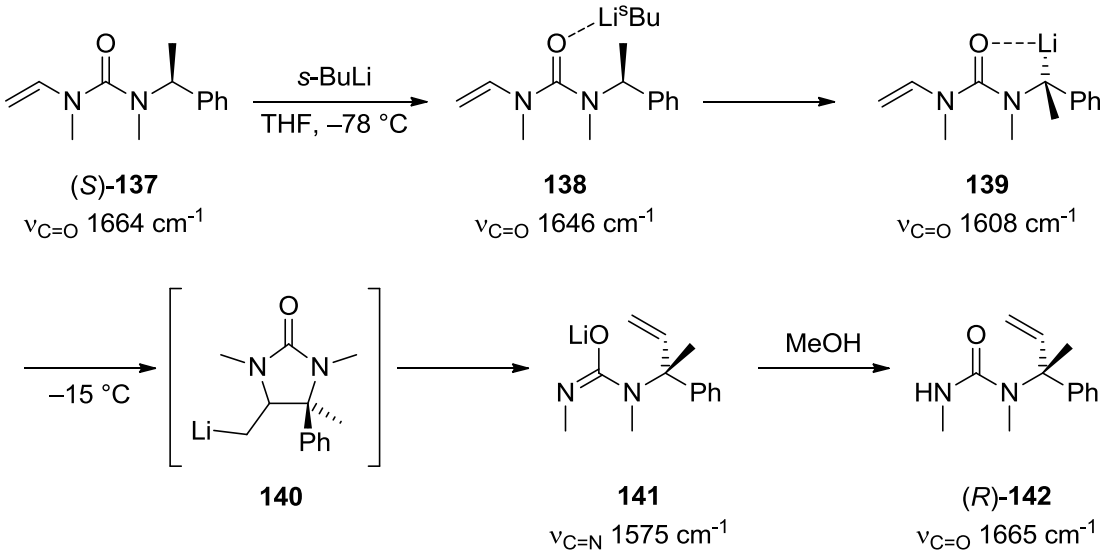
With the pioneering work by Beak, Smith, Collum, Campos and O'Brien, the use of *in situ* ReactIR™ spectroscopy for monitoring lithiation reactions has become more commonplace. Recently Coldham applied the use of *in situ* ReactIR™ monitoring to the lithiation of *N*-Boc tetrahydroisoquinoline **135**.[116] It was shown that only partial lithiation occurred at –78 °C due to the fact that the *N*-Boc rotamers of **135** did not

interconvert at low temperature. However, with *n*-BuLi in THF at –50 °C, complete benzylic lithiation of *N*-Boc tetrahydroisoquinoline **135** ($\nu_{C=O}$ 1696 cm^{-1}) occurred to give lithiated species **136** ($\nu_{C=O}$ 1635 cm^{-1}) (Scheme 2.10)



Scheme 2.10

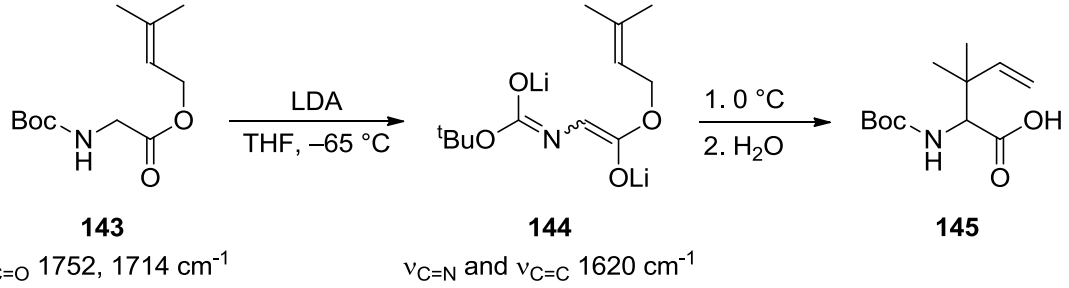
Clayden and co-workers have used the technique for monitoring the organolithium mediated intramolecular arylation and vinylation of ureas.[117-119] In one study, treatment of vinyl urea (*S*)-**137** ($\nu_{C=O}$ 1664 cm^{-1}) with *s*-BuLi in Et_2O at –78 °C led to the formation of pre-lithiation complex **138** ($\nu_{C=O}$ 1646 cm^{-1}) and then lithiated species **139** ($\nu_{C=O}$ 1608 cm^{-1}). Upon warming the reaction to –15 °C, rearrangement to **141** ($\nu_{C=N}$ 1575 cm^{-1}) occurred through intermediate **140**. Finally, quenching the reaction with MeOH resulted in the formation of rearranged product (*R*)-**142** ($\nu_{C=O}$ 1665 cm^{-1}) (Scheme 2.11).[118]



Scheme 2.11 Organolithium mediated rearrangement of (*S*)-**137**

Researchers at Pfizer have used *in situ* ReactIR™ spectroscopy to assess the stability of intermediates in an Ireland-Claisen rearrangement.[120] Treatment of *N*-Boc ester **143** ($\nu_{C=O}$ 1752, 1714 cm^{-1}) with >2.0 eq. of LDA at –65 °C resulted in the formation of

conjugated enolate **144** ($\nu_{C=N}$ and $\nu_{C=C}$ 1620 cm^{-1}). Subsequent warming to 0 °C caused rearrangement to acid **145** (Scheme 2.12).



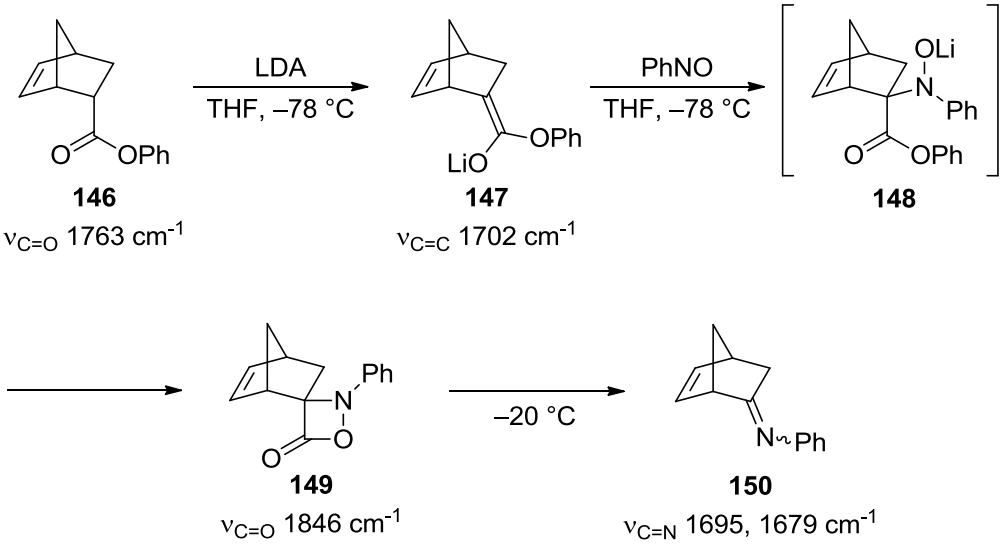
143
$\nu_{C=O}$ 1752, 1714 cm^{-1}

144
$\nu_{C=N}$ and $\nu_{C=C}$ 1620 cm^{-1}

145

Scheme 2.12

To date, as far we are aware, only one example detailing the ReactIR™ spectroscopic monitoring of the trapping of an organolithium species has been reported. In 2008, Yamamoto published an investigation into the trapping and rearrangement of a lithium enolate.[121] Phenyl ester **146** ($\nu_{C=O}$ 1763 cm^{-1}) was subjected to LDA in THF at –78 °C and the rapid formation of lithium enolate **147** ($\nu_{C=C}$ 1702 cm^{-1}) was observed. Subsequent addition of nitrosobenzene resulted in fast trapping and formation of oxazetidin-4-one **149** ($\nu_{C=O}$ 1846 cm^{-1}) *via* **148**, within 1 min. Upon warming to –20 °C, **149** underwent fragmentation resulting in the formation of imine isomers **150** ($\nu_{C=N}$ 1695, 1679 cm^{-1}) (Scheme 2.13). The observation of oxazetidin-4-one **149** by *in situ* ReactIR™ spectroscopy was used as proof of the reaction mechanism.



146
$\nu_{C=O}$ 1763 cm^{-1}

147
$\nu_{C=C}$ 1702 cm^{-1}

148

149
$\nu_{C=O}$ 1846 cm^{-1}

150
$\nu_{C=N}$ 1695, 1679 cm^{-1}

Scheme 2.13

In situ IR monitoring of lithiation reactions has allowed real time visualisation of reaction progress and the ability to investigate the effect of solvents, temperature and additives. ReactIR™ spectroscopic monitoring of lithiation reactions has been used for the direct observation of pre-lithiation complexes and other reaction intermediates, hence allowing elucidation of reaction mechanisms. Additionally, the technique has been used recently to study the rotation of Boc rotamers of *N*-Boc heterocycles at low temperature. However, the incredibly powerful technique has not previously been applied to the systematic study of the lithiation/trapping of *N*-Boc heterocycles.

Whilst ReactIR™ spectroscopic monitoring of lithiation reactions is a powerful technique, there are significant limitations. The absolute concentration of a species in a reaction is impossible to determine from the absorbance alone. Calibration curves can be obtained for some species, although this is not possible for transitory, unstable organolithium intermediates. Additionally, due to the corrosive nature of *s*-BuLi, the reactions need to be run at low concentration to avoid damaging the ReactIR™ probe. Therefore, in order to generate a reliable signal to noise ratio, measurements cannot be recorded more frequently than every minute. This prevents drawing accurate comparisons about relatively fast lithiation reactions. Also, the temperature dependence of the IR spectrum makes it difficult to vary the reaction temperature within an experiment.

2.2 *In situ* ReactIR™ Spectroscopic Monitoring of *N*-Boc Heterocycle Lithiations

Building upon previous work within the O'Brien group, both published[95,99] and unpublished,[122] the development of a definitive guide for the time required for complete lithiation of a range of *N*-Boc heterocycles with a range of diamines was undertaken. The substrates chosen for study are shown in Figure 2.2. Heterocycles that have previously been widely studied for asymmetric lithiation/trapping methodologies such as *N*-Boc pyrolidine **12** and *N*-Boc piperidine **10** were included, together with substrates at the main focus of this thesis, *N*-Boc piperazines **117**, **151** and **152**. The effect of ring size was of interest and therefore *N*-Boc azepine **153** and *N*-Boc imidazolidine **154** were chosen as substrates. The effect of heteroatoms and substituents in the 4-position of piperidines was of interest and therefore *N*-Boc morpholine **155** and substituted *N*-Boc piperidines **49**, **66**, **68**, **97**, **98** and **156** were also chosen for study.

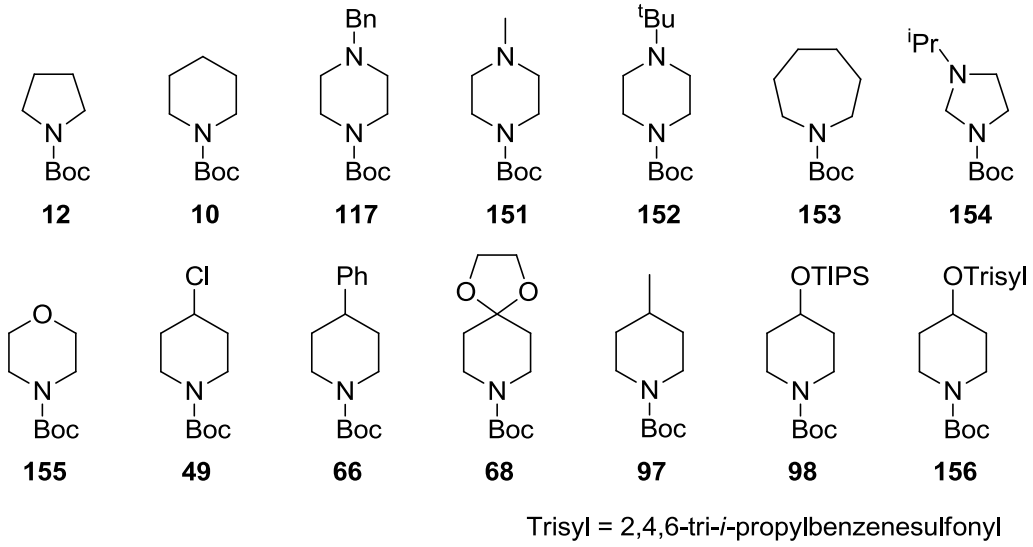


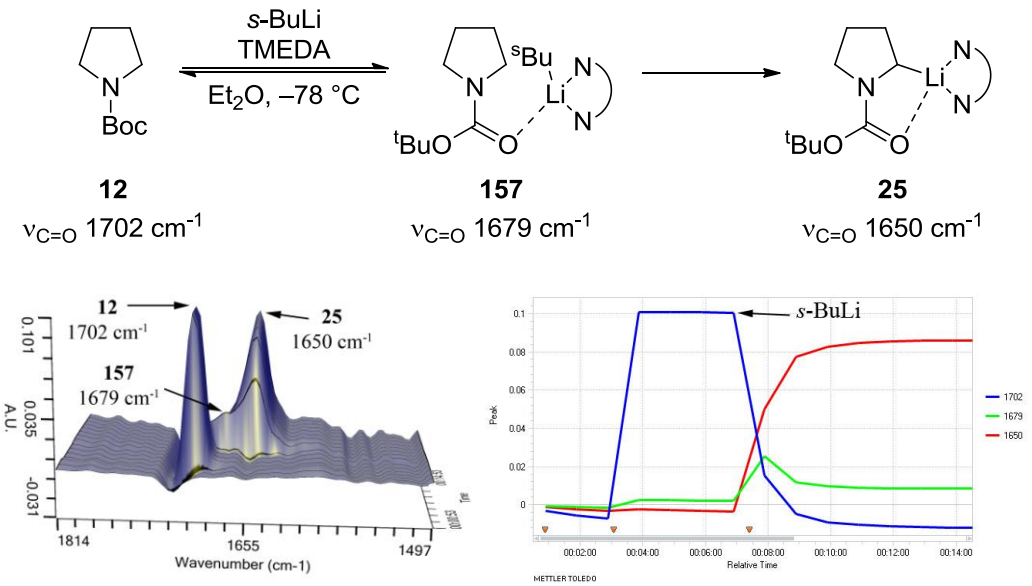
Figure 2.2 *N*-Boc heterocycles used for the *in situ* ReactIR™ spectroscopic study of lithiation times

The diamines employed were TMEDA, (–)-sparteine and the (+)-sparteine surrogate (+)-**26**. In general, reactions were performed by pre-mixing a solution of *N*-Boc heterocycle and diamine at –78 °C in Et_2O before addition of *s*-BuLi. An IR spectrum was recorded every minute and the time taken for the lithiation to reach completion was determined based on the decrease in $\nu_{C=O}$ for the starting material and the corresponding

increase in $\nu_{C=O}$ for the lithiated species. No attempt to trap the lithiated intermediates was undertaken, except in the case of *N*-Boc morpholine **155**.

Since Beak's pioneering report of the asymmetric lithiation/trapping of *N*-Boc pyrrolidine **12**,[42] it has been the heterocycle of choice for the development of many new asymmetric deprotonation methodologies.[36] Therefore, initial *in situ* ReactIR™ spectroscopic studies focused on verifying the results obtained within the O'Brien group with *N*-Boc pyrrolidine **12**.[122]

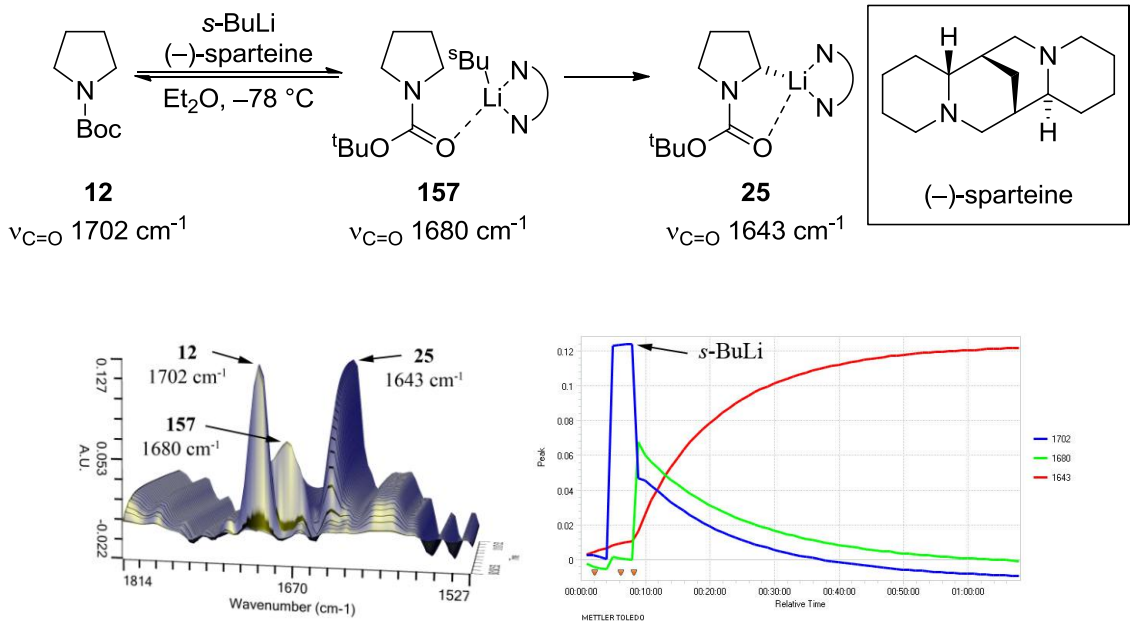
ReactIR™ monitoring of the addition of *s*-BuLi to **12** at –78 °C in Et_2O in the presence of TMEDA was performed (Scheme 2.14). The data are presented in two forms. Firstly, the 3D plot shows the progress of the reaction over time and the appearance and disappearance of signals within the carbonyl region can clearly be seen. Secondly, the 2D plot shows the change in absorbance at specific wavelengths over time, with *N*-Boc pyrrolidine **12** shown in blue, the pre-lithiation complex **157** in green and the lithiated species **25** in red. In this case, addition of *s*-BuLi to **12** caused the partial disappearance of the signal at $\nu_{C=O}$ 1702 cm^{-1} and a new signal being observed at $\nu_{C=O}$ 1679 cm^{-1}. Due to the overwhelming literature precedent and the signal's transitory nature, this was assigned to the pre-lithiation complex **157**. A second new signal was observed at $\nu_{C=O}$ 1650 cm^{-1} and assigned to the lithiated intermediate **25**. The data shows that complete lithiation occurs within 5 min at –78 °C. This agrees with previous work in the O'Brien group.[122]



Scheme 2.14 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi/TMEDA. The position of the arrow shows the time when the indicated reagent was added to the reaction mixture

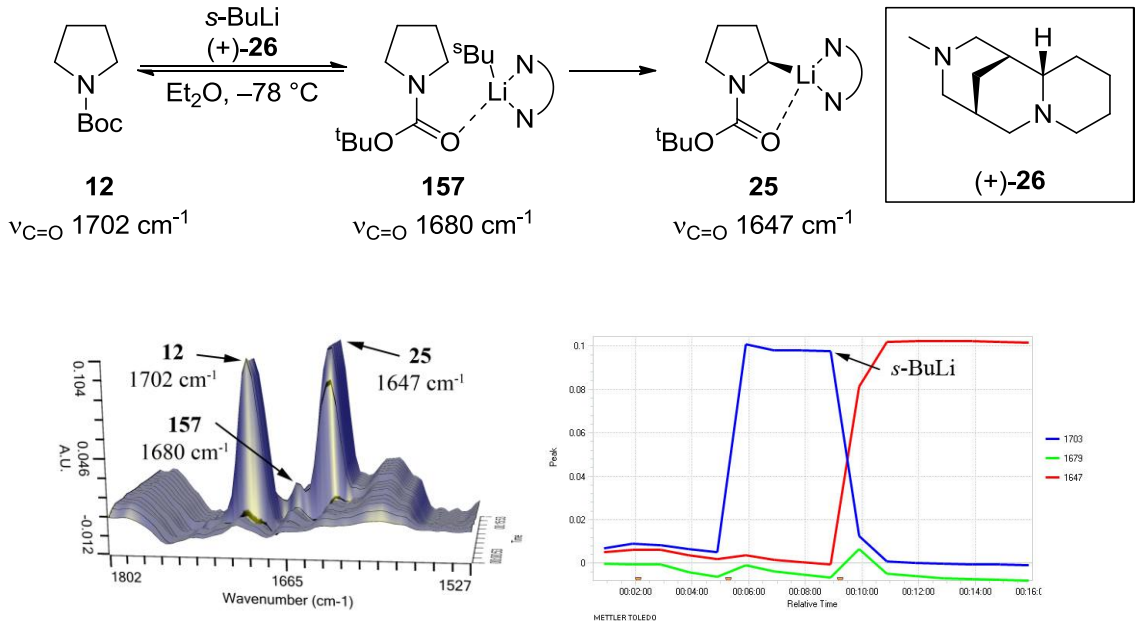
The fact that the lithiation was complete within 5 min shows that the 3.5 h lithiation time originally used by Beak was unnecessary.[34] The structures of **157** and **25** shown (and those presented throughout this chapter) are possibly oversimplified, as aggregated species may have formed. Nonetheless, work by Beak proposed similar structures of a pre-lithiation complex and lithiated intermediate with *i*-PrLi/(–)-sparteine (see Scheme 1.11).[11]

An analogous reaction was performed in the presence of (–)-sparteine (Scheme 2.15). Addition of *s*-BuLi to a mixture of **12** ($\nu_{C=O}$ 1702 cm^{-1}) and (–)-sparteine resulted in formation of the pre-lithiation complex **157** ($\nu_{C=O}$ 1680 cm^{-1}). Due to the lithiation with *s*-BuLi/(–)-sparteine being slower than with *s*-BuLi/TMEDA more of the pre-lithiation complex **157** was initially observed. Complete consumption of both starting material **12** and pre-lithiation complex **157** to give 2-litio-*N*-Boc pyrrolidine **25** ($\nu_{C=O}$ 1643 cm^{-1}) occurred within 1 h. Clearly, the lithiation event does not require the long lithiation times (4–6 h) originally reported.[42,62]



Scheme 2.15 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi/(–)-sparteine.

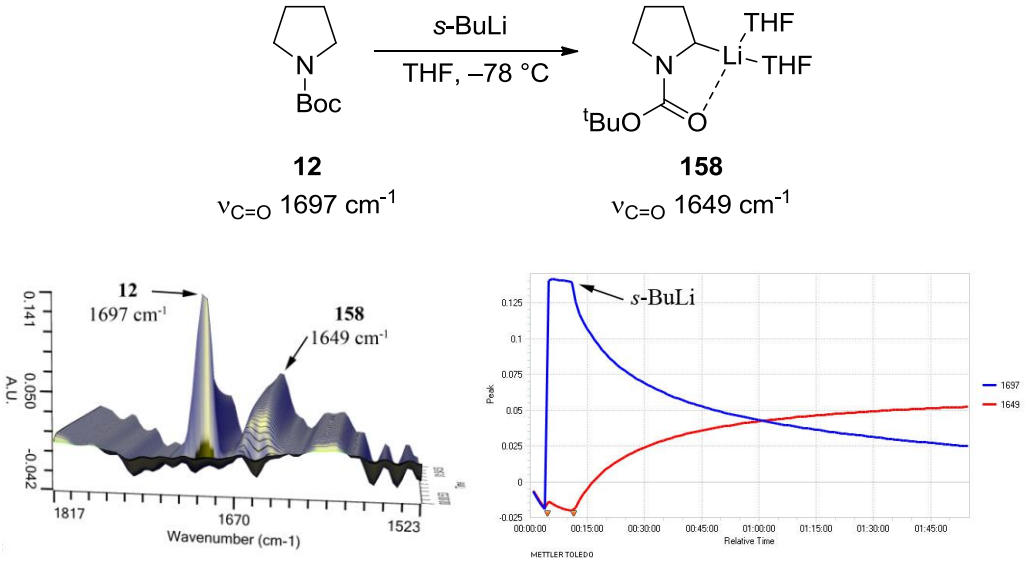
Lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi and (+)-sparteine surrogate (+)-**26** proceeded rapidly *via* pre-lithiation complex **157** ($\nu_{C=O}$ 1680 cm^{-1}) to give lithiated *N*-Boc pyrrolidine **25** ($\nu_{C=O}$ 1647 cm^{-1}) in under 2 min (Scheme 2.16). The 5 h lithiation time reported by O'Brien and co-workers was unnecessary.[48]



Scheme 2.16 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi/(+)-sparteine surrogate (+)-**26**

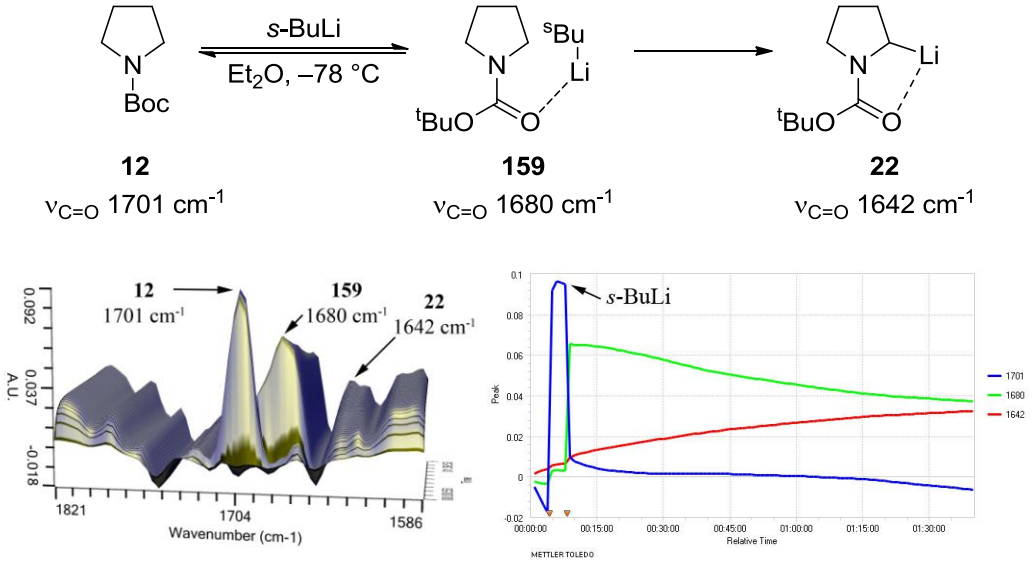
As can been seen from these two results, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(+)-**26** was an order of magnitude faster than with *s*-BuLi/(–)-sparteine, corroborating observations made using competition experiments by O'Brien and co-workers (see Scheme 1.14).[53] This trend has also been reported using *in situ* ReactIR™ spectroscopy studies on *N*-Boc piperidine **10**.[95]

In 2010, O'Brien and co-workers reported the diamine-free lithiation of *N*-Boc pyrrolidine **12** using *s*-BuLi in THF at a range of temperatures. When the lithiation was performed for 1 h at –78 °C, followed by electrophile trapping, yields of up to 89% of *α*-substituted pyrrolidines were reported.[59] This indicated that complete lithiation was occurring within 1 h. To confirm this observation, ReactIR™ monitoring of this lithiation of *N*-Boc pyrrolidine **12** in THF was performed (Scheme 2.17). Interestingly, addition of *s*-BuLi to **12** ($\nu_{C=O}$ 1697 cm^{-1}) in THF did not result in an observable peak for the pre-lithiation complex. The only new species to be identified was lithiated species **158** ($\nu_{C=O}$ 1649 cm^{-1}). Lithiation was sluggish, taking 90 min to reach completion. However, the yield of *α*-substituted pyrrolidines obtained by O'Brien after a lithiation time of 1 h (89%) indicates that the reaction was nearly complete after this time. The solution structure of organolithium **158** is unknown. It is possibly a monomeric species coordinated by two molecules of THF. However, other aggregation states are possible.



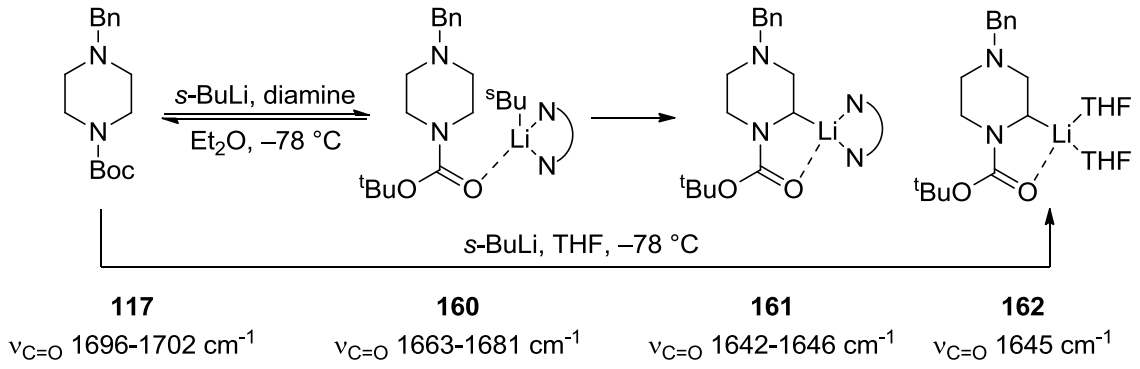
Scheme 2.17 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi in THF

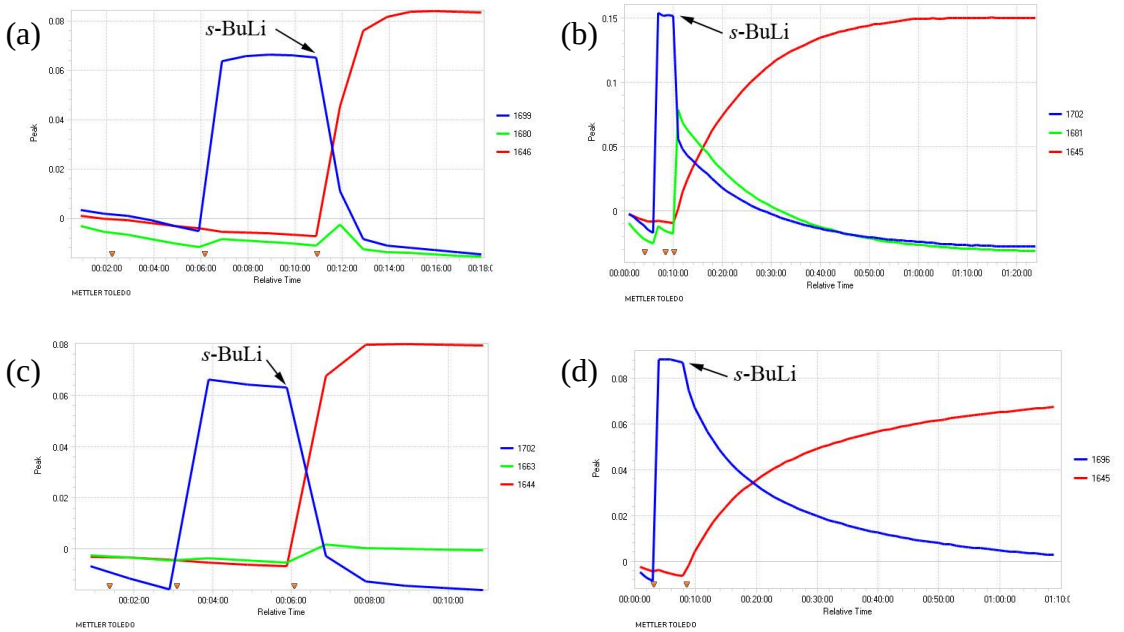
An experiment to determine the background rate of the lithiation of **12** in Et_2O in the absence of a diamine was also conducted (Scheme 2.18). A previous report had shown that lithiation for 1 h with *s*-BuLi in Et_2O at –78 °C followed by trapping resulted in only an 8% yield of an *α*-substituted pyrrolidine.[59] Addition of *s*-BuLi to **12** ($\nu_{C=O}$ 1701 cm^{-1}) in Et_2O at –78 °C resulted in almost complete formation of pre-lithiation complex **159** ($\nu_{C=O}$ 1680 cm^{-1}). As expected, lithiation to give **22** ($\nu_{C=O}$ 1642 cm^{-1}) was slow, with only a small amount of lithiated species being observed within 90 min. The structure of the pre-lithiation complex **159** is unknown. Due to the poor de-aggregating effect of the relatively non-coordinating Et_2O solvent, lithiation may be effected by an aggregate.



Scheme 2.18 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi in Et_2O

With the investigations into the optimum lithiation times for *N*-Boc pyrrolidine **12** with a range of ligands confirming previous results and observations, attention was turned to *N*-Boc piperazines. Lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was performed under standard conditions (Et_2O, –78 °C), using the three chosen diamines and under diamine-free conditions in THF. The results of this investigation are presented in Scheme 2.19. As expected, lithiation of *N*-Boc-*N′*-benzyl piperazine **117** ($\nu_{C=O}$ 1696-1702 cm^{-1}) proceeded *via* a pre-lithiation complex **160** ($\nu_{C=O}$ 1663-1681 cm^{-1}) in all cases except under diamine-free conditions (Scheme 2.19d) to give lithiated species **161** ($\nu_{C=O}$ 1642-1646 cm^{-1}) or **162** ($\nu_{C=O}$ 1645 cm^{-1}). It is worth noting that when (+)-**26** was used, pre-lithiation complex **160** was observed at a lower frequency ($\nu_{C=O}$ 1663 cm^{-1}) than when TMEDA or (–)-sparteine were employed ($\nu_{C=O}$ 1680-1681 cm^{-1}).

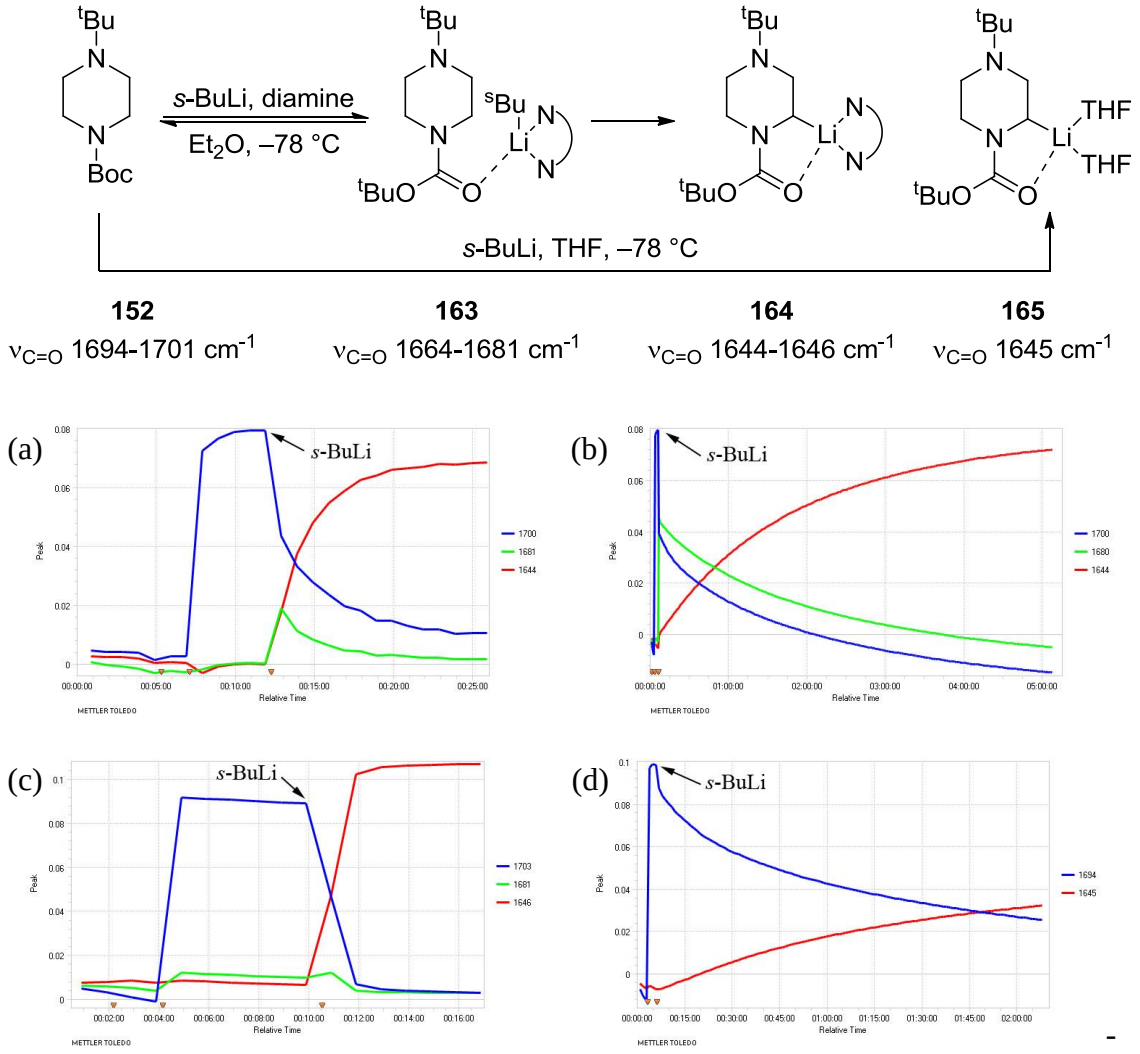




Scheme 2.19. Lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi and ligands, (a) TMEDA, (b) (–)-sparteine, (c) (+)-**26**, (d) THF

Unsurprisingly, the reactivity order of the ligands is the same as seen with *N*-Boc pyrrolidine **12** and *N*-Boc piperidine **10**. Use of *s*-BuLi and (+)-sparteine surrogate (+)-**26** results in the fastest lithiation, with *N*-Boc-*N′*-benzyl piperazine **117** being completely converted into lithiated species **161** within 2 min (Scheme 2.19c). With TMEDA, lithiation to **161** was complete within 5 min (Scheme 2.19a) and with (–)-sparteine lithiation was complete within 1 h (Scheme 2.19b). The use of diamine-free conditions in THF resulted in lithiation to **162** being almost complete within 1 h, with the pre-lithiation complex not being observed (Scheme 2.19d). The times required for lithiation are similar to those seen for *N*-Boc pyrrolidine **12**.

The effect of the protecting group on *N*-Boc piperazine was assessed by ReactIR™ monitoring of *N*-Boc-*N′*-*t*-butyl piperazine **152** ($\nu_{C=O}$ 1694-1701 cm^{-1}) (Scheme 2.20). As now expected, lithiation with *s*-BuLi/diamines proceeded *via* a pre-lithiation complex **163** ($\nu_{C=O}$ 1664-1681 cm^{-1}) to lithiated piperazine **164** ($\nu_{C=O}$ 1644-1646 cm^{-1}).

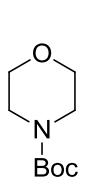
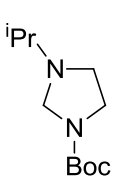
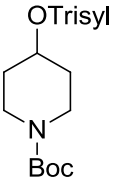
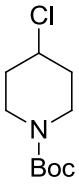
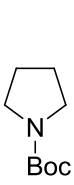
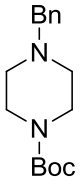
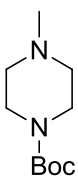


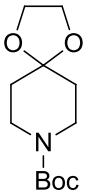
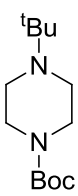
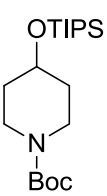
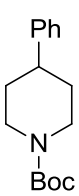
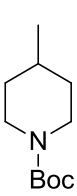
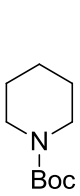
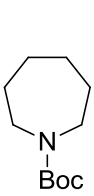
Scheme 2.20 Lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** with *s*-BuLi and ligands, (a) TMEDA, (b) (–)-sparteine, (c) (+)-**26**, (d) THF

Although the reactivity order of the ligands remained the same, the *t*-butyl group resulted in much slower lithiation than seen with *N*-Boc-*N′*-benzyl piperazine **117**. For example, lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** with *s*-BuLi/(+)-sparteine surrogate (+)-**26** took 5 min to reach completion (Scheme 2.20c) whereas with *N*-Boc-*N′*-benzyl piperazine **117**, lithiation was complete with 2 min (see Scheme 2.19c). Similarly, lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** with *s*-BuLi and (–)-sparteine took more than 5 h (Scheme 2.20b) but was complete with 1 h with the *N*-benzyl

analogue **117** (see Scheme 2.19b). This difference in lithiation times is remarkable considering the distance of the nitrogen protecting group from the actual site of *α*-lithiation.

ReactIR™ monitoring studies with *s*-BuLi and diamines were performed with the full range of *N*-Boc heterocycles depicted in Figure 2.2. The results are summarised in Table 2.1 with *in situ* ReactIR™ traces detailed in the experimental section (see Chapter 6.3). A full series of experiments with each *N*-Boc heterocycle and each diamine was not performed. However, sufficient experimentation was completed to provide a reactivity series for all 14 substrates. Table 2.1 details the time taken, in minutes, for complete lithiation of a particular *N*-Boc heterocycle using 1.3 eq. of *s*-BuLi and diamine at –78 °C (unless otherwise stated). Different diamines provided different relative time scales, with *s*-BuLi/(+)-sparteine surrogate (+)-**26** or TMEDA resulting in relatively fast lithiations and *s*-BuLi/(–)-sparteine resulting in slow lithiations. The different reactivities of these lithiation systems allowed a relative order for very reactive and very unreactive *N*-Boc heterocycles to be established. Table 2.1 is ordered with the *N*-Boc heterocycles most reactive towards lithiation first and the most reticent last. Substrates were prepared using literature procedures[59] or were available from elsewhere within the group.[70,122,123]

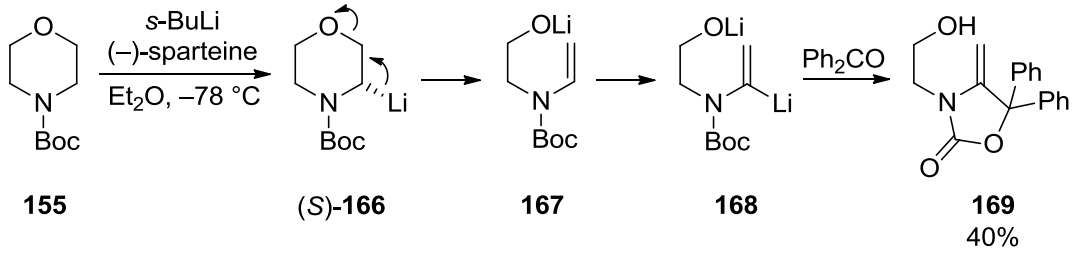
	 **155**	 **154**	 **156**	 **49**	 **12**	 **117**	 **151**
TMEDA			1[a]	2[a]	5	5	8
(–)-Sparteine	1[a]	2	10[a]	30[a]	60	60	90
(+)-**26**					2	2	2

	 **68**	 **152**	 **98**	 **66**	 **97**	 **10**	 **153**
TMEDA		13	40	60	45[b], 25[c]	50[b], 35[c]	120[c]
(–)-Sparteine		> 300					
(+)-**26**	4	5	30	20			

[a] 2.6 eq. of *s*-BuLi and diamine were used. [b] Reaction performed at –60 °C. [c] Reaction performed at –50 °C.

Table 2.1 Reactivity series of commonly used *N*-Boc heterocycles

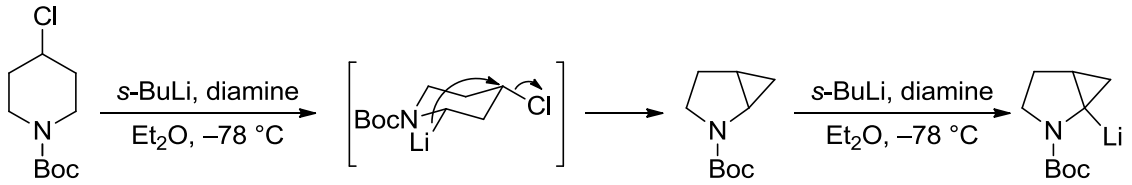
N-Boc morpholine **155** was found to undergo lithiation extremely rapidly, reaching completion within one minute when employing the slowest lithiation system, namely, *s*-BuLi and (–)-sparteine. Lithiation was performed using 2.6 eq. of *s*-BuLi and (–)-sparteine followed by trapping with benzophenone (Scheme 2.21). The trapping step was not monitored by ReactIR™ spectroscopy. Rapid deprotonation resulted in the formation of lithiated species (*S*)-**166** (presumed stereochemistry), which was not stable.[122] Under the reaction conditions ring-opening of 2-lithio-*N*-Boc morpholine (*S*)-**166** occurred to give alkoxide **167**. A subsequent vinylic lithiation gave **168**.[75] Trapping with benzophenone and subsequent cyclisation resulted in oxazolidinone **169** being isolated in 40% yield. Due to the rapid vinylic lithiation of **167**, 2.6 eq. of *s*-BuLi were required to ensure complete formation of **168**. A similar ring-opening has been observed by Lautens for a related bicyclic system.[124]



155 (*S*)-**166** **167** **168** **169** 40%

Scheme 2.21 Mechanism of the formation of **169**

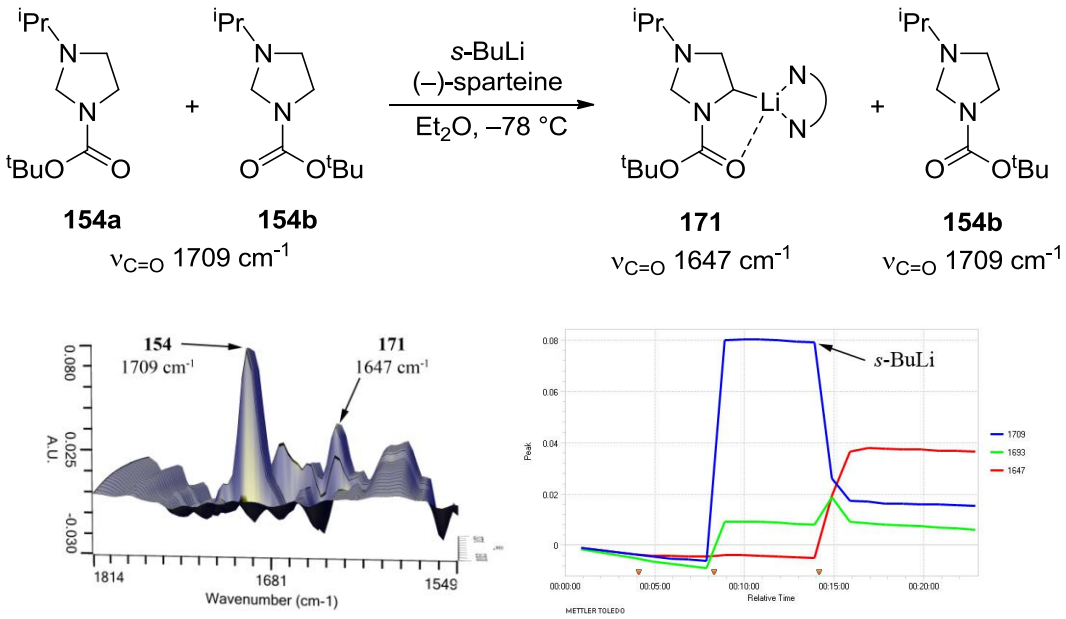
In order to determine the time required for the lithiation of 4-chloro *N*-Boc piperidine **49** and 4-OTrisyl *N*-Boc piperidine **156**, 2.6 eq. of *s*-BuLi/diamine were required. After the first rate determining lithiation of **49** to give **50**, intramolecular cyclisation occurred to give a azabicyclo[3.1.0]hexane **51**. A second rapid lithiation of the acidic cyclopropyl proton then occurred to give **170** (Scheme 2.22).[69]



49 **50** **51** **170**

Scheme 2.22 Mechanism of lithiation of **49**

Lithiation of *N*-Boc imidazolidine **154** was the second fastest lithiation monitored. Reaction with *s*-BuLi and (–)-sparteine resulted in a rapid (2 min) but partial lithiation to **171** at –78 °C (Scheme 2.23). Coldham has previously noted (by ^{1}H NMR spectroscopy) that the barrier to rotation of *N*-Boc rotamers **154a** and **154b** at –78 °C was >100 h, explaining the partial lithiation observed.[125] Only *N*-Boc rotamer **154a** underwent lithiation to **171**; Coldham has shown that lithiation of rotamer **154b** does not occur, possibly due to steric hindrance from the *N*-*i*-Pr group.



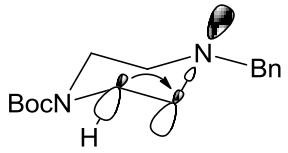
Scheme 2.23 Partial lithiation of *N*-Boc imidazolidine **154**

The effect of ring size on the lithiation times can be clearly seen. As previously observed using ReactIR™ spectroscopy, the lithiation of *N*-Boc pyrrolidine **12** was significantly faster than the lithiation of *N*-Boc piperidine **10**.[95,99] This study shows lithiation of the former using *s*-BuLi/TMEDA was complete within 5 min at –78 °C (see Scheme 2.14), whereas with *N*-Boc piperidine **10**, complete lithiation required 50 min at –60 °C and 35 min at –50 °C. The seven-membered analogue *N*-Boc azepine **153** took even longer to lithiate, requiring 120 min at –50 °C to reach completion. Previous attempts at the lithiation/trapping of *N*-Boc azepine **153** with *s*-BuLi/TMEDA at –78 °C for 3-3.5 h resulted in poor yields of isolated products, which can now be accounted for by slow lithiation.[34,101]

As previously noted, the time required for complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was considerably shorter than for lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152**. This was assumed to be due to steric factors even though the sterically demanding group is far removed from the site of lithiation. *N*-Boc-*N′*-methyl piperazine **151** has a similar steric footprint and reactivity to *N*-Boc-*N′*-benzyl piperazine **117**, adding support to this proposition.

Interestingly, the lithiation of *N*-Boc-*N′*-benzyl piperazine **117** takes a considerably shorter time than the lithiation of *N*-Boc piperidine **10**. Considering both systems are six-membered, the geometry of the heterocycle/*s*-BuLi/diamine complex would be

expected to be similar. It is possible that for *N*-Boc piperazines, back donation from the *α*-proton C-H σ bonding orbital into the anti-periplanar, low energy antibonding σ* C-N orbital makes the *α*-proton more acidic than that in *N*-Boc piperidine **10** (Figure 2.3). However, it is possible that this is an oversimplification and that the energy of the transition state structures governs lithiation rates.[43,72]

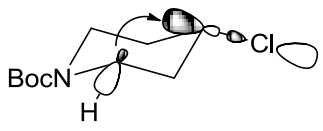


117

Figure 2.3 Frontier molecular orbital explanation for the increased acidity of **117**

The above argument cannot explain the increase in reactivity of *N*-Boc imidazolidine **154** in comparison with *N*-Boc pyrrolidine **12** as the former cannot adopt the necessary anti-periplanar geometry. Alternatively, the rate acceleration seen with *N*-Boc morpholine **155**, *N*-Boc piperazine **117** and *N*-Boc imidazolidine **154** could be due to the acidifying effect of a *β*-heteroatom through simple electron withdrawal.

The effect of the substituents on *N*-Boc piperidine is illuminating. Electron withdrawing substituents in the 4-position (OTrisyl and chloro) result in the time required for lithiation to be significantly reduced. Substituted piperidines **49** and **156** undergo complete lithiation with *s*-BuLi/TMEDA within 1 min and 2 min respectively, whereas the parent *N*-Boc piperidine **10** takes 50 min at –60 °C. It has been postulated that the difference in reactivity between 4-chloro-*N*-Boc piperidine **49** and *N*-Boc piperidine **10** is due to overlap of the C-H σ bonding orbital and the σ* antibonding orbital of the C-Cl bond (Figure 2.4).[70] This effectively makes the reactive *α*-proton more acidic, resulting in increased reactivity.



49

Figure 2.4 Frontier molecular orbital explanation for the increased acidity of **49**

4-Methyl *N*-Boc piperidine **97** has similar lithiation times to *N*-Boc piperidine **10**, with the methyl substituent having little effect on reactivity: 45 min and 50 min respectively

with *s*-BuLi/TMEDA at –60 °C. 4-Phenyl and 4-OTIPS piperidines **66** and **98** undergo lithiation slightly faster than *N*-Boc piperidine **10**. The relative lithiation times of 4-phenyl *N*-Boc piperidine **60** and 4-OTIPS *N*-Boc piperidine **98** are interesting. The use of *s*-BuLi/TMEDA results in 4-OTIPS *N*-Boc piperidine **98** undergoing complete lithiation in 40 min, whereas 4-phenyl *N*-Boc piperidine **66** takes 60 min for lithiation to reach completion, indicating that silyl-protected piperidine **98** is lithiated more readily. Conversely phenyl piperidine **66** underwent complete lithiation faster than silyl-protected piperidine **98** when using *s*-BuLi/(+)-sparteine surrogate (+)-**26** (20 min and 30 min respectively). It is possible that this switch in relative rates is due to sterics. The bulky OTIPS group of **98** may clash with the relatively more bulky ligand (+)-**26**, thus slowing the reaction.

Lithiation of acetal-protected piperidine **68** was rapid using *s*-BuLi and (+)-sparteine surrogate (+)-**26** (4 min). However, only partial lithiation occurred. It is not known why this is the case but the same outcome was noted in an earlier study in the group.[122] It is noteworthy that asymmetric lithiation/trapping of acetal protected piperidine **68** has been performed using Alexakis' diamine, giving a 53% yield after trapping with Me_3SiCl (see Scheme 1.31).[73]

In situ ReactIR™ spectroscopy is an incredibly powerful tool for studying the time taken for the lithiation of *N*-Boc heterocycles. This study has detailed the wide reactivity of *N*-Boc heterocycles towards deprotonation and highlighted patterns in the effect of substrate structure and diamine on lithiation times. Building upon earlier studies, this work has provided definitive lithiation times for a range of commonly used substrates and should act as a guide for further methodology development. Previous methods for determining the optimum lithiation times relied upon several lithiation/trapping reactions and analysis of the yields and enantioselectivities of these reactions, or alternatively, the use of competition experiments. The use of ReactIR™ spectroscopy to directly observed lithiation times not only simplifies the determination of lithiation times, but also does away with the reliance on the sometimes troublesome electrophilic trapping step.

2.3 *In situ* ReactIR™ Spectroscopic Monitoring of 2-Lithio-*N*-Boc Heterocycle Trapping

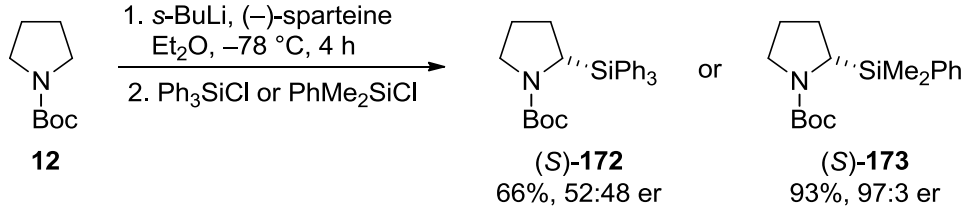
2.3.1 Subtleties of Electrophilic Trapping of 2-Lithio-*N*-Boc Heterocycles

It is tempting to assume that electrophilic trapping is a straightforward process with the electrophiles reacting rapidly with the highly reactive lithiated *N*-Boc heterocycles. There are several reports that hint that this may not be the case. Specifically, it is well known that alkyl lithium reagents can react slowly with chlorosilanes.[126-130]

As shown in Schemes 1.33 and 1.34 the trapping of lithiated *N*-Boc piperidine **10** with certain electrophiles ($PhMe_2SiCl$, methyl iodide and dimethyl sulfate) resulted in products with lower levels of enantioenrichment than expected.[95] This was attributed to slow electrophile trapping at low temperature (–78 °C). As the reaction warmed up towards room temperature the enantioenriched lithiated intermediate became configurationally unstable.[61,131] Subsequent trapping led to the observed low enantioselectivity. A second example is shown in Scheme 1.36. Coldham's DTR of *N*-Boc piperidines was only successful when Me_3SiCl was used as an electrophile. This was due to the fact that Me_3SiCl was relatively unreactive towards the lithiated *N*-Boc piperidine **10**, which allowed discrimination between the diastereomeric organolithium complexes.[76]

Slow trapping of lithiated *N*-Boc heterocycles is not just limited to *N*-Boc piperidine **10**. The trapping of lithiated *N*-Boc pyrrolidine **12** by Me_3SiCl may or may not be slow, but trapping clearly occurred at a temperature at which the lithiated intermediate was configurationally stable, as evidenced by the high er of the *α*-silyl pyrolidine product (see Scheme 1.7). This was not the case when trapping with sterically hindered silyl electrophiles. Products with poor levels of enantioselectivity were isolated, presumably due to the poor reactivity of the silanes towards the organolithium intermediates at low temperatures.[132-134] For example, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine followed by trapping with Ph_3SiCl gave silyl pyrrolidine (*S*)-**172** in 52:48 er (66% yield) (Scheme 2.24).[132] Trapping with the less hindered $PhMe_2SiCl$ led to products with excellent levels of enantioenrichment and (*S*)-**173** was obtained in 93% yield and 97:3 er. Although trapping lithiated *N*-Boc pyrrolidine **12** with $PhMe_2SiCl$

proceeded without complication, slow trapping was suspected with the analogous lithiated *N*-Boc piperidine **10**.[95]



Scheme 2.24

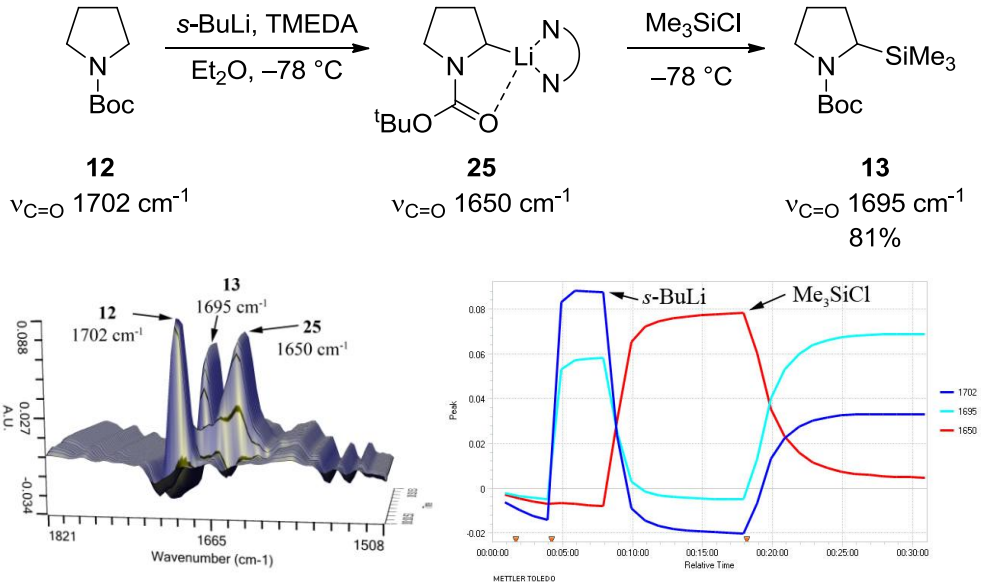
The empirical evidence detailed suggests that the trapping rates of electrophiles with different *N*-Boc heterocycles may be markedly different. Unfortunately, drawing firm conclusions from isolated yields and enantioselectivities is difficult and provides scant information on the actual rates of electrophile trapping. It was envisaged that ReactIR™ spectroscopy could provide more useful information on the time required for trapping with different electrophiles and *N*-Boc heterocycles. Additionally, the effect of different diamines, solvents and temperatures on the time taken for trapping could be directly quantified.

2.3.2 *In situ* ReactIR™ Spectroscopic Monitoring of Electrophilic Trapping

The ReactIR™ spectroscopic investigation of the rate of electrophile trapping was focused on three *N*-Boc heterocycles: *N*-Boc pyrrolidine **12**, *N*-Boc 4-phenyl piperidine **66** and *N*-Boc-*N′*-benzyl piperazine **117** (see Figure 2.1). The substituted piperidine **66** was chosen over *N*-Boc piperidine **10** as lithiation times at –78 °C for the latter were too long to be practical (see Table 2.1).

A comparison of the time required for complete trapping with the three lithiated substrates using Me_3SiCl as an electrophile was performed. The chlorosilane was chosen as an electrophile due to the fact that it is known to trap organolithiums slowly in some cases. This could allow any difference due to the nature of the *N*-Boc heterocycles to become evident. Reactions were generally performed at –78 °C to allow useful comparisons with previously reported reactions. Racemic lithiation using *s*-BuLi/TMEDA in Et_2O was chosen due to the short lithiation time.

To start with, *s*-BuLi was added to a stirred solution of *N*-Boc pyrrolidine **12** ($\nu_{C=O}$ 1702 cm^{-1}) and TMEDA in Et_2O at –78 °C (Scheme 2.25). Complete lithiation occurred within 5 min to give lithiated *N*-Boc pyrrolidine **25** ($\nu_{C=O}$ 1650 cm^{-1}). Then, Me_3SiCl was added to the reaction. Formation of *α*-silyl *N*-Boc pyrrolidine **13** ($\nu_{C=O}$ 1695 cm^{-1}) was observed (light blue line), and was complete within 15 min, as can be seen from the 3D and 2D graphs. The reaction was then quenched with aqueous ammonium chloride at –78 °C. Following work-up and purification, **13** was isolated in 81% yield from this specific experiment. The pre-lithiation complex has not been included on the 2D graph for the sake of clarity. Although it appears that the 2D plot shows starting material **12** reforming upon addition of the electrophile, the increase in absorbance at $\nu_{C=O}$ 1702 cm^{-1} is due to the broadness of the peak for the product, *α*-silyl *N*-Boc pyrrolidine **13** ($\nu_{C=O}$ 1695 cm^{-1}).

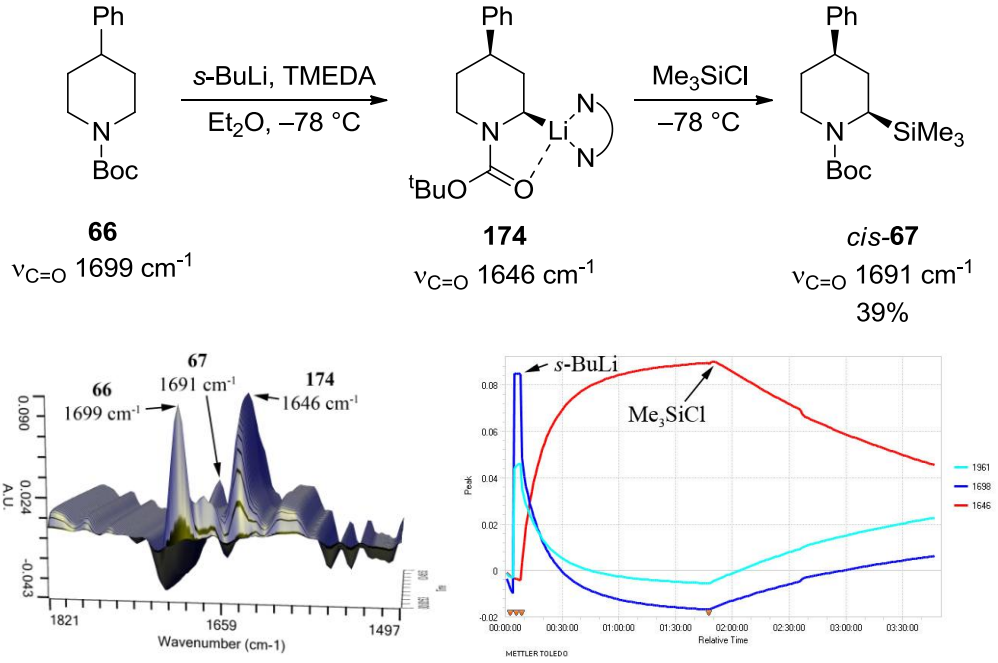


Scheme 2.25 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **12** with *s*-BuLi/TMEDA and Me_3SiCl. The position of the arrows show the time when the indicated reagents was added to the reaction mixture

This result is identical to that reported by Beak, *α*-silyl *N*-Boc pyrrolidine **13** was obtained in 81% yield when lithiation of *N*-Boc pyrrolidine **12** was accomplished with *s*-BuLi/TMEDA followed by addition of Me_3SiCl and subsequent warming to room temperature.[34]

When lithiation of *N*-Boc 4-phenyl piperidine **66** ($\nu_{C=O}$ 1699 cm^{-1}) was performed using *s*-BuLi/TMEDA to give lithiated species **174** ($\nu_{C=O}$ 1646 cm^{-1}), followed by trapping

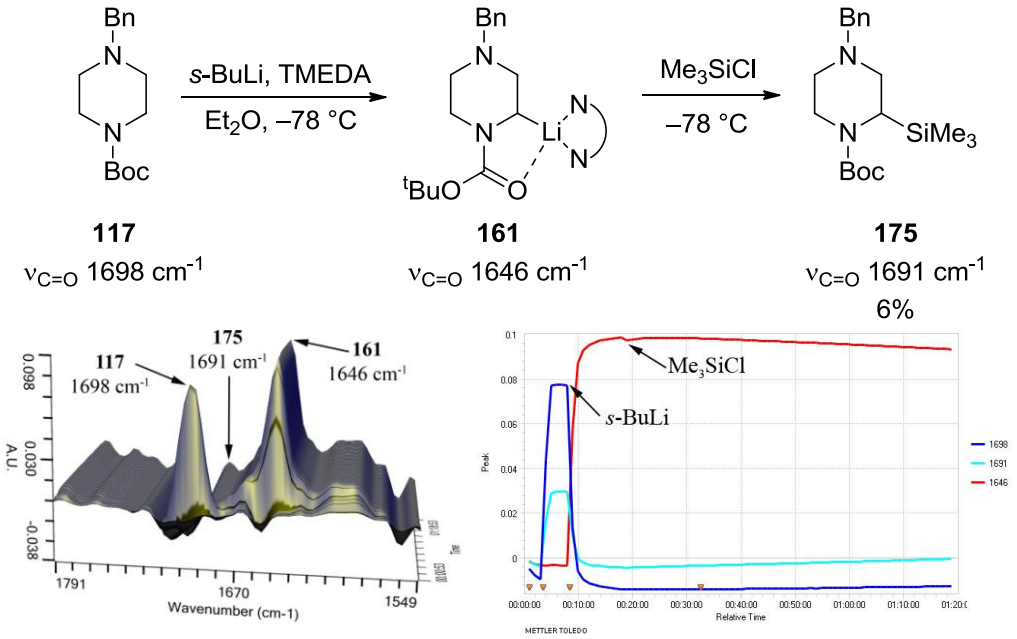
with Me_3SiCl, 2-silyl piperidine *cis*-**67** ($\nu_{C=O}$ 1691 cm^{-1}) formed slowly at –78 °C (Scheme 2.26). The rate of trapping was much slower than with *N*-Boc pyrrolidine **12**, as clearly shown by the 2D graph in Scheme 2.25. Trapping was incomplete after 2 h at –78 °C. At this point, the reaction was quenched with aqueous ammonium chloride and *cis*-*α*-silyl *N*-Boc-piperidine *cis*-**67** was isolated in 39% yield with 49% recovered starting material **66**. When Beak performed the same reaction, but allowed the reaction to warm to room temperature before quenching, *cis*-**67** was obtained in 99% yield.[34] Silyl piperidine *cis*-**67** was obtained as a single diastereomer due to an equatorial orientation of the phenyl ring, preferential equatorial lithiation and trapping with retention (see Scheme 1.42).[74]



Scheme 2.26 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **66** with *s*-BuLi/TMEDA and Me_3SiCl

When an analogous reaction using *N*-Boc-*N′*-benzyl piperazine **117** ($\nu_{C=O}$ 1698 cm^{-1}) was performed, the rate of trapping was considerably slower than with *N*-Boc 4-phenyl piperidine **66**. Very little trapping by Me_3SiCl to give **175** ($\nu_{C=O}$ 1695 cm^{-1}) was observed by ReactIR™ spectroscopy. The reaction was quenched after 1 h at –78 °C and *α*-silyl-*N*-Boc piperazine **175** was isolated in only 6% yield with 87% recovered starting material **117** (Scheme 2.27). When the same reaction was warmed to room temperature prior to quenching *α*-silyl-*N*-Boc piperazine **175** was obtained in a 68% yield (see

Scheme 3.4).[135] ReactIR™ spectroscopy clearly shows that the low yield of products *cis*-**67** and **175** was due to inefficient trapping and not the lithiation step.

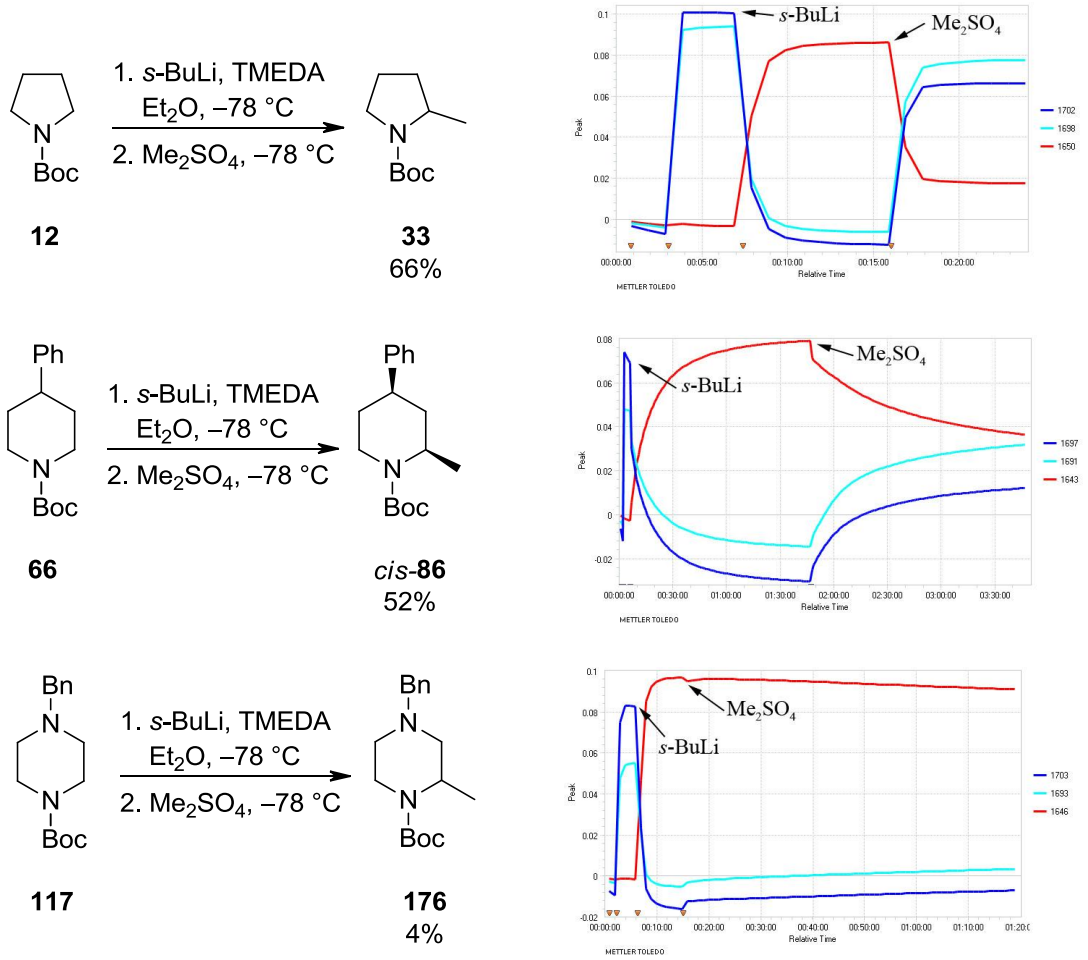


Scheme 2.27 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **117** with *s*-BuLi/TMEDA and Me_3SiCl

These three experiments show that there is a dramatic difference in the time taken for trapping with Me_3SiCl for the three *N*-Boc heterocycles **12**, **66** and **117**. Historically, the standard operating procedure for lithiation/trapping reactions involved warming the reactions to room temperature slowly (over many hours) after addition of the electrophile. This procedure has unwittingly allowed the isolation of products in excellent yields in the cases of 4-phenyl piperidine **66** and *N*-Boc-*N′*-benzyl piperazine **117** as trapping only proceeds quickly upon warming. In addition, for some substrates, trapping is complete relatively quickly at –78 °C and so long trapping times are not required.

Work within the O'Brien group hinted at the slow trapping of lithiated *N*-Boc piperidine **10** with methyl iodide and dimethyl sulfate.[95] Therefore, *in situ* ReactIR™ monitoring of trapping using these electrophiles was investigated. Trapping rates with dimethyl sulfate and isolated product yields along with the 2D ReactIR™ traces are shown in Scheme 2.28. It can be seen that trapping of the lithiated intermediate of *N*-Boc pyrrolidine **12** was fast, with complete trapping occurring within 3 min to give **33**, which was isolated in 66% yield. Trapping of lithiated *N*-Boc 4-phenyl piperidine **66** was much slower,

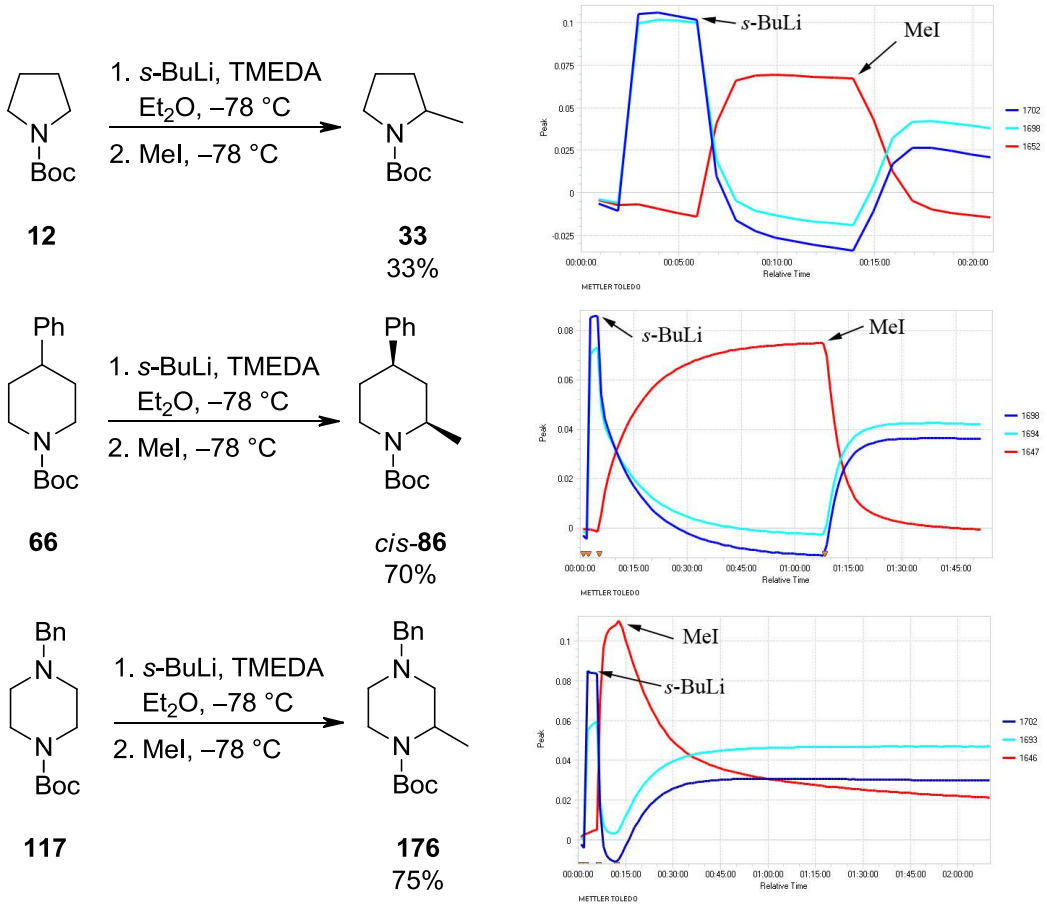
when the reaction was quenched after 2 h at –78 °C only a 52% yield of *cis*-**86** was obtained (due to incomplete trapping). Trapping of lithiated *N*-Boc-*N*′-benzyl piperazine **117** was even slower, with only a 4% yield of **176** obtained when quenching after 1 h at –78 °C.



Scheme 2.28 *In situ* ReactIR™ spectroscopic monitoring of lithiation/trapping with *s*-BuLi/TMEDA and dimethyl sulfate

Lithiation of *N*-Boc heterocycles **12**, **66** and **117** followed by trapping with methyl iodide showed the same order of trapping rates as with dimethyl sulfate (Scheme 2.29). Trapping of the lithiated intermediate from *N*-Boc pyrrolidine **12** was fast, with complete trapping occurring within 3 min at –78 °C to give **33** in 33% yield. This low yield is puzzling but, it is worth noting that a racemic lithiation of *N*-Boc pyrrolidine **12** and trapping with methyl iodide has not been previously reported. Trapping of lithiated *N*-Boc 4-phenyl piperidine **66** was much slower, taking 30 min at –78 °C to reach completion, giving *cis*-**86** in 70% yield. Trapping of lithiated *N*-Boc-*N*′-benzyl

piperazine **117** was much slower, being almost complete after 2 h at –78 °C, and led to the desired substituted *N*-Boc piperazine **176** in 75% yield.



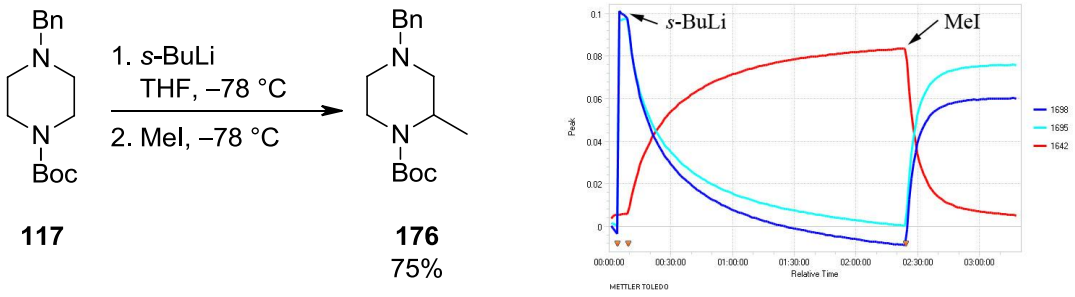
Scheme 2.29 *In situ* ReactIR™ spectroscopic monitoring of lithiation/trapping with *s*-BuLi/TMEDA and methyl iodide

The trend that lithiated *N*-Boc pyrrolidine **12** traps faster than lithiated *N*-Boc 4-phenyl piperidine **66**, which in turn traps faster than lithiated *N*-Boc-*N′*-benzyl piperazine **117** holds true for all three electrophiles. The differences in the rates at which the lithiated substrates are trapped are considerable. It is postulated that the trapping of lithiated *N*-Boc-*N′*-benzyl piperazine **117** is slower than the trapping of lithiated *N*-Boc 4-phenyl piperidine **66** due to the fact that the *α*-carbanion of *N*-Boc-*N′*-benzyl piperazine **117** is more stable due to back donation into the low energy σ* of the anti-periplanar C-N bond. This is the same rationale as given for the rapid lithiation of **117** (see Figure 2.3).

The ReactIR™ monitoring of the methylation of lithiated *N*-Boc heterocycles shows conclusively that methyl iodide traps faster than dimethyl sulfate. It was expected that the opposite would be the case, with the harder dimethyl sulfate reacting faster with the

hard organolithium. Although direct observation of the trapping of lithiated *N*-Boc piperidine **10** has not been performed in this investigation, O'Brien's previous work on the lithiation of *N*-Boc piperidine **10** and subsequent trapping with methylating agents is consistent with the observation that methyl iodide traps faster than dimethyl sulfate at –78 °C. A slightly higher enantiomeric ratio of 2-methyl *N*-Boc piperidine (*R*)-**74** was obtained when using methyl iodide (64:36 er) compared to dimethyl sulfate (60:40 er) (see Scheme 1.33). The fact that methyl iodide reacts faster ensures that trapping probably occurred at a lower temperature. Therefore, less epimerisation of the newly created stereocentre through configurational instability was observed. This work has shown that Me_3SiCl traps lithiated *N*-Boc heterocycles slower than both methyl iodide and dimethyl sulfate. This observation is contradicted by the fact that silyl piperidine (*R*)-**64** was obtained in an excellent 86:14 er when trapping lithiated *N*-Boc piperidine **10** with the relatively unreactive Me_3SiCl (see Scheme 1.32). A lower enantioselectivity of (*R*)-**64** would be expected due to the presumed slow trapping with Me_3SiCl.

The effect of different ligands on the trapping times was investigated next. To start with, lithiation of *N*-Boc-*N′*-benzyl piperazine **117** under diamine-free conditions (*s*-BuLi/THF at –78 °C) followed by trapping with methyl iodide was performed. Complete trapping within 1 h at –78 °C occurred and **176** was isolated in 75% yield (Scheme 2.30). In contrast, when TMEDA in Et_2O was used, complete trapping took 2 h (see Scheme 2.29). It is possible that the reduction in steric bulk surrounding the lithium centre of the organolithium intermediate allowed faster trapping.

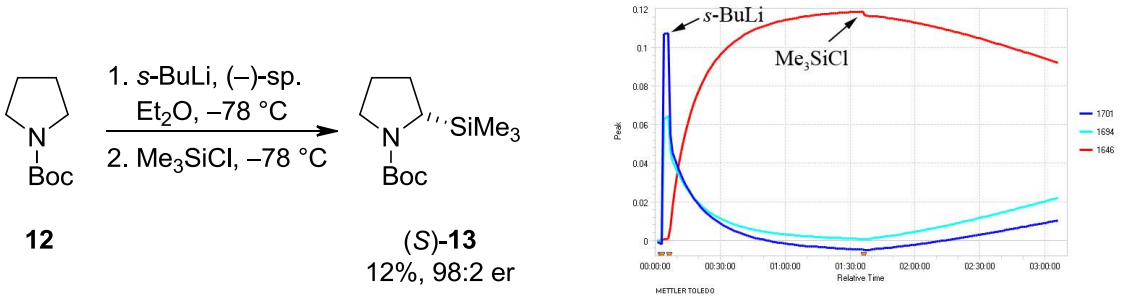


117 → **176** 75%

Scheme 2.30 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **117** with *s*-BuLi in THF and methyl iodide

To investigate whether increasing the steric bulk of the diamine would have an effect on trapping rates, the lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine in Et_2O at –78 °C followed by trapping with Me_3SiCl was investigated. It can be seen from the

2D ReactIR™ spectrum in Scheme 2.31 that the trapping of lithiated *N*-Boc pyrrolidine **12** with Me_3SiCl in the presence of (–)-sparteine was very slow. When the reaction was quenched with aqueous ammonium chloride after 90 min at –78 °C, silyl *N*-Boc pyrrolidine (*S*)-**13** was isolated in 12% yield and 98:2 er (determined by CSP-GC), along with 84% recovered starting material **12**.

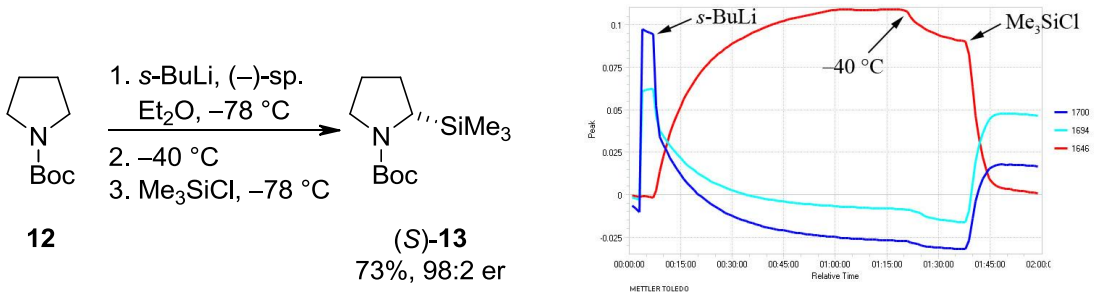


Scheme 2.31 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **12** with *s*-BuLi/(–)-sparteine and Me_3SiCl at –78 °C

For comparison, the analogous reaction with *s*-BuLi/TMEDA resulted in complete trapping within 15 min at –78 °C (see Scheme 2.25). These two results show that, for relatively unreactive electrophiles, the diamine has a considerable effect on the rates of not only lithiation, but also of the electrophilic trapping step.

Beak and others have previously reported excellent results for the lithiation/trapping of *N*-Boc pyrrolidine **12** with *s*-BuLi, bulky chiral diamines and Me_3SiCl. When employing *s*-BuLi/(–)-sparteine, silyl *N*-Boc pyrrolidine (*S*)-**13** was isolated in 76% yield and 98:2 er (see Scheme 1.7).[42] This indicates that although trapping with Me_3SiCl is slow at –78 °C, trapping occurs as the reaction warms slowly to room temperature. Importantly, trapping occurs at a temperature below the point at which 2-lithio-*N*-Boc pyrrolidine **25** becomes configurationally unstable.

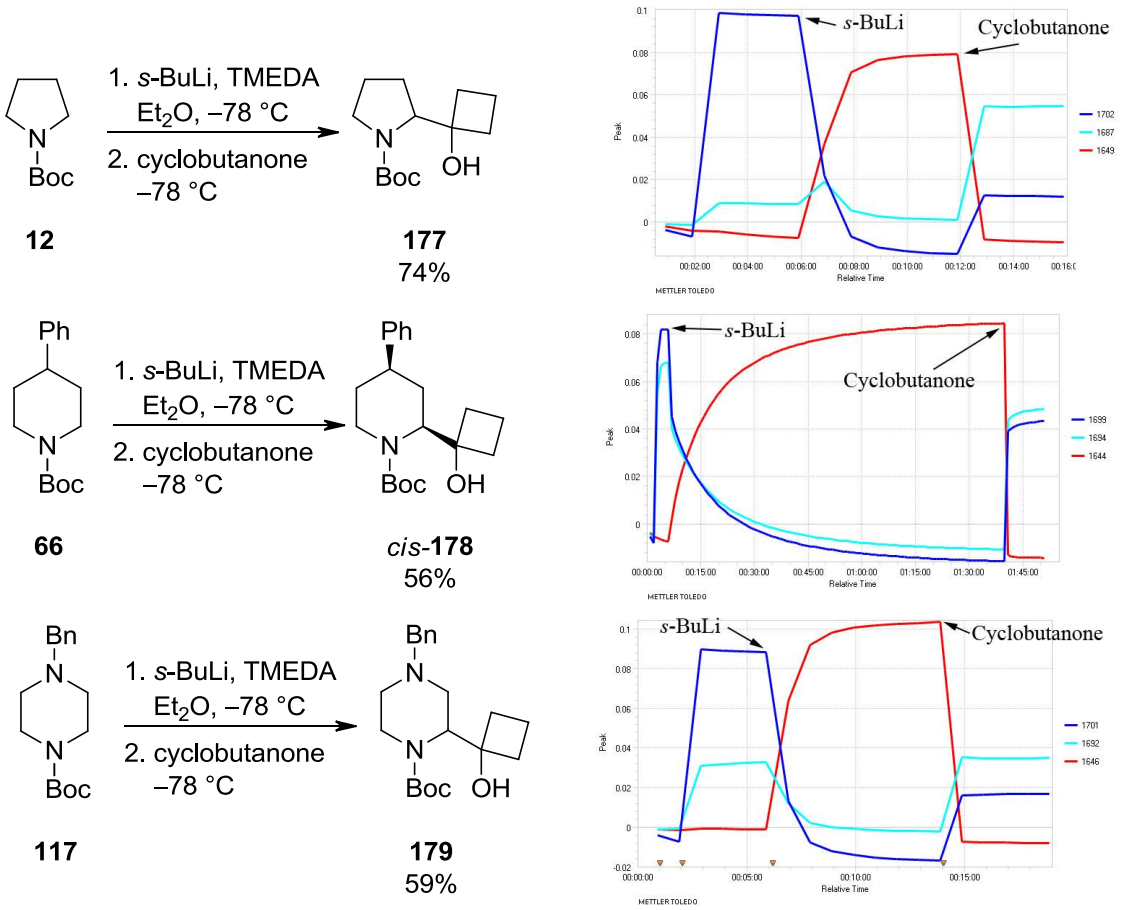
Recent work within the O'Brien group has shown that lithiated *N*-Boc pyrrolidine **12** is configurationally stable at –40 °C in the presence of (–)-sparteine for at least 1 h.[60] Therefore, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine at –78 °C was performed and the reaction was then allowed to warm to –40 °C. Once the ReactIR™ spectrum had stabilised, Me_3SiCl was added (Scheme 2.32). Complete trapping was observed within 10 min at –40 °C and silyl *N*-Boc pyrrolidine (*S*)-**13** was isolated in 73% yield and 98:2 er.



Scheme 2.32 *In situ* ReactIR™ spectroscopic monitoring of the lithiation of **12** with *s*-BuLi/(–)-sparteine at –78 °C and trapping with Me_3SiCl at –40 °C

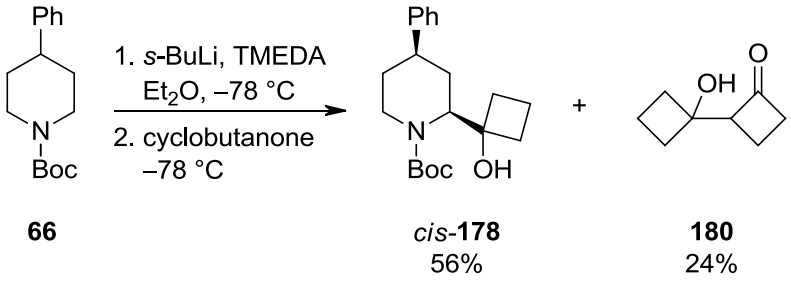
The lithiation/trapping of *N*-Boc pyrrolidine **12** utilising Me_3SiCl as the electrophile has historically been the test reaction for ligand screens and new methodology development. This ReactIR™ spectroscopic investigation has shown that the electrophile trapping in this case is not as straightforward as previously assumed. It is possible that this subtlety has had a detrimental effect on previous methodology development with potentially useful diamines being discarded due to inefficient trapping by Me_3SiCl at low temperatures. One example may be the large ligand screen performed by Coldham and O'Brien for the asymmetric lithiation of *N*-Boc piperidine **10**.[73]

Although there was reason to suspect trapping with Me_3SiCl, methyl iodide and dimethyl sulfate would be relatively sluggish, there was no empirical evidence to suggest that this would be the case with other commonly used electrophiles. With this in mind, a broader electrophile range was investigated to determine the effects of *N*-Boc heterocycle structure and diamine structure on the time required for trapping. First, cyclobutanone was employed as the electrophile; it was predicted to trap quickly and would not generate diastereomeric products. Lithiation of the three chosen *N*-Boc heterocycles was accomplished using *s*-BuLi/TMEDA in Et_2O at –78 °C. As expected, trapping of lithiated *N*-Boc pyrrolidine **12** with cyclobutanone was fast, with complete trapping occurring in less than 1 min, giving **177** in 74% yield with 12% recovered *N*-Boc pyrrolidine **12** (Scheme 2.33). Trapping of lithiated *N*-Boc 4-phenyl piperidine **66** and *N*-Boc-*N′*-benzyl piperazine **117** were also complete within 1 min giving *cis*-**178** and **179** in 56% and 59% yield respectively. Starting materials **66** and **117** were recovered from these reactions in 31% and 29% respectively.



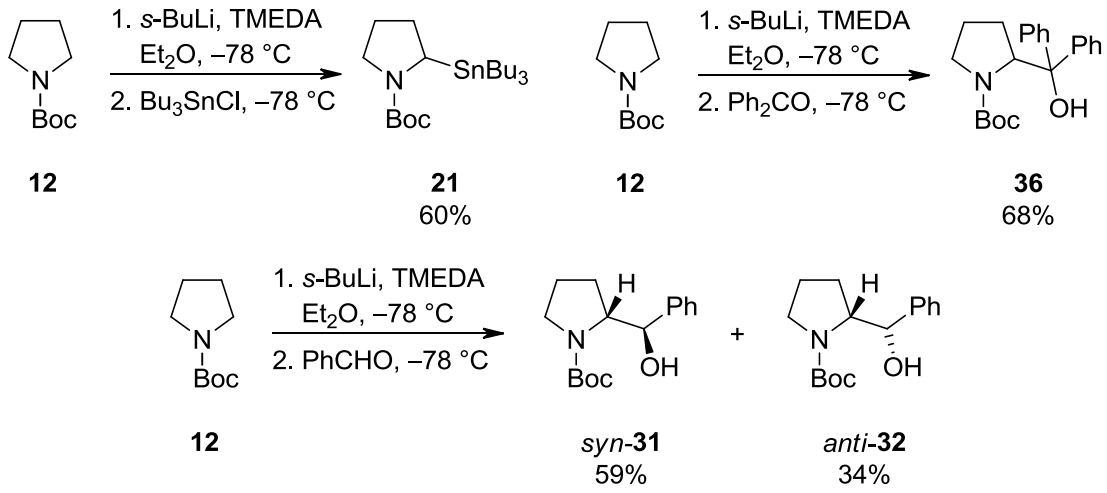
Scheme 2.33 *In situ* ReactIR™ spectroscopic monitoring of lithiation/trapping with *s*-BuLi/TMEDA and cyclobutanone

The moderate yields (56-74%) and recovery of significant quantities of starting materials (12-31%) of these three reactions can be attributed to enolisation of cyclobutanone by the lithiated *N*-Boc heterocycle, thus destroying the lithiated intermediate and regenerating starting material. This was confirmed by the observation of an aldol product of cyclobutanone **180** by ^{1}H NMR spectroscopy. By-product **180** was isolated in 24% yield in the case of *N*-Boc 4-phenyl piperidine **66** (Scheme 2.34).



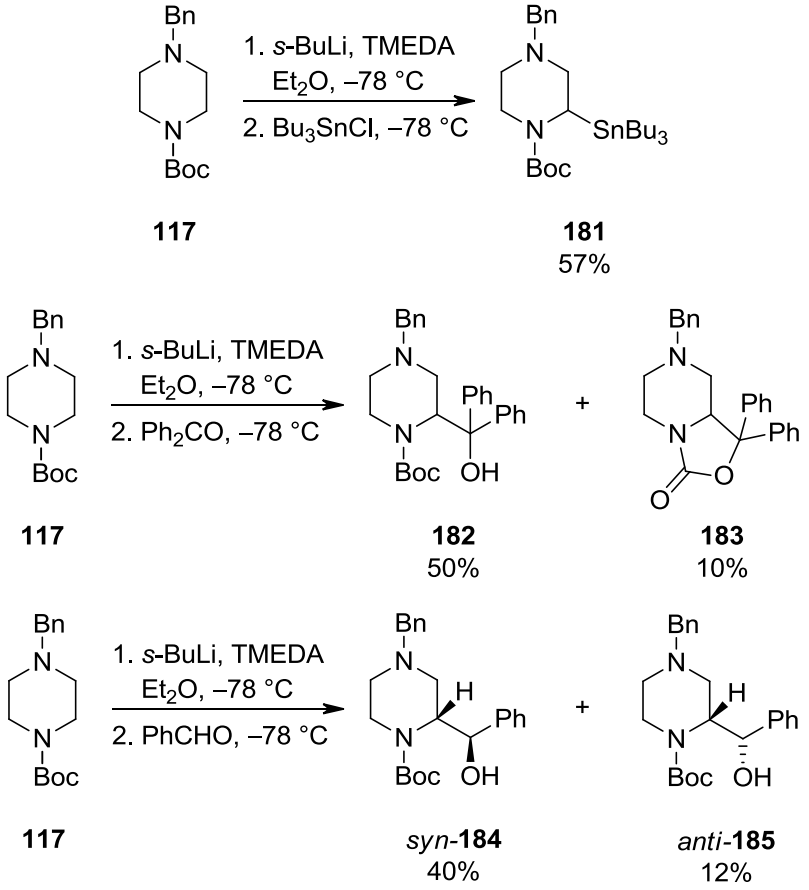
Scheme 2.34

The trapping times of other electrophiles with lithiated *N*-Boc pyrrolidine **12** and *N*-Boc-*N′*-benzyl piperazine **117** in the presence of TMEDA were also studied. Trapping of the lithiated intermediate derived from *N*-Boc pyrrolidine **12** was performed with Bu_3SnCl, benzophenone and benzaldehyde and the results are summarised in Scheme 2.35. In all cases, complete trapping took less than 1 min at –78 °C to give products **21**, **31**, **32** and **36** in good to excellent yields (full ReactIR™ traces are presented in Chapter 6.3).



Scheme 2.35

Similarly, trapping of the lithiated intermediate of *N*-Boc-*N′*-benzyl piperazine **117** (the slowest to trap with Me_3SiCl) was performed with Bu_3SnCl, benzophenone and benzaldehyde. Complete trapping in less than 1 min at –78 °C was observed giving products **181-185** in moderate to good yields (Scheme 2.36). When trapping with benzophenone, a small amount of oxazolidinone **183** was formed through cyclisation by attack of the intermediate lithium alkoxide onto the carbamate carbonyl.



Scheme 2.36

The relative stereochemistry of *syn*-**184** was assigned unambiguously by X-ray crystallography. As expected, the piperazine adopts a chair conformation with the *α*-substituent in the axial position to reduce $A^{1,3}$-type strain between the substituent and the Boc group. The X-ray crystal structure of *syn*-**184** (with 50% thermal ellipsoids) is shown in Figure 2.5.

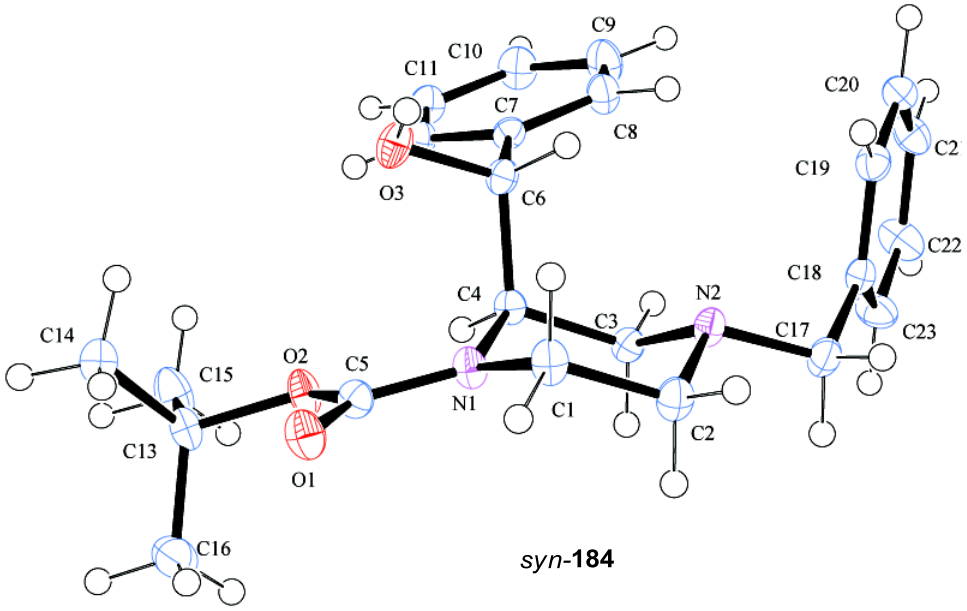
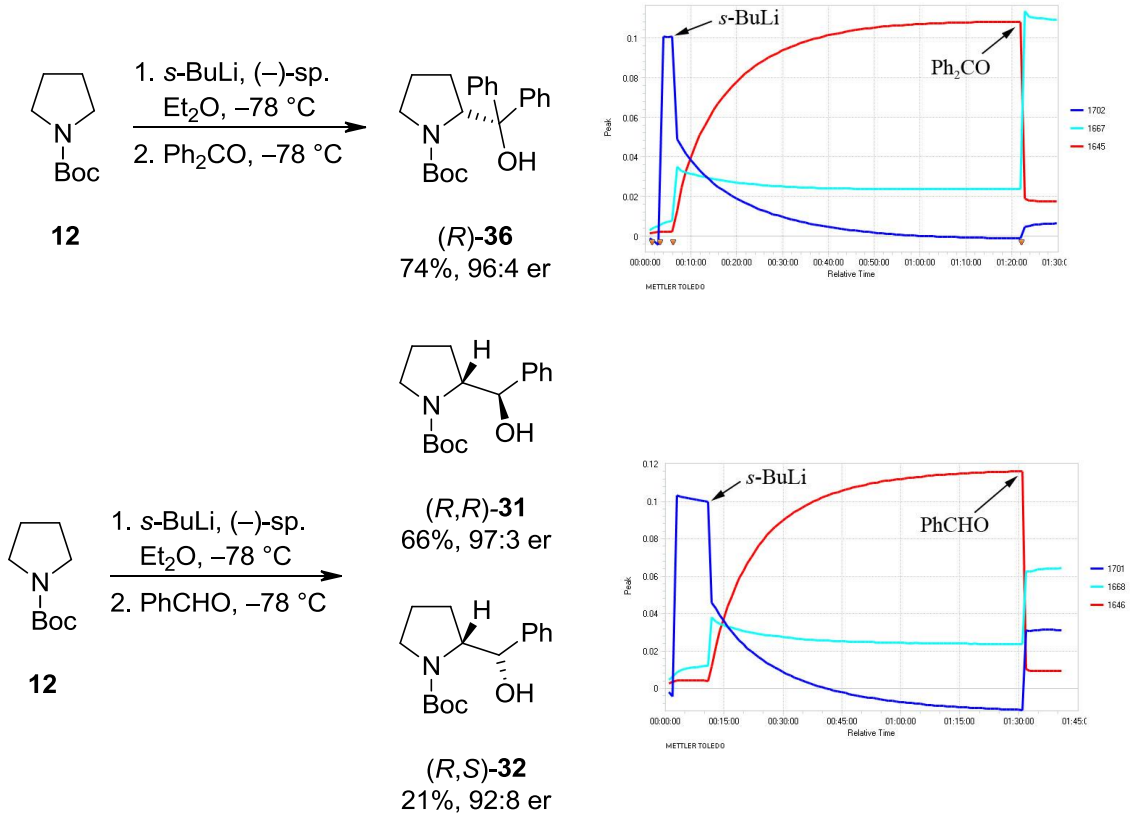


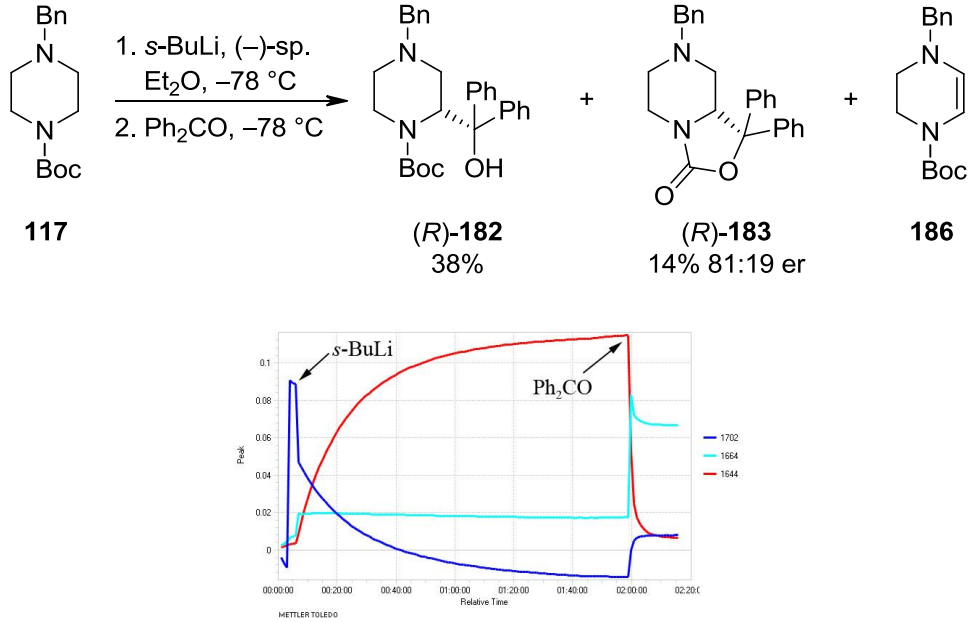
Figure 2.5 X-Ray Structure of *syn*-**184** with thermal ellipsoids shown at 50%

Since the trapping with cyclobutanone, Bu_3SnCl, benzophenone or benzaldehyde was fast even with *N*-Boc-*N'*-benzyl piperazine **117**, it was interesting to discover whether the use of a bulky diamine would slow down the rate of trapping with these 'fast' electrophiles. To this end, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi/(–)-sparteine in Et_2O at –78 °C was performed and trapping with benzophenone and benzaldehyde was performed. In both cases, trapping was complete within 1 min at –78 °C (Scheme 2.37). With benzophenone, alcohol (*R*)-**36** was isolated in 74% and 96:4 er. The use of benzaldehyde gave diastereomeric alcohols (*R*,*R*)-**31** in 66% and 97:3 er and (*R*,*S*)-**32** in 21% and 92:8 er.



Scheme 2.37 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **12** with *s*-BuLi/(–)-sparteine and 'fast' electrophiles

Lithiation of *N*-Boc-*N′*-benzyl piperazine **117** using *s*-BuLi/(–)-sparteine in Et_2O at –78 °C followed by trapping with benzophenone was performed to determine whether the combination of a bulky diamine and *N*-Boc-*N′*-benzyl piperazine **117** would result in slower trapping. However, trapping with benzophenone occurred within 1 min at –78 °C to give alcohol (*R*)-**182** in 38% yield and oxazolidinone (*R*)-**183** in 14% yield in 81:19 er (Scheme 2.38). Unfortunately, a CSP-HPLC method to determine the er of (*R*)-**182** could not be found. The overall yield was modest due the formation of alkene by-product **186**, which was observed in a 20:80 ratio by ^{1}H NMR spectroscopy (relative to the combined amount of (*R*)-**182** and (*R*)-**183**) but unfortunately could not be isolated. The formation of this by-product will be discussed in detail in Chapter 4.



Scheme 2.38 *In situ* ReactIR™ spectroscopic monitoring of the lithiation/trapping of **117** with *s*-BuLi/(–)-sparteine and benzophenone

These experiments show that the use of a bulky diamine does not slow the trapping step with 'fast' electrophiles, at least not beyond the resolution of the ReactIR™ equipment (1 min), even when using *N*-Boc-*N′*-benzyl piperazine **117**.

Work detailed within this section has shown that trapping of lithiated *N*-Boc heterocycles is not necessarily a straight forward process. Building upon empirical evidence from previous reports, this investigation has shown that Me_3SiCl, methyl iodide and dimethyl sulfate react much more slowly with lithiated *N*-Boc heterocycles than the other electrophiles examined. Figure 2.6 details the reactivity series of the electrophiles investigated to date.

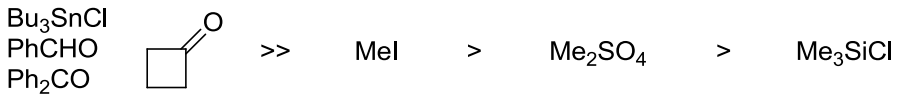


Figure 2.6

Remarkable differences in the rate of trapping of different lithiated *N*-Boc heterocycles with 'slow' electrophiles have been uncovered. Trapping of lithiated *N*-Boc pyrrolidine **12** was relatively fast, allowing the synthesis of highly enantioenriched *α*-substituted pyrrolidines. Conversely, trapping of lithiated *N*-Boc-*N′*-benzyl piperazine **117** was

extremely slow which, as will be detailed in Chapter 4, has consequences for the asymmetric lithiation of *N*-Boc piperazines.

2.4 Conclusions and Future Work

In situ ReactIR™ spectroscopy has been used to monitor the time taken for the complete lithiation of a range of commonly used *N*-Boc heterocycles by observing the changes in the carbonyl stretch ($\nu_{C=O}$) of the Boc group. Without resorting to a full study of the reaction kinetics, a reactivity series of lithiation substrates has been prepared with the three most widely used diamines: TMEDA, (–)-sparteine and the (+)-sparteine surrogate (+)-**26**. This study has confirmed that lithiation reactions of *N*-Boc heterocycles using *s*-BuLi in the presence of TMEDA or (+)-**26** are relatively rapid compared with those facilitated by *s*-BuLi/(–)-sparteine. In most cases the historically lengthy reaction times are unnecessary. Figure 2.7 shows the *N*-Boc heterocycles in order of reactivity towards deprotonation.

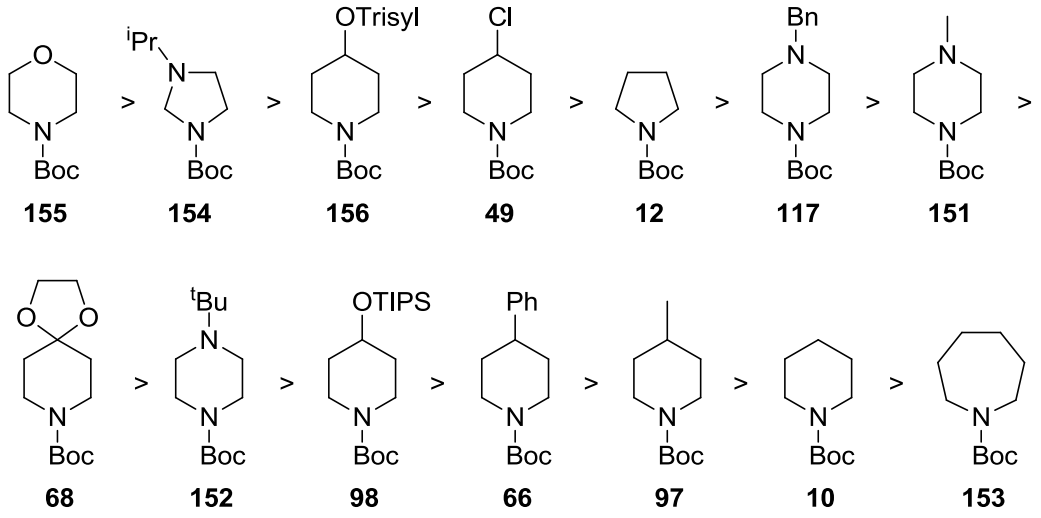


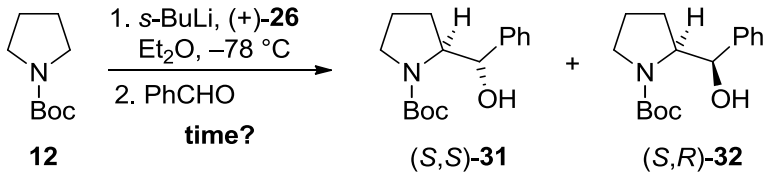
Figure 2.7 Order of reactivity of *N*-Boc heterocycles towards deprotonation

Additionally, this chapter reports the first study of the trapping times of lithiated *N*-Boc heterocycles with different electrophiles. It has been shown that electrophiles can be classed as either 'fast' or 'slow' trapping. When employing 'slow' electrophiles (Me_3SiCl, methyl iodide and dimethyl sulfate), trapping of lithiated *N*-Boc-*N'*-benzyl piperazine **117** is considerably slower than trapping of lithiated *N*-Boc 4-phenyl piperidine **66**, which in turn is considerably slower than the trapping of lithiated *N*-Boc pyrrolidine **12**. There is no obvious reason for the large differences between the three heterocycles. The time taken for complete trapping is increased as the steric bulk around the lithiated centre increases. This investigation has shown that this effect can explain some of the lower enantiomeric ratios observed when using *N*-Boc piperidine **10** and

'slow' trapping electrophiles. For 'fast' electrophiles, trapping occurs within one minute regardless of substrate or diamine. This fact shows that the long trapping times (1-16 h) are not necessary except with 'slow electrophiles'.

It would be interesting to assess the effect of the (+)-sparteine surrogate (+)-**26** on rates of trapping with 'slow' electrophiles in comparison with (–)-sparteine to assess whether the sterically less bulky ligand results in faster trapping.

The use of *in situ* ReactIR™ spectroscopy to study the times required for complete lithiation and electrophile trapping could be used to make a specific target molecule in the shortest time possible. For example, lithiation of *N*-Boc pyrrolidine **12** with *s*-BuLi and the (+)-sparteine surrogate (+)-**26** at –78 °C, followed by trapping with benzaldehyde could conceivably be complete within 5 min (Scheme 2.39).



Scheme 2.39

Chapters 3 and 4 will show how the data generated through ReactIR™ spectroscopy was used to optimise the lithiation/trapping of *N*-Boc piperazines.

Chapter Three: Racemic Lithiation/Trapping of *N*-Boc Piperazines

Nitrogen heterocycles hold a privileged position within pharmaceutical compounds. The 'top 200 brand-name drugs by sales in 2012' shows that 36 contain piperazine, pyrrolidine or piperidine part structures.[107] A 2003 study showed that piperazines are one of the most common fragments found in orally-active drugs, with more than 70 drugs containing the group.[136] In fact, a recent study has shown that the piperazine moiety is the fourth most common ring in drugs approved by the FDA between 1983 and 2012, with 51 of 1175 drugs containing the group.[137] Additionally, many commercially available screening molecules and bioactive compounds contain a piperazine. One analysis suggests that 5.4% of the ZINC database and 7.7% of the ChEMBL database contain piperazines.[138] However, very few drugs contain piperazines which are substituted at carbon. Examples include Indinavir, a protease inhibitor for treatment of HIV,[139] and Vestipitant,[140] a neurokinin-1 antagonist under development for the treatment of nausea and anxiety (Figure 3.1).

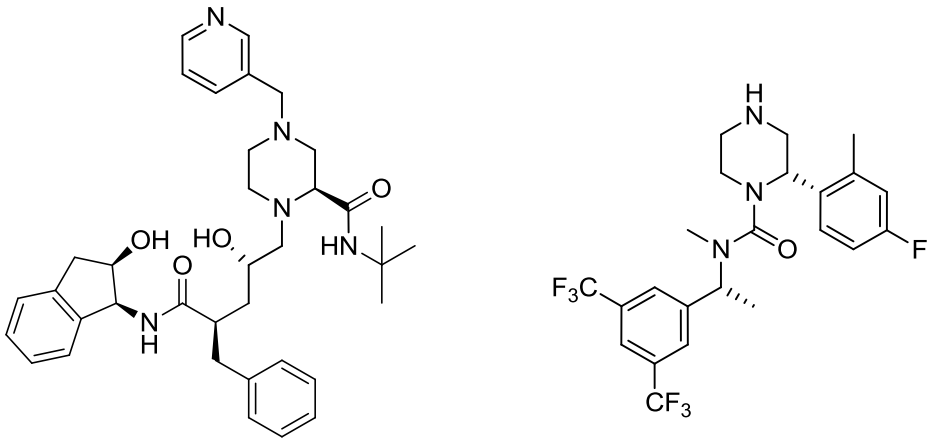


Figure 3.1

Although there are a multitude of excellent methods for the synthesis of piperazines substituted at carbon, the lithiation/trapping of *N*-Boc piperazines is relatively under developed.

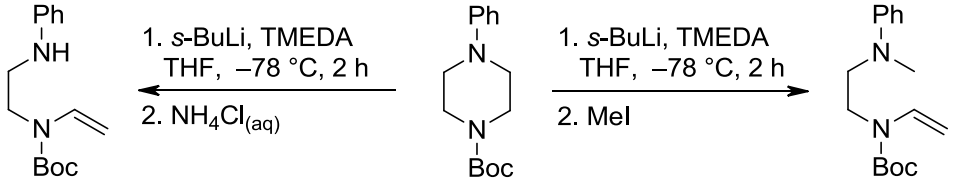
This chapter details studies into the racemic lithiation/trapping of *N*-Boc piperazines, examining the scope and limitations of substrates and electrophiles. First, the synthesis

and lithiation of a range of commonly used and novel *N*-Boc piperazines is discussed. Second, an investigation into the racemic lithiation/Negishi coupling of *N*-Boc piperazines is described.

3.1 Overview of Synthesis of Substituted Piperazines

3.1.1 Overview of Racemic Lithiation/Trapping of *N*-Boc Piperazines

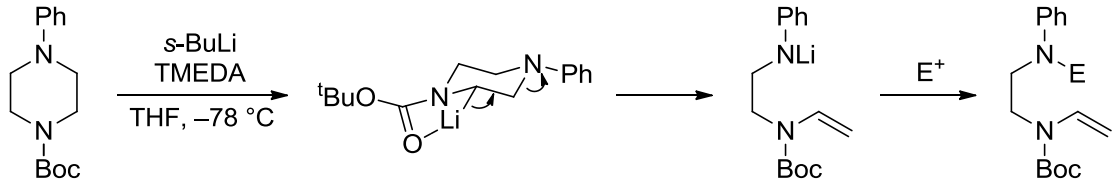
The first attempt at the *α*-lithiation/trapping of *N*-Boc piperazines was carried out by Wermuth *et al* in 1997.[141] *N*-Boc-*N′*-phenyl piperazine **187** was deprotonated using *s*-BuLi/TMEDA in THF at –78 °C. When methyl iodide was used as the electrophile, rather than isolating the expected *α*-substituted piperazine, ring fragmentation and *N*-methylation occurred to give vinyl carbamate **188** in 45% yield (Scheme 3.1). Alternatively, quenching the lithiation after 2 h with aqueous ammonium chloride resulted in isolation of secondary amine **189** in 65% yield.



189 65% **187** **188** 45%

Scheme 3.1

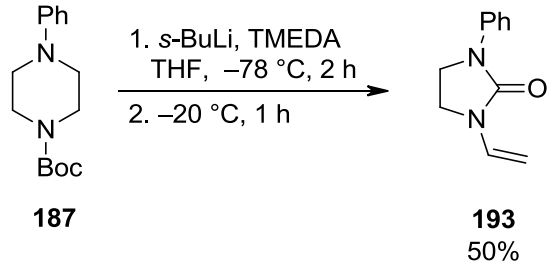
The proposed mechanism of ring fragmentation is shown in Scheme 3.2 and is analogous to that shown in Scheme 2.21 for the fragmentation of *N*-Boc morpholine **155**. Equatorial deprotonation of *N*-Boc-*N′*-phenyl piperazine **187** affords lithiated intermediate **190**. This can undergo *β*-elimination, enabled by the antiperiplanar arrangement of the Li-C and C-N bonds, to give lithium amide **191**. The phenyl ring provides charge stabilisation and facilitates ring fragmentation. Upon addition of the electrophile, trapping occurs on nitrogen to give vinyl carbamate **192**.



187 **190** **191** **192**

Scheme 3.2 Mechanism of ring fragmentation of *N*-Boc-*N′*-phenyl Piperazine **187**

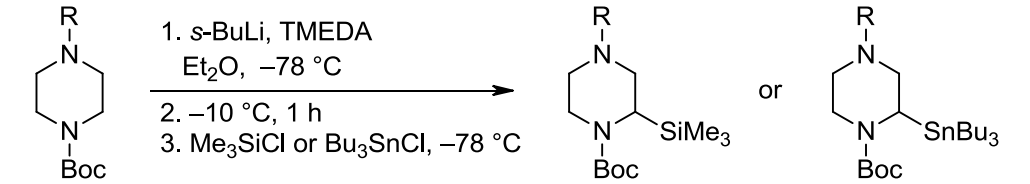
When the lithiated intermediate was warmed to –20 °C for 1 h, imidazolidinone **193** was isolated in 50% yield (Scheme 3.3). Imidazolidinone **193** was formed through ring fragmentation and subsequent nucleophilic attack of the lithium amide onto the carbonyl of the Boc group.



187 **193** 50%

Scheme 3.3

The first *α*-substituted *N*-Boc piperazine synthesised through directed lithiation was reported by van Maarseveen and co-workers in 2005.[135] Both *N*-Boc-*N′*-benzyl piperazine **117** and *N*-Boc-*N′*-methyl piperazine **151** were subjected to *s*-BuLi/TMEDA in Et_2O, first at –78 °C and then at –10 °C for 1 h. Subsequent trapping with Me_3SiCl or Bu_3SnCl gave *α*-substituted benzyl piperazines **175** and **181** in 68% and 71% yield respectively (Scheme 3.4). Alternatively, *α*-substituted methyl piperazines **194** and **195** were isolated in 5% and 82% yield respectively. No explanation for the low yield obtained when using *N*-Boc-*N′*-methyl piperazine **194** and Me_3SiCl was provided. However, this reaction will be discussed in more detail later in this Chapter (see Scheme 3.34).



117: R = Bn
151: R = Me

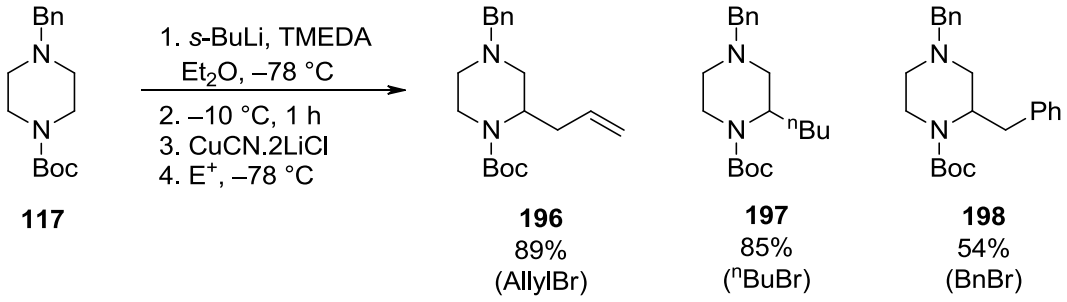
175: R = Bn, 68%
194: R = Me, 5%

181: R = Bn, 71%
195: R = Me, 82%

Scheme 3.4 Racemic lithiation/trapping of **117** and **151**

The lithium/copper transmetallation strategy developed by Dieter[93] was employed to expand the electrophile scope to include alkyl halides (Scheme 3.5). *N*-Boc-*N′*-benzyl piperazine **117** was deprotonated with *s*-BuLi/TMEDA and transmetallation was achieved through the addition of a CuCN.2LiCl solution. Trapping with allyl bromide

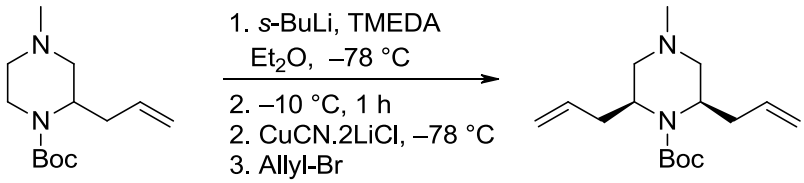
or *n*-butyl bromide gave **196** and **197** in good yields of 89% and 85% respectively. Use of benzyl bromide as electrophile gave **198** in a lower yield (54%). Additionally, the lithium/copper transmetalation methodology also worked well with *N*-Boc-*N′*-methyl piperazine **151** and alkyl halide electrophiles.



117 → **196** 89% (AllylBr); **197** 85% (^{n}BuBr); **198** 54% (BnBr)

Scheme 3.5 Racemic lithiation/transmetallation/trapping of *N*-Boc-*N′*-benzyl Piperazine **117**

Using a protocol developed by Beak for the synthesis of disubstituted piperidines,[74,75] van Maarseveen also investigated the synthesis of 2,6-diallylated piperazine through deprotonation of 2-allyl-*N*-Boc piperazine **199**. Lithiation at the least hindered 6-position using *s*-BuLi/TMEDA followed by transmetalation to the organocuprate and trapping with allyl bromide gave *cis*-**200** in 83% yield (Scheme 3.6).

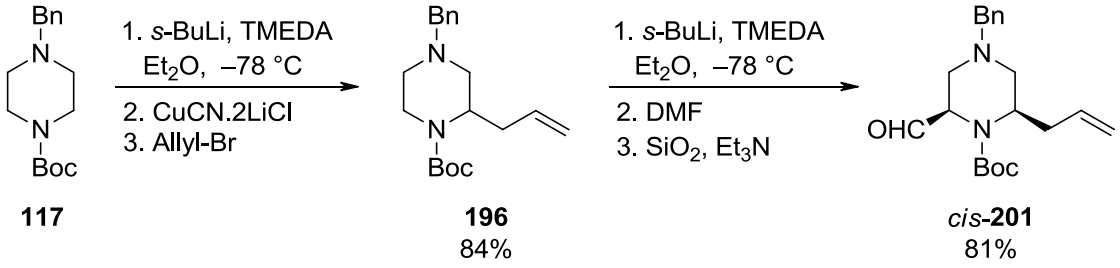


199 → *cis*-**200** 83%

Scheme 3.6

The *cis*-relative stereochemistry of 2,6-allyl piperazine *cis*-**200** was tentatively assigned by analysis of coupling constants in the ^{1}H NMR spectrum. This stereochemical assignment is surprising. It is expected that the allyl group of **199** would adopt an axial orientation in order to reduce $A^{1,3}$-type strain. In analogy to piperidines,[74] equatorial deprotonation and retentive trapping would lead to a 2,6-*trans* configuration (see Scheme 1.40). The stereochemical assignment is probably incorrect as evidenced by experiments detailed in Chapter 4 (see Scheme 4.37).

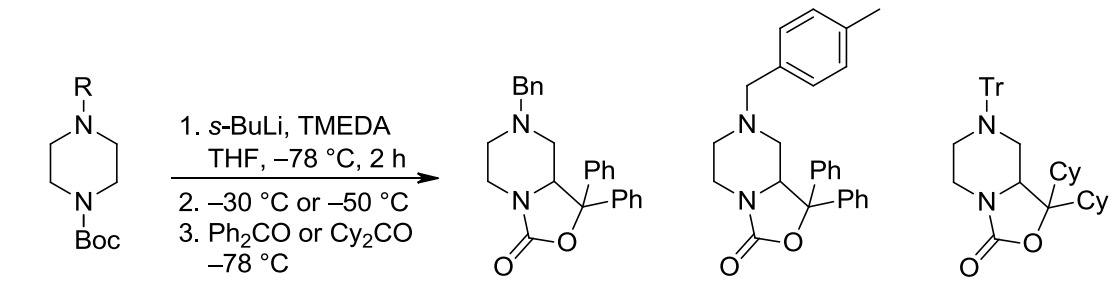
Building on the chemistry developed by van Maarseveen and co-workers, Martin reported the synthesis of *cis*-2,6-disubstituted *N*-Boc piperazines whilst investigating the synthesis of analogues of (–)-alstonerine.[142] 2-Allyl *N*-Boc piperazine **196** was synthesised in 84% yield according to van Maarseveen's procedure.[135] A second *α*-lithiation was carried out, followed by trapping with DMF to give a mixture of aldehyde epimers. Exposure to silica gel and Et_3N caused equilibration of the epimeric aldehydes (*via* enolisation) to provide *cis*-disubstituted piperazine *cis*-**201** in 81% yield (Scheme 3.7). This equilibration process is well established with *N*-Boc piperidines.[143]



117 **196** 84% *cis*-**201** 81%

Scheme 3.7

In 2006, Takeda Pharmaceuticals reported the use of three *N*-Boc piperazine substrates **117**, **202** and **203** in racemic lithiation/trapping methodology.[144] As an example, *N*-Boc-*N′*-benzyl piperazine **117** was deprotonated using *s*-BuLi/TMEDA in THF at –78 °C for 2 h. The reaction was warmed to –30 °C and immediately cooled to –78 °C again before addition of benzophenone. Oxazolidinone **183** was isolated in 64% yield (Scheme 3.8). Reinscheid also reported the synthesis of **183** using the same method in 2008.[145]



117: R = Bn
202: R = *p*-TolCH$_2$
203: R = Tr

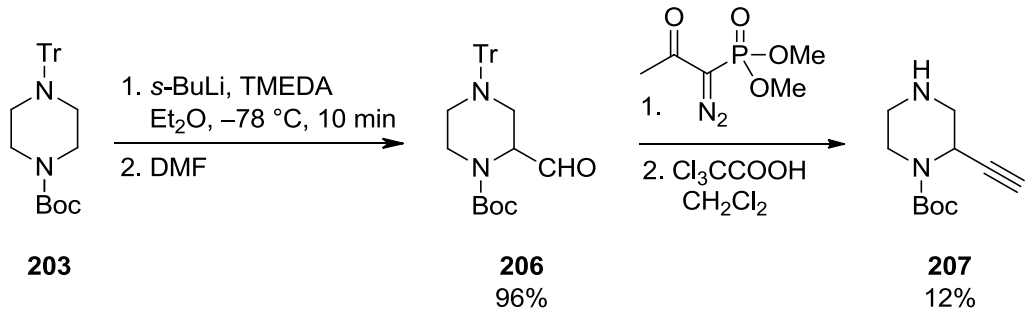
183 64% (Ph_2CO) **204** 82% (Ph_2CO) **205** 74% (Cy_2CO)

Scheme 3.8 Racemic lithiation/trapping of **117**, **202** and **203**

The use of 4-methylbenzyl protected *N*-Boc piperazine **202** as a substrate was also described by Takeda. Lithiation under the same conditions and trapping with

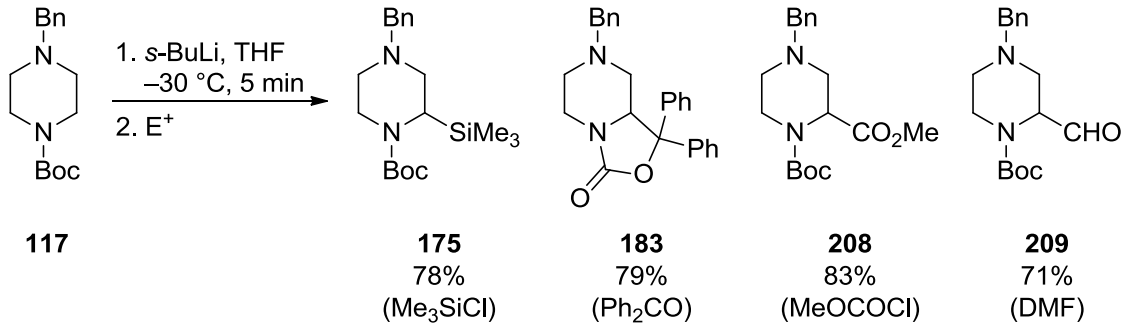
benzophenone gave oxazolidinone **204** in 82% on a 0.3 mol scale (Scheme 3.8). Additionally, the first use of *N*-Boc-*N′*-trityl piperazine **203** as a substrate was also reported. Racemic lithiation was accomplished using *s*-BuLi/TMEDA at –78 °C for 2 h, followed by warming to –50 °C. Subsequent cooling and trapping with dicyclohexyl ketone then gave oxazolidinone **205** in 74% yield (Scheme 3.8). The use of long lithiation times at –78 °C and warming before trapping, as used by van Maarseveen and Takeda, have been shown to be unnecessary by the ReactIR™ spectroscopic investigation reported in Chapter 2.

A second example of the use of *N*-Boc-*N′*-trityl piperazine **203** as a substrate was reported by Bikam Pharmaceuticals.[146] Racemic lithiation of *N*-Boc-*N′*-trityl piperazine **203** was performed using *s*-BuLi/TMEDA, but the reaction was left for only 10 min before the addition of the electrophile (DMF). Aldehyde **206** was obtained in an excellent 96% yield (Scheme 3.9). Elaboration to an alkyne from aldehyde **206** was achieved using the Ohira-Bestmann reagent in 40% yield. Selective removal of the trityl group under weakly acidic conditions (1% w/v Cl_3CCOOH/CH_2Cl_2, 0 °C) gave secondary amine **207** in 29% yield and in 12% overall yield from **206**.



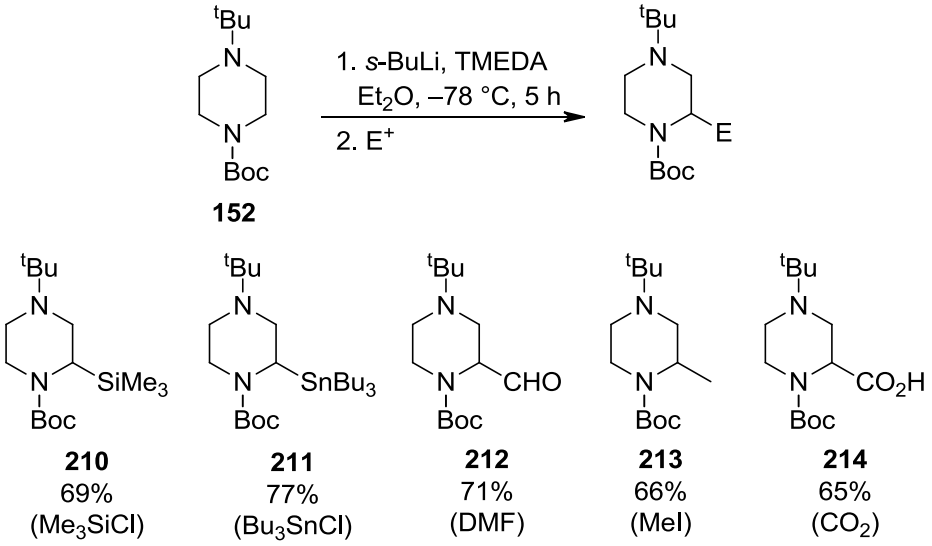
Scheme 3.9

The diamine-free lithiation methodology developed in the O'Brien group for the lithiation of *N*-Boc pyrrolidine **12** (see Scheme 1.16) was also applied to the lithiation of *N*-Boc-*N′*-benzyl piperazine **117**.[59] Lithiation with *s*-BuLi using THF as a coordinating solvent was carried out at –30 °C for 5 min before trapping (Scheme 3.10). A range of electrophiles were used, giving 2-substititued piperazines **175**, **183**, **208** and **209** in 71-83% yield.



Scheme 3.10 Racemic lithiation/trapping of *N*-Boc-*N′*-benzyl Piperazine **117** at –30 °C in THF

In 2010, Coldham showed that *N*-Boc-*N′*-*tert*-butyl piperazine **152** was also amenable to racemic deprotonation/trapping in preparation for development of a dynamic thermodynamic resolution method to asymmetric *α*-substituted piperazines.[147] *N*-Boc-*N′*-*tert*-butyl piperazine **152** was lithiated using *s*-BuLi/TMEDA in Et_2O at –78 °C for 5 h. A range of electrophiles were used, giving *α*-substituted piperazines **210-214** in 65-77% yield (Scheme 3.11).

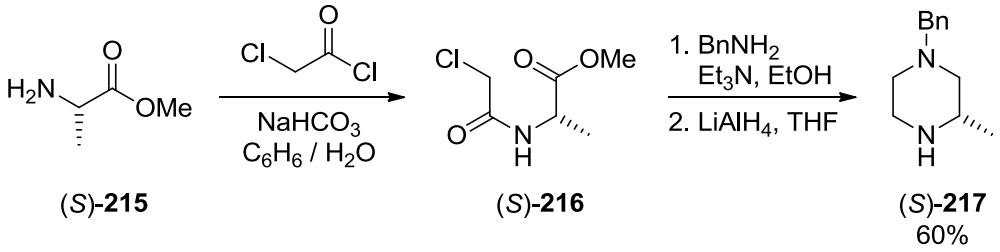


Scheme 3.11 Racemic lithiation/trapping of *N*-Boc-*N′*-*t*-butyl Piperazine **152**

3.1.2 Alternative Methods for the Synthesis of Substituted Piperazines

The most commonly used method to access enantiopure *α*-substituted piperazines involves the manipulation of protected amino acids, generally available from the chiral pool. This method has been utilised for the synthesis of mono- and 2,5-disubstitiuted

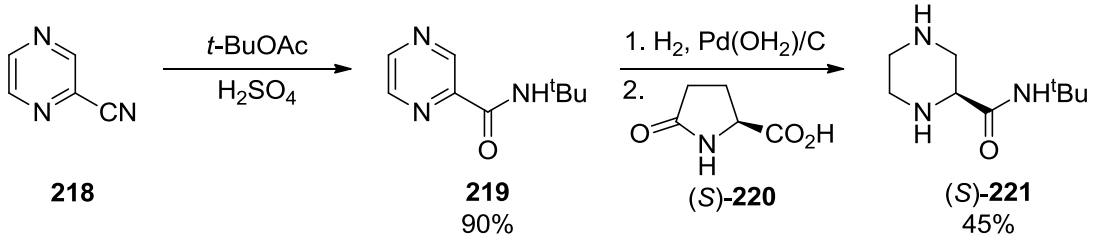
piperazines.[148,149,150] A representative procedure is shown in Scheme 3.12.[151] The methyl ester of D-alanine (*S*)-**215** was acylated with chloroacetyl chloride to give amide (*S*)-**216**. Exposure to benzylamine formed an intermediate di-keto piperazine, and after reduction with $LiAlH_4$, enantiopure *α*-methyl piperazine (*S*)-**217** was isolated in 60% yield over 3 steps.



(*S*)-**215** (*S*)-**216** (*S*)-**217** 60%

Scheme 3.12

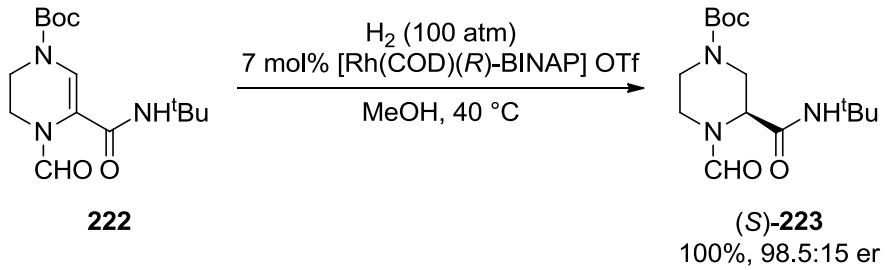
Classical resolution has been a widely used strategy for the synthesis of enantioenriched substituted piperazines. In one example, the enantiopure piperazine moiety of the protease inhibitor Indinavir (see Figure 3.1) was synthesised on a process scale by Merck, starting from pyrazine **218**.[152] A Ritter reaction using *t*-butyl acetate and H_2SO_4 generated amide **219** in 90% yield. Hydrogenation of the pyrazine ring using $Pd(OH)_2/C$ and subsequent classical resolution of the resulting piperazine using pyroglutamic acid (*S*)-**220** (which was recycled) gave (*S*)-**221** in 45% yield (Scheme 3.13).



218 **219** 90% (*S*)-**220** (*S*)-**221** 45%

Scheme 3.13

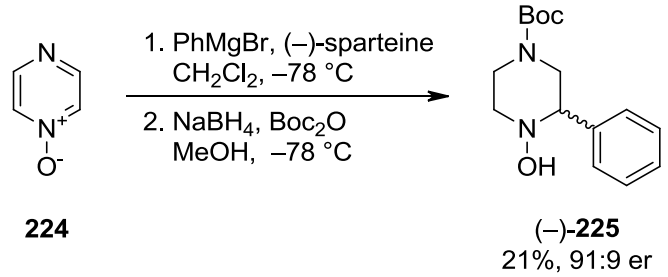
Alternatively, the enantioenriched piperazine group of Indinavir can be synthesised through asymmetric hydrogenation of tetrahydropyrazine **222** with a rhodium/(*R*)-BINAP catalyst system. Piperazine (*S*)-**223** was isolated in 100% yield with 98.5:1.5 er (Scheme 3.14).[153]



222 (*S*)-**223** 100%, 98.5:15 er

Scheme 3.14

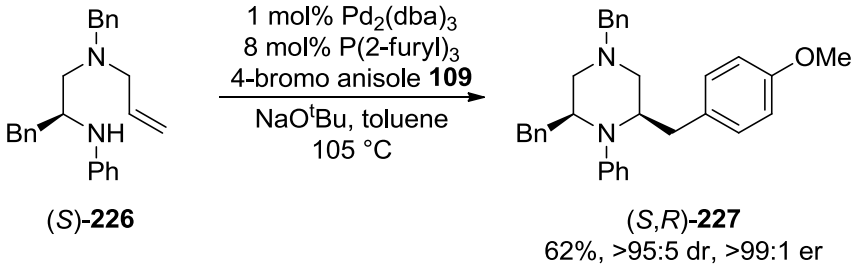
A one-pot procedure for the synthesis of enantioenriched 2-aryl *N*-Boc piperazine *N*′-oxides from pyrazine *N*-oxides has been reported by Almqvist.[154] Pyrazine *N*-oxide **224** was treated with phenyl magnesium bromide in the presence of (–)-sparteine. Reduction in the same pot with $NaBH_4$ followed by Boc protection gave piperazine *N*-oxide (–)-**225** in 21% yield and 91:9 er, with unknown absolute stereochemistry (Scheme 3.15).



224 (–)-**225** 21%, 91:9 er

Scheme 3.15

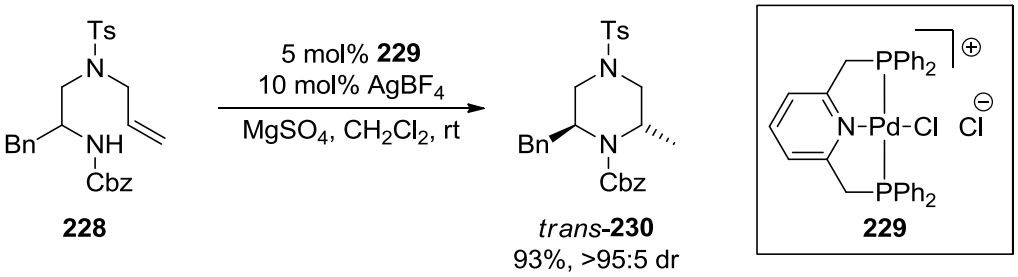
Transition metal catalysis has recently been used by several groups for the synthesis of piperazines. In 2007, Wolfe reported the synthesis of *cis*-2,6-disubstituted piperazines through a palladium-catalysed carboamination reaction of an acyclic amino-alkene precursor and aryl bromides.[155] In one example, when enantiopure (*S*)-**226** (derived from valine) was subjected to 1 mol% $Pd_2(dba)_3$ and 8 mol% tri-2-furyl phosphine in the presence of 4-bromoanisole **109**, (*S*,*R*)-**227** was isolated in 62% yield and >95:5 dr as a single enantiomer (Scheme 3.16).



(*S*)-**226** (*S*,*R*)-**227**
62%, >95:5 dr, >99:1 er

Scheme 3.16

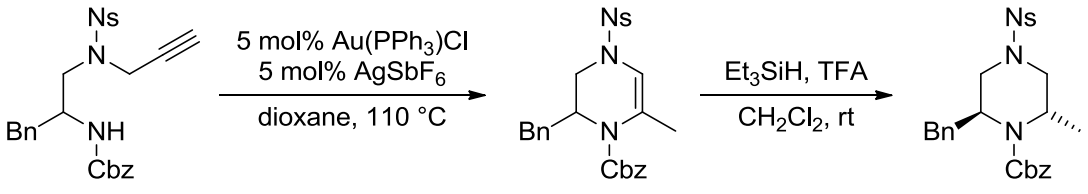
In 2008, a synthesis of *trans*-2,6-disubstitiuted piperazines through palladium catalysed hydroamination was reported.[156] In one example, racemic acyclic precursor **228** was subjected to 5 mol% palladium catalyst **229** and 10 mol% $AgBF_4$ resulting in the formation of *trans*-2,6-disubstitiuted piperazine *trans*-**230** in 93% yield and >95:5 dr (Scheme 3.17).



228 *trans*-**230** **229**
93%, >95:5 dr

Scheme 3.17

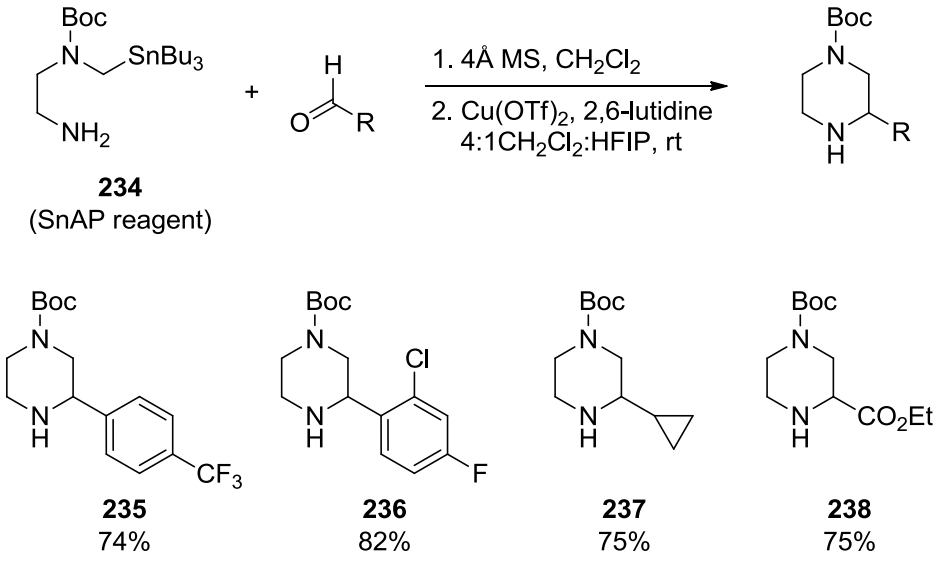
Recently, Nelson and co-workers have developed a gold catalysed synthesis of substituted piperazines.[138] When racemic alkyne **231** was subjected to 5 mol% $Au(PPh_3)Cl$ and 5 mol% $AgSbF_6$ in dioxane at 100 °C, alkene **232** was isolated in 90% yield. Subsequent reduction with triethylsilane and TFA gave 2,6-disubstituted piperazine *trans*-**233** in 68% yield and 88:12 dr (Scheme 3.18).



231 **232** *trans*-**233**
90% 68%, 88:12 dr

Scheme 3.18

Bode has reported the use of his SnAP (tin amine protocol) reagents for the synthesis of piperazines.[157] Imines were formed *in situ* from amine **234** and aldehydes in the presence of 4 Å MS, before addition of copper(II) triflate (Scheme 3.19). A range of piperazines were isolated in good yields. Examples included aryl piperazines **235** and **236**, alkyl piperazine **237** and ester **238** (74-82% yields). Additionally, a range of 2,5- and 2,6-disubstituted piperazines were synthesised using this methodology. Mechanistically, it was proposed that the reaction proceeds *via* a copper(II) promoted stabilised carbon centred radical that can undergo *endo* cyclisation with the intermediate imine.[158]



Scheme 3.19 Racemic synthesis of piperazines using SnAP reagent **234**

In summary, there are a plethora of excellent methods for the racemic synthesis of α-substituted piperazines. Additionally, several highly diastereoselective methods for the formation of 2,5- and 2,6-disubstiituted piperazines have been recently developed. However, the enantioselective syntheses generally rely on the use of chiral pool starting materials or classical resolution of racemic piperazines rather than asymmetric synthesis.

3.2 Racemic Lithiation/Trapping of *N*-Boc Piperazines

One main goal of the research disclosed within this thesis was the development of a general asymmetric lithiation/trapping protocol of *N*-Boc piperazines. In order to generate robust asymmetric methodology, the racemic lithiation/trapping of *N*-Boc piperazines was first investigated. The lithiation/trapping of a range of *N*-Boc piperazines has been accomplished by other groups since the first report by van Maarseveen.[135] However, lithiation times are often lengthy and warming steps have been incorporated into the methodology. This report details attempts to develop a more general, racemic lithiation/trapping procedure.

Several differentially protected *N*-Boc piperazines were used in this investigation (Figure 3.2). Several substrates that had been used in previous work, namely *N*-benzyl, *N*-methyl, *N*-*t*-butyl and *N*-trityl protected piperazines **117**, **151**, **152** and **203** were synthesised, along with three novel substrates **239**-**241**.

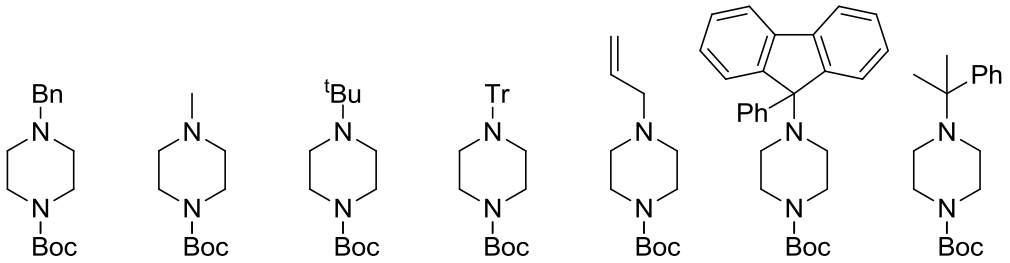
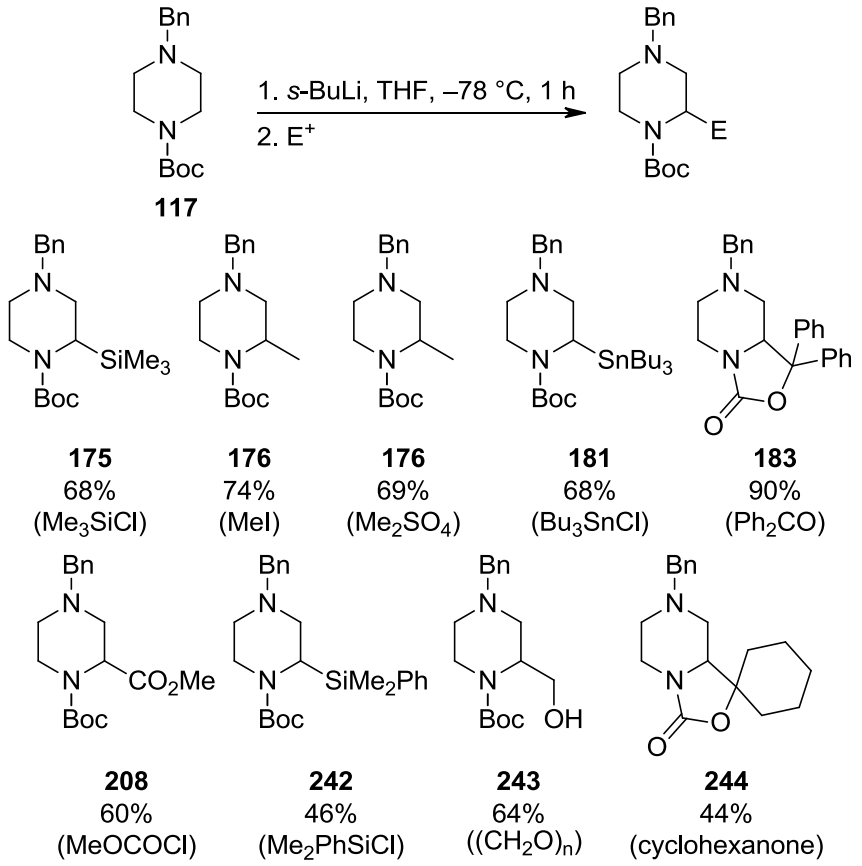


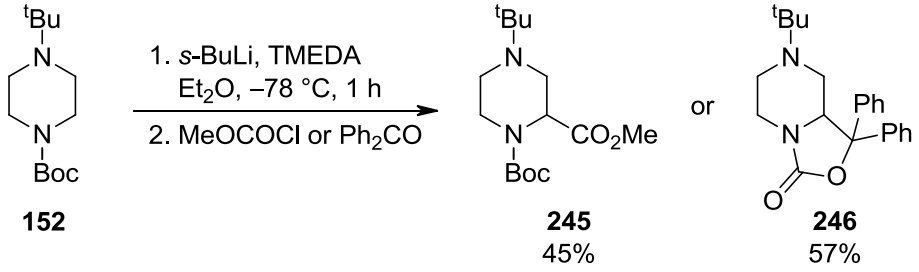
Figure 3.2 Protected *N*-Boc piperazines used for racemic lithiation/trapping studies

N-Boc-*N′*-benzyl piperazine **117** was the most attractive substrate to work with. It is commercially available, simple to make on a multigram scale,[59] orthogonally protected with many simple means of deprotection[35] and contains a UV chromophore that facilitates the development of simple CSP-HPLC methods. Work within the O'Brien group has shown that the racemic deprotonation of *N*-Boc-*N′*-benzyl piperazine **117** can be performed using a diamine-free protocol (*s*-BuLi, THF, –78 °C, 1 h).[59] Investigations began using this methodology and trapping with a range of electrophiles gave *α*-substituted *N*-Boc piperazines **175**, **176**, **181**, **183**, **208** and **242-244** in 44-90% yield (Scheme 3.20). This method was consistently higher yielding than the 'high temperature' diamine-free protocol (–30 °C, 5 min, THF).



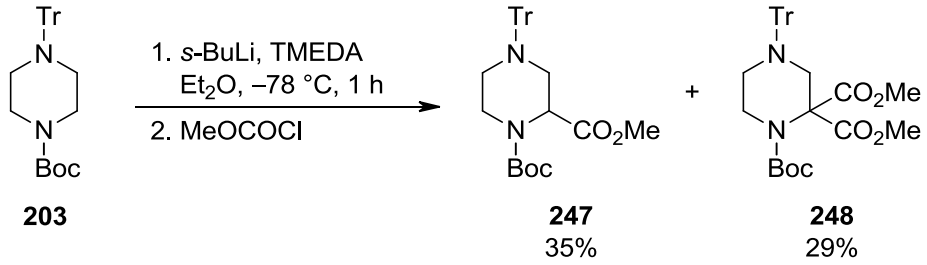
Scheme 3.20 Racemic lithiation/trapping of *N*-Boc-*N′*-benzyl Piperazine **117**

As presented in Chapter 2, *in situ* ReactIR™ spectroscopy has shown that lithiation of *N*-Boc-*N′*-benzyl piperazine **117** reached completion within 1 h using the diamine-free procedure (see Scheme 2.19d). However, under diamine-free conditions, the lithiation of sterically more demanding *N*-Boc-*N′*-*t*-butyl piperazine **152** was incomplete after 2 h (see Scheme 2.20d). In contrast, lithiation using *s*-BuLi/TMEDA in Et_2O at –78 °C was complete within 15 min (see Scheme 2.20a). Subsequent trapping with either methyl chloroformate or benzophenone gave ester **245** or oxazolidinone **246** in 45% and 57% yield respectively (Scheme 3.21).



Scheme 3.21 Racemic lithiation/trapping of *N*-Boc-*N′*-*t*-butyl Piperazine **152**

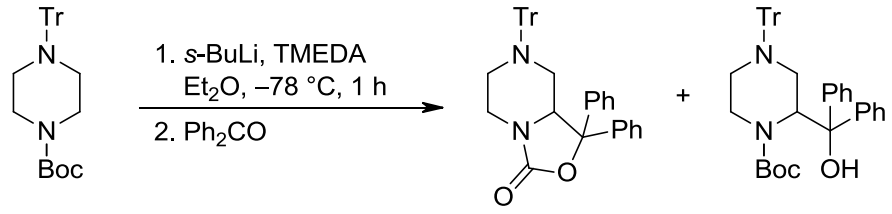
As previously discussed, the *N*-trityl group has been used successfully as a protecting group for piperazines undergoing lithiation/trapping reactions (see Schemes 3.8 and 3.9). This investigation began by examining the electrophile scope of the racemic lithiation of *N*-Boc-*N′*-trityl piperazine **203**. Due to concerns that a high degree of steric hindrance may render lithiation with *s*-BuLi/THF impractically slow, the *s*-BuLi/TMEDA system was employed (1 h at –78 °C in Et_2O). Trapping with methyl chloroformate gave the desired **247** in 35% yield along with disubstituted *N*-Boc piperazine **248** in 29% yield (Scheme 3.22). Diester **248** formed from deprotonation of the more acidic *α*-proton of **247**, either by residual *s*-BuLi or the intermediate lithiated piperazine, followed by a second trapping with methyl chloroformate.



203 **247** 35% **248** 29%

Scheme 3.22

The use of benzophenone as an electrophile resulted in the formation of oxazolidinone **249** in 50% yield and alcohol **250** in 11% yield (Scheme 3.23). It is possible that if the reaction was left for sufficient time at room temperature before quenching, complete cyclisation to give oxazolidinone **249** as a single product would result.

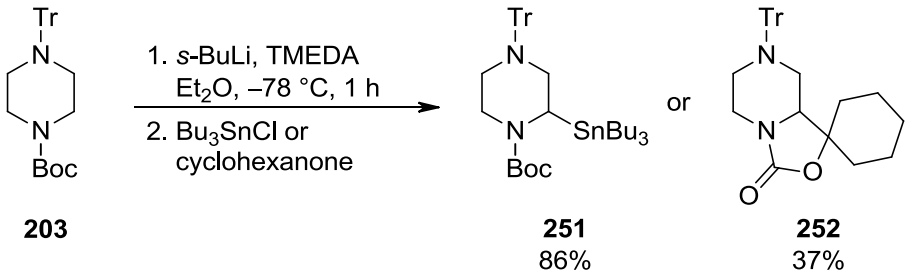


203 **249** 50% **250** 11%

Scheme 3.23

Lithiation of *N*-Boc-*N′*-trityl piperazine **203** and trapping with Bu_3SnCl or cyclohexanone resulted in stannane **251** and oxazolidinone **252** in 86% and 37% yield respectively (Scheme 3.24). The poor yield of **252** can potentially be attributed to enolisation of cyclohexanone by the lithiated piperazine intermediate. Cyclohexanone

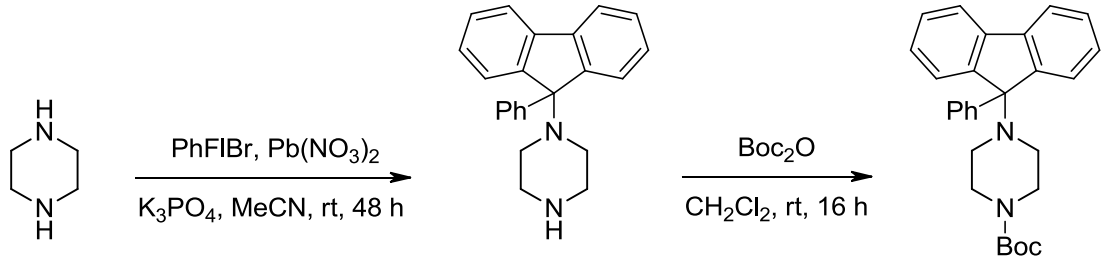
routinely gives the lowest yields of all the electrophiles used for the racemic lithiation/trapping of *N*-Boc piperazines.



203 **251** 86% **252** 37%

Scheme 3.24 Racemic lithiation/trapping of *N*-Boc-*N′*-trityl Piperazine **203**

Other novel bulky protecting groups were investigated as substrates for the racemic lithiation/trapping methodology. The 9-phenylfluoren-9-yl (PhFl) protecting group is an infrequently used bulky protecting group for amines, and has comparable steric bulk to the trityl group.[35,159] It is more stable to removal under acidic conditions but it can be easily removed using hydrogenolysis.[160] Synthesis of the desired substrate, *N*-Boc-*N′*-PhFl piperazine **240**, started with mono-protection of piperazine **253** using 9-bromo-9-phenylfluorene (PhFlBr), with $Pb(NO_3)_2$ as a bromide scavenger, to give **254** in 83% yield (Scheme 3.25). 9-Bromo-9-phenylfluorene is commercially available or can be easily prepared from 9-fluoreneone on a multi-gram scale.[161] Boc protection of the remaining secondary amine gave *N*-Boc-*N′*-PhFl piperazine **240** in 92% yield (Scheme 3.25).

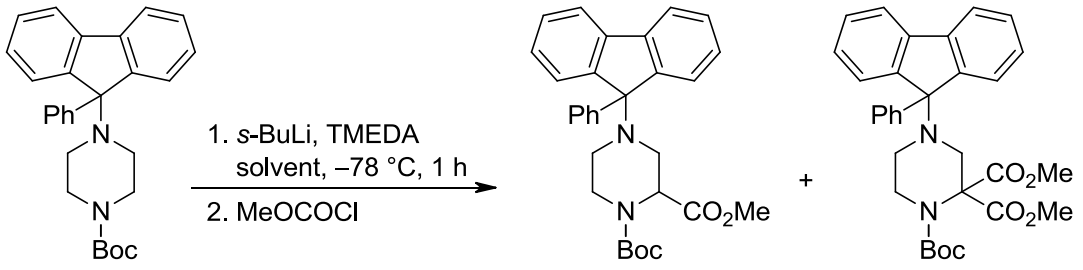


253 **254** 83% **240** 92%

Scheme 3.25

Racemic lithiation of *N*-Boc-*N′*-PhFl piperazine **240** under standard conditions (*s*-BuLi/TMEDA, Et_2O, –78 °C, 1 h) was investigated. Following trapping with methyl chloroformate, *α*-substituted piperazine **255** and diester **256** were isolated in 36% and 17% yield respectively, along with recovered starting material **240** (43%) (Table 3.1,

entry 1). The overall poor yield was attributed to the low solubility of **240** in Et_2O. To improve the yield, solvents that are better at dissolving highly hydrophobic compounds were investigated. In fact, MTBE[57,95] and toluene[54] have both previously been used in asymmetric lithiation reactions. *N*-Boc-*N′*-PhFl piperazine **240** was soluble in MTBE when heated, and stayed in solution even when cooled to –78 °C. Using MTBE as a solvent, *α*-substituted piperazine **255** was isolated in 58% yield with 23% recovered starting material **240** (entry 2). *N*-Boc-*N′*-PhFl piperazine **240** was fully soluble in toluene with ester **255** being obtained in 77% yield along with **240** (20%) (entry 3). Interestingly, none of the diester **256** was observed with either MTBE or toluene as solvent.



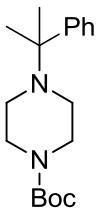
240 **255** **256**

Entry	Solvent	Yield 255 (%)[a]	Yield 256 (%)[a]	Yield 240 (%)[a]
1	Et_2O	36	17	43
2	MTBE	58	-	23
3	Toluene	77	-	20

[a] Yield after flash column chromatography.

Table 3.1 Effect of solvent on the racemic lithiation/trapping of *N*-Boc-*N′*-PhFl piperazine **240**

During an investigation into the asymmetric lithiation/trapping methodology of *N*-Boc piperazines (see Chapter 4) it became clear that bulky protecting groups were essential to the success of the methodology. To this end, the use of *N*-Boc-*N′*-cumyl piperazine **241** as a substrate was considered (Figure 3.3).

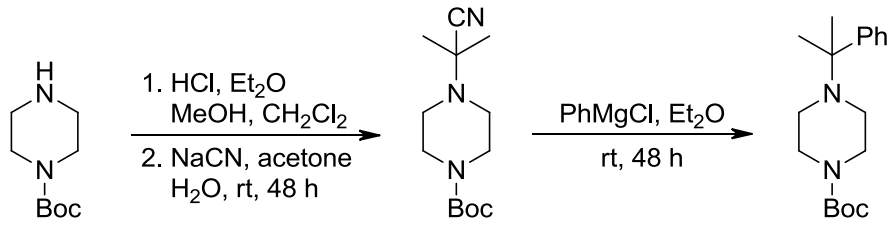


241

Figure 3.3

Originally, the cumyl group found utility as a protecting group for amides. It was introduced as such by Snieckus as a directing group for the *ortho*-metalation of amides.[162] The cumyl group was simultaneously discovered by Clayden and used in the *α*-lithiation of *N*-cumyl protected benzamides and subsequent de-aromatising anionic cyclisations.[163,164] Coldham has previously reported the use of a cumyl protecting group for the lithiation/trapping of the corresponding *N*-Boc imidazolidine, although no attempt at removing the protecting group was detailed.[165]

′The first challenge was to synthesise the desired *N*-Boc-*N′*-cumyl piperazine **241**. This was achieved by a route analogous to that employed by McDermott in the synthesis of *N*-Boc-*N′*-*t*-butyl piperazine **152**.[108] The HCl salt of *N*-Boc piperazine **257** was formed and reacted with NaCN in the presence of acetone to give amino nitrile **258** in 81% yield.[166] A Bruylants reaction with phenyl magnesium chloride displaced the nitrile (presumably *via* formation of the iminium ion) and gave the desired *N*-Boc-*N′*-cumyl piperazine **241** in 77% yield (Scheme 3.26).

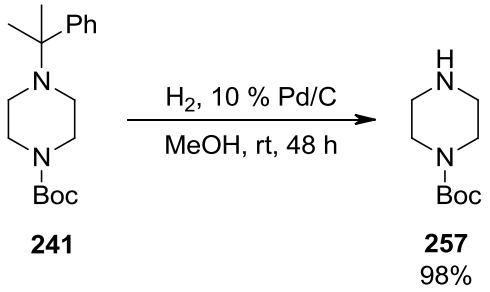


257 **258** 81% **241** 77%

Scheme 3.26

In order for *N*-Boc-*N′*-cumyl piperazine **241** to be a viable substrate for the lithiation/trapping methodology, the cumyl group had to be easily removable to allow further derivatisation of the *α*-substituted *N*-Boc piperazines. It was envisaged that deprotection could be achieved by hydrogenolysis. This proved to be the case,

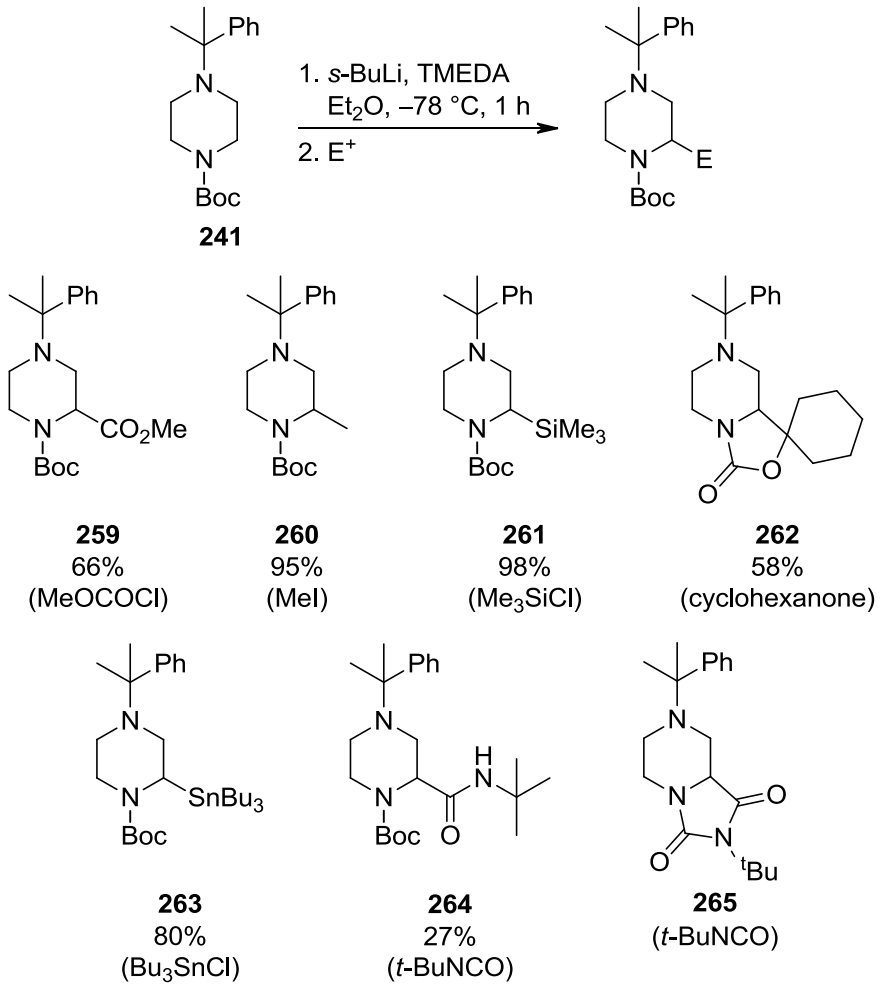
deprotection of **241** to give *N*-Boc piperazine **257** occurred readily using H_2 (1 atm.) and catalytic Pd/C for 48 h (Scheme 3.27). Alternatively, rapid deprotection can be achieved using transfer hydrogenolysis using Pearlman's catalyst and ammonium formate in EtOH at reflux for 2 h (see Scheme 4.22).



241 **257** 98%

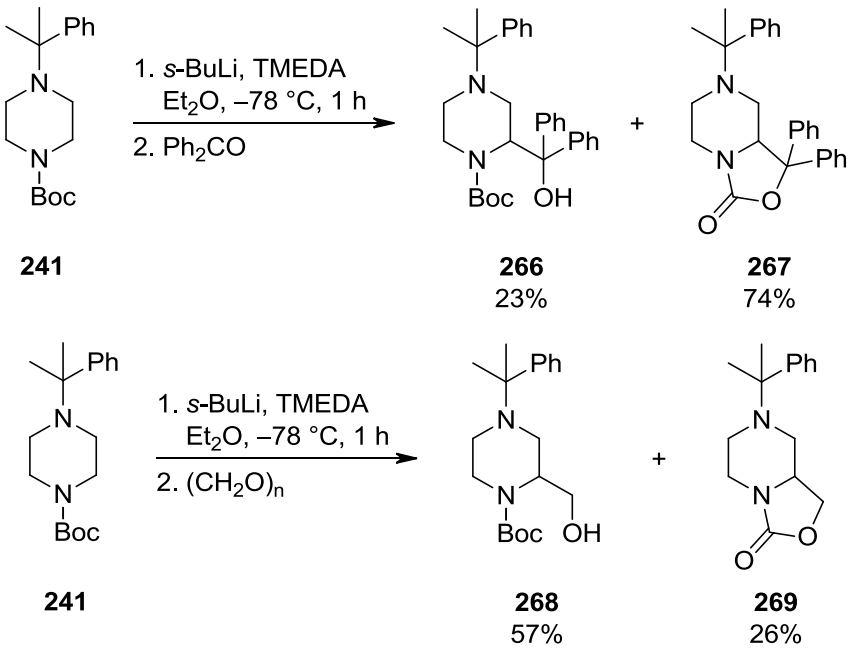
Scheme 3.27

Having tackled the synthesis and deprotection of *N*-Boc-*N′*-cumyl piperazine **241**, the racemic lithiation/trapping methodology was investigated. Racemic lithiation under standard conditions (*s*-BuLi/TMEDA, Et_2O, –78 °C, 1 h) followed by trapping with a range of electrophiles gave **259-264** in 27-98% yield (Scheme 3.28). Amide **264** (from the reaction with *t*-butyl isocyanate) was isolated in a poor 27% yield. In this reaction a considerable amount of cyclised product **265** was observed by the ^{1}H NMR spectrum of the crude mixture. Unfortunately, cyclised product **265** could not be isolated cleanly by flash column chromatography.



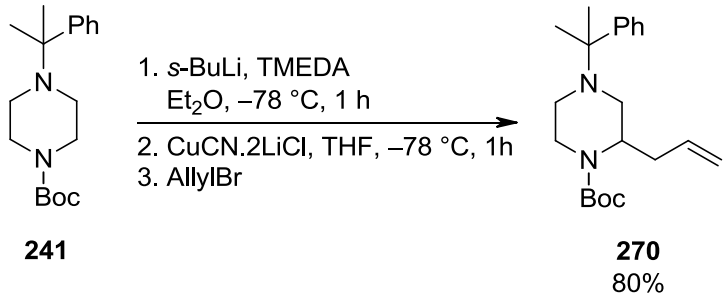
Scheme 3.28 Racemic lithiation/trapping of *N*-Boc-*N′*-cumyl Piperazine **241**

Lithiation of *N*-Boc-*N′*-cumyl piperazine **241** followed by trapping with benzophenone gave a mixture of uncyclised alcohol **266** (23%) and oxazolidinone **267** (74%) (Scheme 3.29). When trapping with paraformaldehyde a mixture of uncyclised **268** and cyclised **269** were obtained. They were isolated in 57% and 26% yields respectively.



Scheme 3.29 Racemic lithiation/trapping of *N*-Boc-*N′*-trityl Piperazine **241**

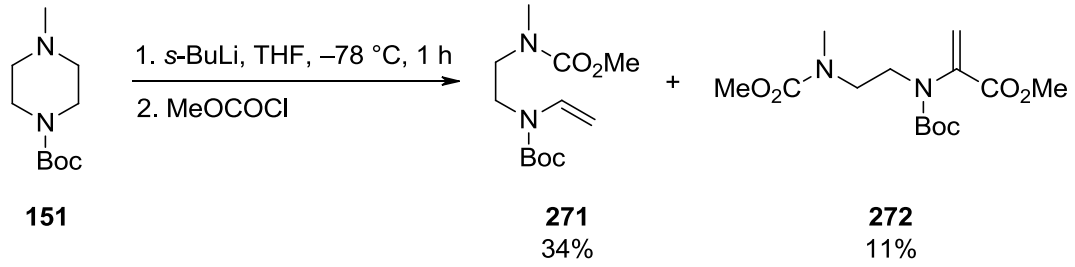
Transmetalation from lithium to copper followed by trapping with allyl bromide, using the protocol developed by Dieter,[93] and applied to *N*-Boc piperazines by van Marrseveen,[135] was highly successful giving *α*-allyl piperazine **270** in 80% yield (Scheme 3.30).



Scheme 3.30

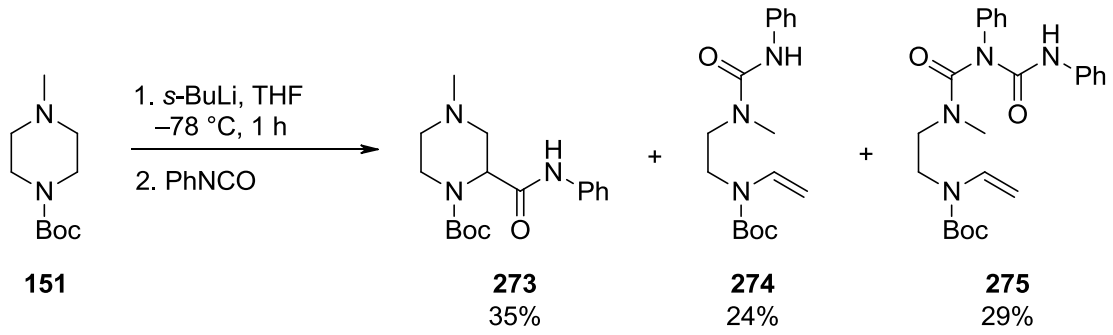
Although racemic lithiation/trapping of **117**, **152**, **203**, **240** and **241** proceeded smoothly to give *α*-substituted piperazines, other substrates proved more problematic. In fact, a range of unexpected products were encountered when trapping certain substrates with particular electrophiles. For example, lithiation of *N*-Boc-*N′*-methyl piperazine **151** using the diamine-free protocol followed by trapping with methyl chloroformate gave rise to fragmentation by-products **271** and **272** in 33% and 11% yield respectively (Scheme 3.31). None of the desired *α*-substituted piperazine was observed by ^{1}H NMR

spectroscopy. Both by-products **271** and **272** were formed through ring fragmentation followed by *N*-acylation. Product **272** could arise from vinylic α-lithiation/trapping of vinyl carbamate **271**, as previously observed with *N*-Boc morpholine **155** (see Scheme 2.21).



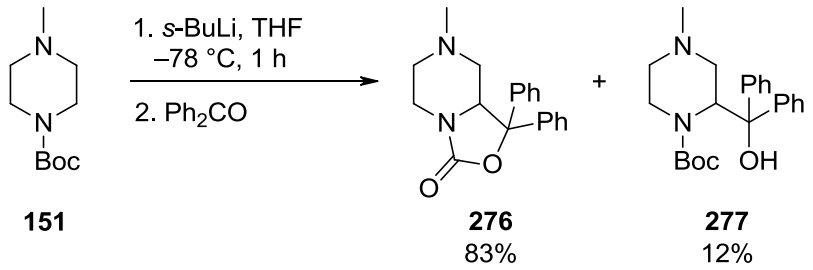
Scheme 3.31

Lithiation/trapping of *N*-methyl-*N*′-Boc piperazine **151** with phenyl isocyanate gave a 35% yield of the desired α-substituted piperazine **273** along with by-products **274** (24%) and **275** (29%). It can be envisaged that urea **275** was formed from the anion of **274** reacting with phenyl isocyanate (Scheme 3.32).



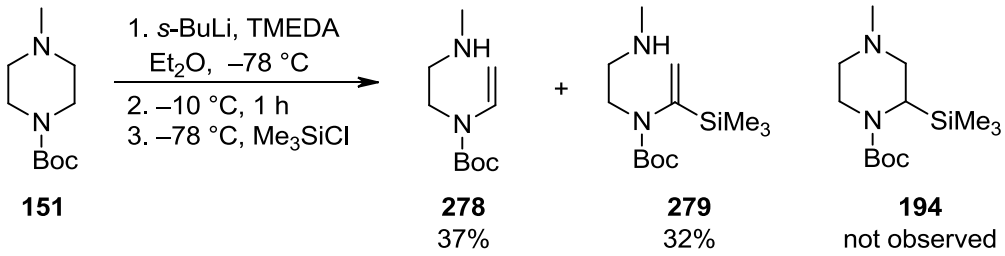
Scheme 3.32

In contrast, under the same lithiation conditions ring fragmentation did not occur with *N*-methyl-*N*′-Boc piperazine **151** when trapping with benzophenone. Here oxazolidinone **276** was isolated in 83% yield along with tertiary alcohol **277** in 12% yield (Scheme 3.33).



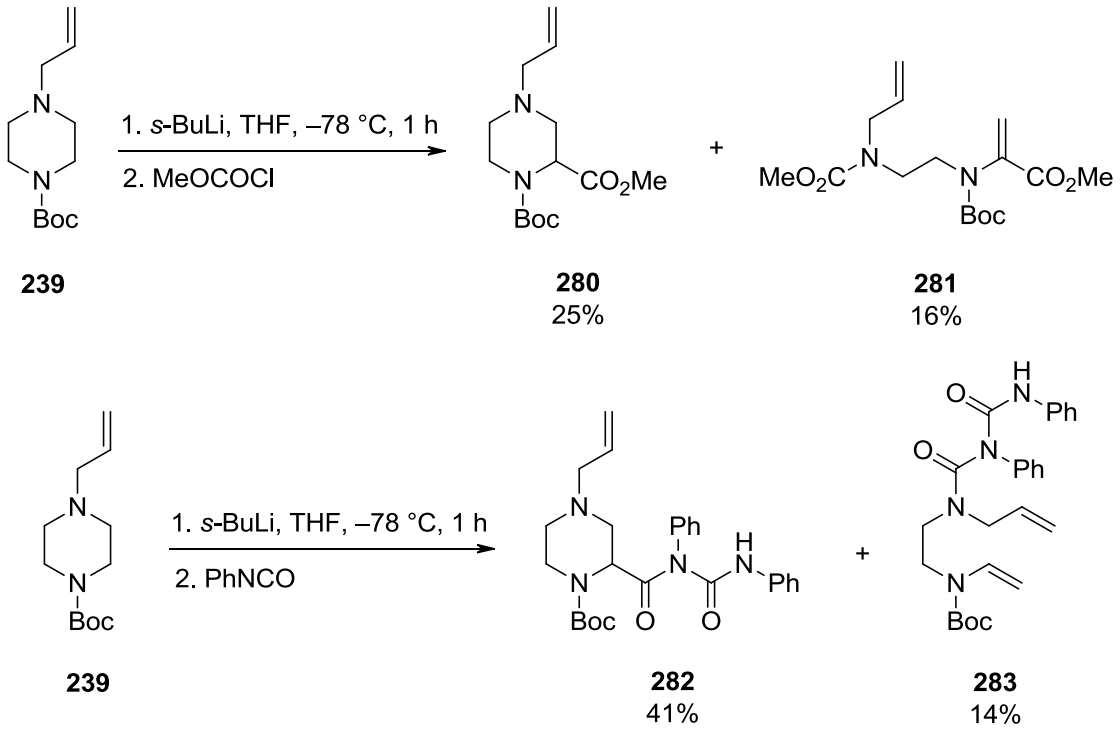
Scheme 3.33

A previous report by van Maarseveen disclosed the racemic lithiation of **151** using *s*-BuLi/TMEDA followed by trapping with Me_3SiCl. Only 5% of the desired 2-silyl piperazine **194** was isolated (see Scheme 3.4).[135] Repeating this work, employing the published conditions, led to the formation of ring fragmentation by-products **278** and **279** in 37% and 32% yield respectively (Scheme 3.34). The desired product **194** was not observed by analysis of the ^{1}H NMR spectrum of the crude product. Vinyl carbamate **278** is thought to arise through fragmentation followed by cleavage of the weak N-Si bond upon aqueous work-up. Vinylic lithiation of the intermediate silyl vinyl carbamate followed by trapping with a second equivalent of Me_3SiCl gave rise to silane **279**, after *N*-desilylation upon aqueous work-up.



Scheme 3.34

The ring-opening side-reaction also arose in the lithiation/trapping of *N*-Boc-*N′*-allyl piperazine **239**. For example, trapping with methyl chloroformate resulted in the desired piperazine ester **280** being formed in 25% yield together with ring-opened product **281** in 16% yield (Scheme 3.35). Ring-fragmentation was a side-reaction when *N*-Boc-*N′*-allyl piperazine **239** was lithiated under diamine-free conditions and trapped with phenyl isocyanate. The desired piperazine **282** and ring-opened by-product **283** were obtained in 41% and 14% yields respectively (Scheme 3.35).

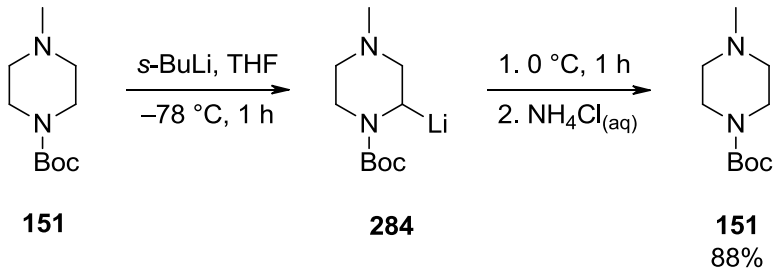


239 **280** 25% **281** 16%

239 **282** 41% **283** 14%

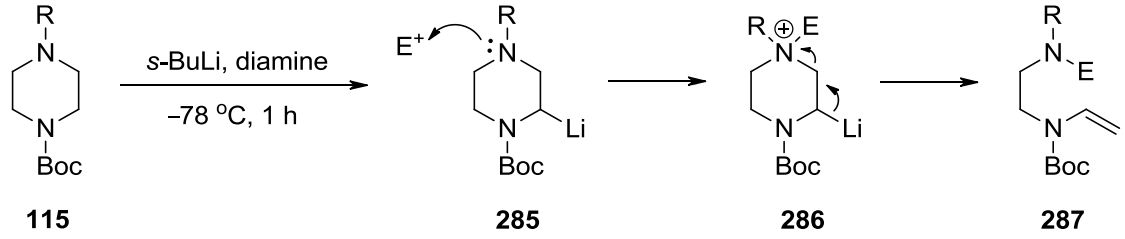
Scheme 3.35

As the side-reaction occurred with some electrophiles and not with others, an investigation into the mechanism by which ring fragmentation occurred was undertaken. Wermuth and co-workers previously showed that ring fragmentation of *N*-Boc-*N′*-phenyl piperazine **187** occurred in the absence of electrophiles.[141] It was postulated that fragmentation of *N*-Boc-*N′*-methyl piperazine **151** was occurring in an analogous fashion, prior to electrophilic trapping. This process could have been driven by slow trapping of lithiated intermediates at low temperatures, a process known to be slow with piperazines and certain electrophiles (see Chapter 2). To evaluate whether ring fragmentation was occurring at elevated temperatures, lithiation of *N*-Boc-*N′*-methyl piperazine **151** was performed using *s*-BuLi in THF at –78 °C for 1 h to give lithiated intermediate **284**. Then, the temperature was raised to 0 °C for 1 h before quenching with aqueous ammonium chloride. Only starting material was returned, with **151** being isolated in 88% yield (Scheme 3.36). No ring fragmentation by-products were observed by ^{1}H NMR spectroscopy of the crude product.



Scheme 3.36

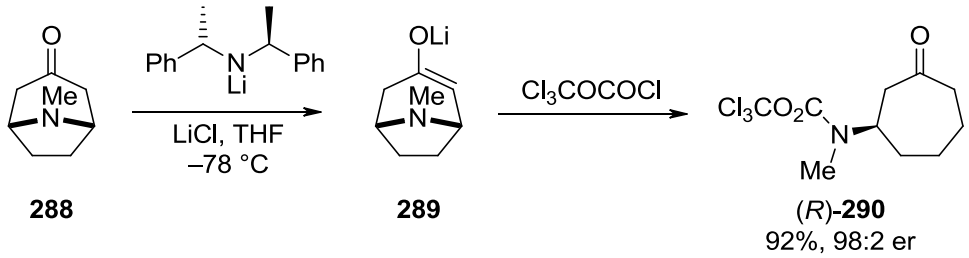
This experiment shows that, unlike the fragmentation seen with *N*-Boc-*N′*-phenyl piperazine **187** and *N*-Boc morpholine **155**, the electrophile has a role to play in ring fragmentation of some *N*-Boc piperazines. The mechanism shown in Scheme 3.37 is proposed to explain the experimental observations. The lithiated intermediate **285** could react through either the organolithium component or through the nitrogen lone pair. The former would be expected. However, the latter explains the observed reaction products. The nitrogen lone pair of the lithiated intermediate **285** could attack the electrophile resulting in a quaternary ammonium species **286**. This in turn could easily undergo elimination to give the vinyl carbamate **287** (Scheme 3.37). The size of the protecting group and the size of the ligands around the lithium centre have an effect on reaction outcome.



Scheme 3.37 Mechanism of ring fragmentation of *N*-Boc piperazines

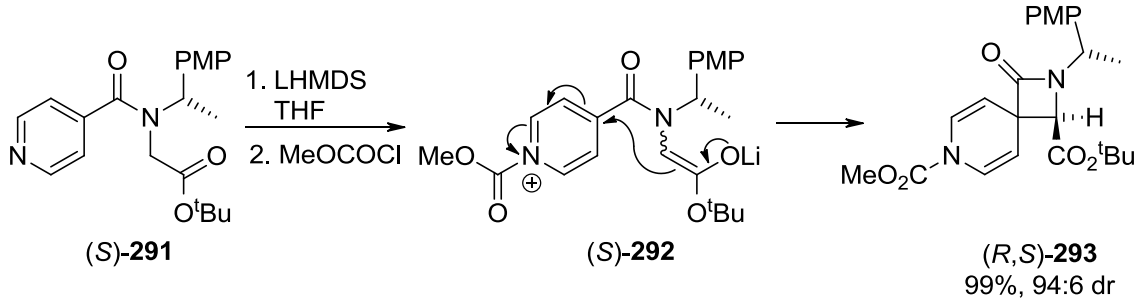
The attack of an electrophile by a nitrogen lone pair in the presence of a much more nucleophilic organolithium was unanticipated. However, there is literature precedent for the attack of a nitrogen lone pair on chloroformates in the presence of lithium enolates. Majewski and co-workers reported the ring-opening of tropinone **288** when investigating functionalisation *via* enantioselective deprotonation with chiral LDA-type bases (Scheme 3.38).[167,168] Generation of the lithium enolate **289** followed by trapping with trichloromethyl chloroformate resulted not in the formation of the desired *β*-keto ester but solely in carbamate (*R*)-**290** (92% yield, 98:2 er). The nitrogen lone pair

attacked the chloroformate and then ring fragmentation occurred. In contrast, the use of benzaldehyde or methyl cyanoformate (Mander's reagent) gave the desired α-substituted ketones with no ring-fragmented products.[169]



Scheme 3.38

Clayden and co-workers have reported a stereoselective de-aromatising cyclization reaction to generate spiro-lactams (Scheme 3.39).[170] Enolate formation from (*S*)-**291** with LHMDS was followed by *N*-acylation with methyl chloroformate to give pyridinium ion (*S*)-**292**, rather than enolate acylation. Subsequent de-aromatising cyclisation gave lactam (*R*,*S*)-**293** in 99% yield and 94:6 dr.

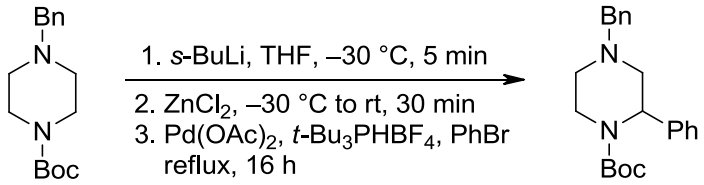


Scheme 3.39

The results presented within this section show clearly that both the *N*-Boc piperazine structure and the electrophile have an effect on the reaction outcome. Fragmentation did not occur during the racemic lithiation/trapping using *N*-benzyl, *N*-*t*-butyl, *N*-PhFl or *N*-cumyl piperazines **117**, **152**, **240** and **241** with any electrophile. However, with *N*-methyl and *N*-allyl piperazines **151** and **239** fragmentation occurs with methyl chloroformate, Me_3SiCl or phenyl isocyanate, although not with benzophenone. These results indicate that the smaller protecting groups of **151** and **239** allow the lone pair of lithiated intermediate **285** to attack some electrophiles, whereas the bulkier protecting groups prevent this pathway. Fragmentation does not occur with benzophenone, possibly due to the hindered nature of the electrophilic carbonyl.

3.3 Investigation of the Synthesis of 2-Aryl *N*-Boc Piperazines

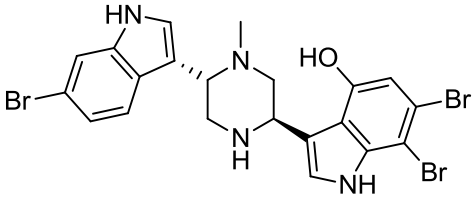
One of the most interesting and synthetically useful modifications to the lithiation/trapping of *N*-Boc heterocycles is the Negishi chemistry developed by Campos.[97-99] Application of the lithiation/Negishi methodology to *N*-Boc-*N′*-benzyl piperazine **151** was performed by O'Brien and Barker, reputedly giving 2-phenyl piperazine **294** in a moderate 55% yield (Scheme 3.40).[59] This is the first and only example of such a Negishi coupling using *N*-Boc piperazines to date.



151 **294** 55%

Scheme 3.40

Enantiopure *α*-aryl piperazines are occasionally found in nature. For example, several members of the dragmacidin family of natural products contain a 2,5-diaryl piperazine moiety. Dragmacidin (Figure 3.4) was isolated from *Dragmacidin sp.*, a Caribbean underwater sponge and exhibits potent *in vitro* cytotoxicity with IC_{50} <10 μg/mL against A-549, HCT-8 and MDAMB human cancer cell lines.[171]

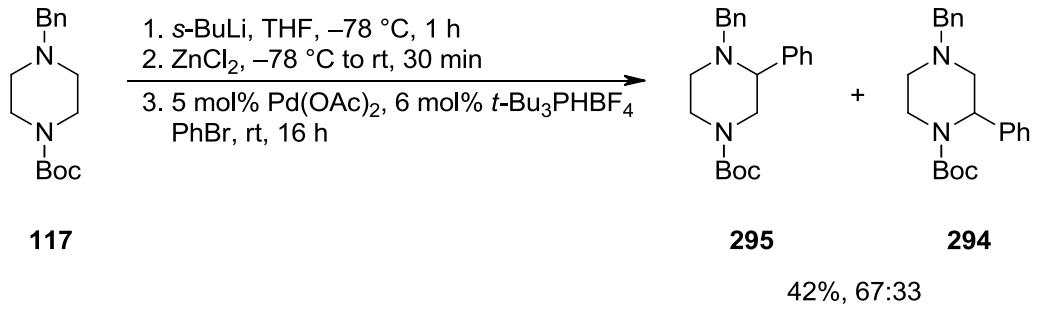


Dragmacidin

Figure 3.4

With the goal of synthesising compounds such as dragmacidin in mind, the *α*-arylation of *N*-Boc-*N′*-benzyl piperazine **117** was investigated. A repeat of the lithiation/arylation reported by Barker and O'Brien was performed, albeit with slightly modified conditions. Lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was performed using *s*-BuLi in THF at –78 °C and the cross-coupling performed at room temperature rather than at

reflux. However, rather than isolating solely **294**, an inseparable 67:33 mixture of regioisomers **295** and **294** was obtained in a combined 42% yield (Scheme 3.41). The presence of 3-phenyl piperazine **295** was confirmed through an independent synthesis of **295**.[154,172]



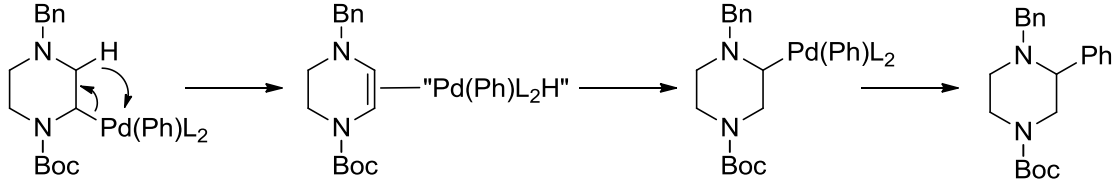
117 **295** **294**

42%, 67:33

Scheme 3.41

Analysis of the ^{1}H NMR spectra published by O'Brien indicated that **294** and **295** were obtained as an approximately 50:50 ratio when the cross-coupling step was performed at reflux. In the original analysis of the ^{1}H NMR spectrum, the regioisomers **294** and **295** were thought to be a 50:50 mixture of *N*-Boc rotamers of **294**. Interestingly, a small amount of *β*-arylated *N*-Boc pyrrolidine was recovered by Campos during the synthesis of glucokinase activator (*R*)-**93** on a large scale (see Scheme 1.46).[98]

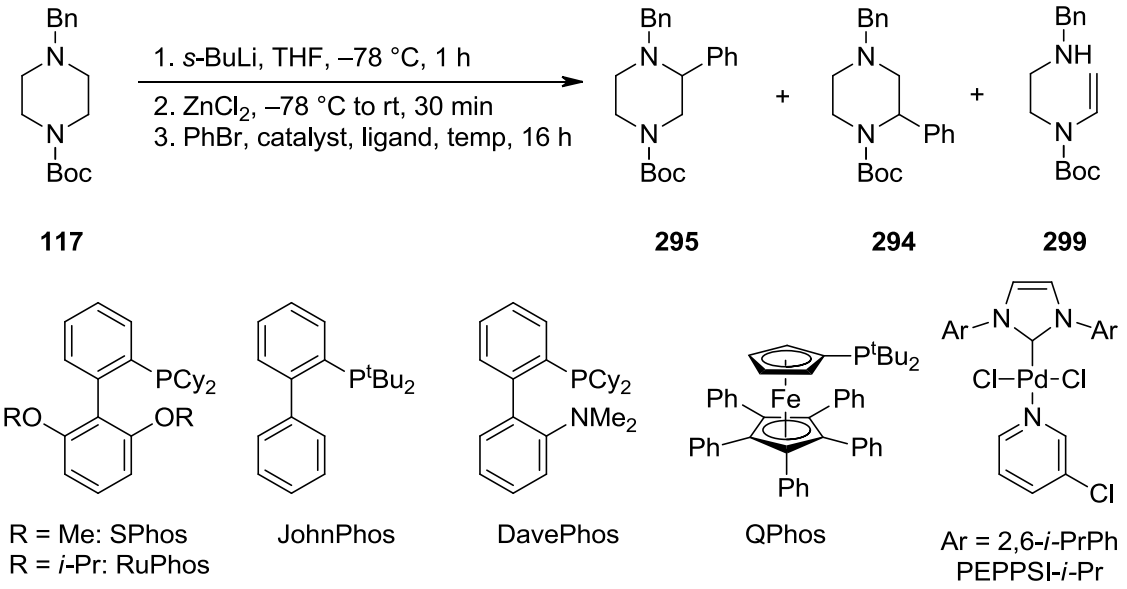
A mechanistic explanation, analogous to that proposed by Knochel for the formation of 2,5-disubsitituted piperidines (see Scheme 1.50),[103] can be provided for the formation of *β*-substituted piperazine **295**. *β*-Hydride elimination of the palladium intermediate **296** could be occurring to give **297**. The resulting "PdPhL$_2$H" complex could undergo *syn*-addition to alkene **297**, placing the palladium preferentially in the sterically less hindered 3-position of **298**. Reductive elimination could then proceed to give the *β*-substituted product **295** (Scheme 3.42).



296 **297** **298** **295**

Scheme 3.42 Mechanism for formation of *β*-substituted piperazine **295**

This argument suggests that steric considerations would determine the resulting ratio of regioisomeric products. In 2013, Baudoin reported the ligand controlled *β*-selective arylation of *N*-Boc piperidine **10** (see Scheme 1.51).[104] The explanation for *β*-selectivity was that the energy of the transition state for the rate determining C-Ar bond forming reductive elimination was lower for formation of the *β*-isomer compared to the *α*-substituted product. Regardless of the cause of regioselectivity, it was envisaged that an exploration of different catalyst and ligand systems would be illuminating. The results of such a study are presented in Table 3.2.



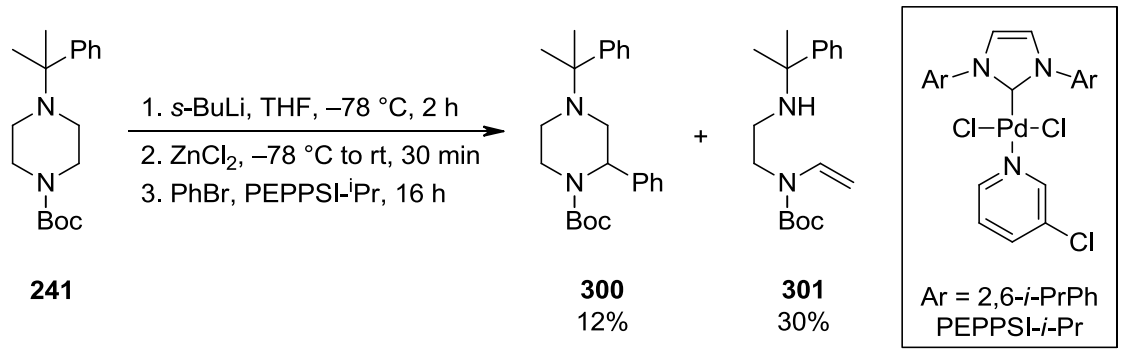
Entry	Catalyst / Ligand (5 mol%)	Temperature	Yield (%)[a] 295 + 294	295:294[b]
1	$Pd(dba)_2$, RuPhos	rt	63	60:40
2	$Pd(dba)_2$, DavePhos[c]	rt	-	-
3	$Pd(dba)_2$, JohnPhos[d]	rt	-	-
4	$Pd(dba)_2$, SPhos[d]	rt	-	-
5	$Pd(dba)_2$, QPhos[d]	rt	-	-
6	PEPPSI-*i*-Pr	rt	38	95:5
7	PEPPSI-*i*-Pr	reflux	37	90:10

[a] Yield after flash column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] 46% yield of vinyl carbamate **299** and 49% recovered **117**. [d] Only vinyl carbamate **299** and starting material **117** observed by analysis of the ^{1}H NMR spectrum; reaction not purified.

Table 3.2 Lithiation/arylation of *N*-Boc-*N′*-benzyl piperazine **117**

The catalyst and ligand system employed by Knochel (5 mol% $Pd(dba)_2$ and 5 mol% RuPhos)[103] was investigated first and a 60:40 mixture of **295** and **294** was isolated in 63% yield (Table 3.2, entry 1). A small range of other monodentate phosphine ligands were investigated. However, no arylation products were observed (entries 2-5). In all four cases, ring fragmentation by-products were observed in the ^{1}H NMR spectra of the crude products. In the reaction employing DavePhos as a ligand, vinyl carbamate **299** was isolated in 46% yield with 49% recovered **117** (entry 2). It is possible that in these cases Zn/Pd transmetalation was slow and the intermediate organozinc species fragmented. The *N*-heterocyclic carbene based PEPPSI-*i*-Pr catalyst system was also investigated.[173,174] Almost complete regiocontrol was attained; a 95:5 mixture of 3-phenyl *N*-Boc piperazine **295** and 2-phenyl *N*-Boc piperazine **294** was isolated in 38% yield when the Negishi reaction was performed at room temperature (Table 3.2 entry 6). In an attempt to improve the yield of arylated products using PEPPSI-*i*-Pr as catalyst the cross coupling step was heated at reflux (entry 7). However, there was no improvement in the yield of **295** and **294** (37%) and the regioselectivity dropped marginally (90:10).

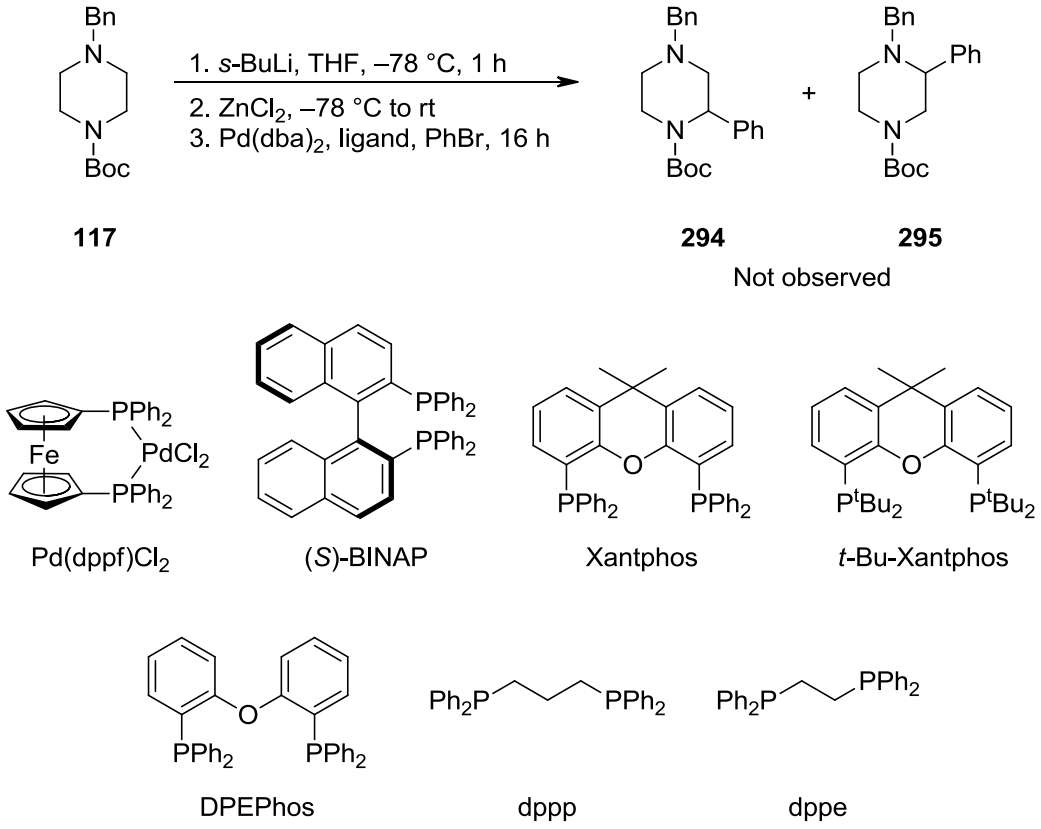
Interestingly, lithiation/arylation of *N*-Boc-*N′*-cumyl piperazine **241** using PEPPSI-*i*-Pr resulted in the formation of *α*-substituted piperazine **300** in 12% yield without any of the *β*-arylated adduct being formed (Scheme 3.43). This reversal of regioselectivity is possibly due to steric considerations, although it could also be due to significantly more complex reasons. Unfortunately, the yield was low; ring fragmented by-product **301** was isolated in 30% yield with 53% recovered starting material. It is possible that the yield was low due to incomplete lithiation of **241** within 2 h in THF at –78 °C. However, the presence of a significant quantity of vinyl carbamate **301** indicates that the cross-coupling step was also problematic.



241 **300** 12% **301** 30%

Scheme 3.43

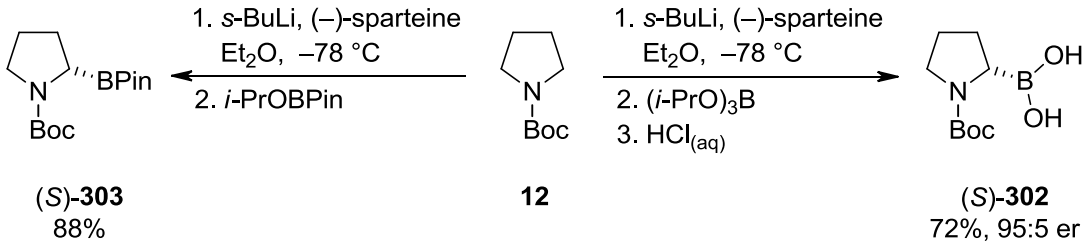
Although this initial result using *N*-Boc-*N′*-cumyl piperazine **241** was promising, the low yield and formation of by-product **301** was problematic. An alternative strategy to achieve regioselectivity was employed. Preventing the intermediate palladium complex from undergoing *β*-hydride elimination could possibly allow the formation of 2-phenyl *N*-Boc piperazine **294** as a single regioisomer. As it is known that the use of bidentate phosphine ligands can prevent *β*-hydride elimination from an alkyl-metal moiety,[175,176] a small screen of bidentate ligands for the lithiation/Negishi coupling reaction was performed. Reactions were carried out using 5 mol% of $Pd(dba)_2$ and 6 mol% of ligand, or with 5 mol% $Pd(dppf)Cl_2$ (Scheme 3.44). Disappointingly, neither **294** nor **295** were observed in any reaction. It is worth noting that in the Campos' original lithiation/arylation report with *N*-Boc pyrrolidine **12**, the use of $Pd(dppf)Cl_2$ gave no product.[97]



Scheme 3.44 Attempted lithiation/arylation of **117** using bidentate phosphine ligands

The lack of any reaction when using bidentate ligands, possibly due to poor transmetallation of the organozinc species, led to the attempted use of boronate coupling partners. In 2007, Whiting reported the use of asymmetric lithiation/trapping chemistry to synthesise the boronic acid and pinacol ester of *N*-Boc pyrolidine **12**.[177] Lithiation

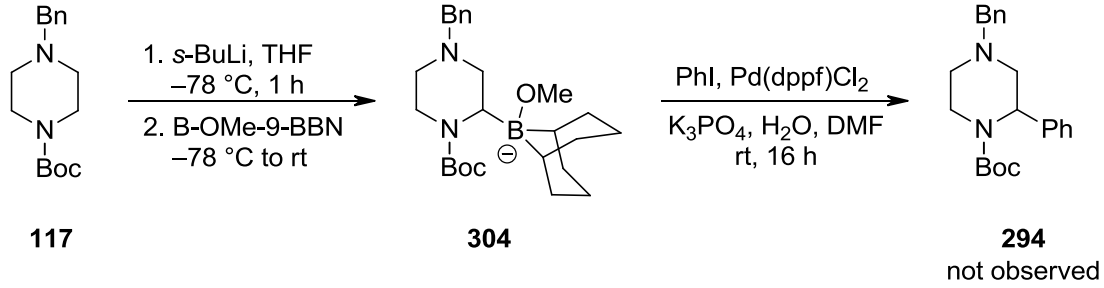
under standard conditions (*s*-BuLi/(–)-sparteine, –78 °C, Et_2O) followed by trapping with tri-isopropyl borate gave boronic acid (*S*)-**302** in 72% yield and 95:5 er (Scheme 3.45). Trapping with isopropoxy pinacol borate gave boronic ester (*S*)-**303** in 88% yield with an unspecified enantiomeric ratio.



Scheme 3.45

It was envisaged that both boronic acids and esters would be poor coupling partners for a sp^2-sp^3 Suzuki-Miyaura coupling reaction. Therefore, the synthesis of an α-9-BBN derivative of *N*-Boc piperazine, a much better coupling partner for sp^2-sp^3 Suzuki-Miyaura reactions, was undertaken.[178,179] In 1998, Marshall reported the total synthesis of (+)-discodermolide and a key step in the synthesis was a one-pot lithiation followed by borylation with B-methoxy-9-BBN then Suzuki-Miyaura coupling catalysed by $Pd(dppf)Cl_2$.[180] This methodology was used in an attempt to synthesise 2-phenyl *N*-Boc piperazine **294**. It was envisaged that the use of a bidentate ligand would prevent β-hydride elimination from the organopalladium species and that transmetalation would prove facile.

Diamine-free lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was followed by trapping with B-methoxy-9-BBN to give boronate complex **304**. Suzuki coupling with iodobenzene catalysed by $Pd(dppf)Cl_2$ was then attempted. Unfortunately, formation of 2-phenyl *N*-Boc piperazine **294** was not observed, with the intermediate trialkyl borane being the only product identified (Scheme 3.46).



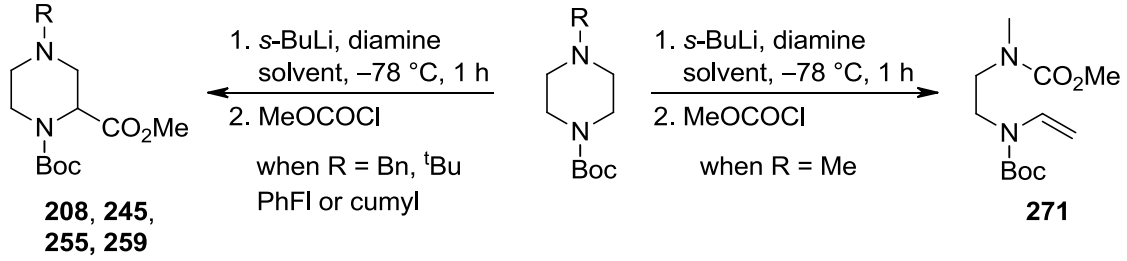
117 **304** **294** not observed

Scheme 3.46

The lack of success when using this approach could be due to the fact that secondary alkyl groups migrate much more slowly than primary alkyl groups.[179] It may be possible to optimise the coupling step with a more sustained effort.[181]

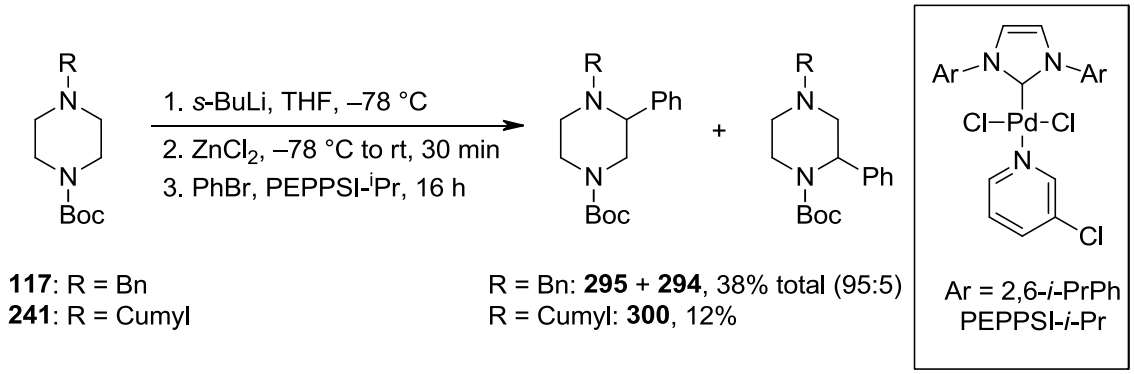
3.4 Conclusions and Future Work

The racemic lithiation/trapping of a range of protected *N*-Boc piperazines has been accomplished. A small range of electrophiles was used, to provide access to a variety of *α*-substituted piperazines. Separation of the enantiomers of many of these compounds was achieved using CSP-HPLC, with a view to the development of an asymmetric lithiation/trapping of *N*-Boc piperazines. When using *N*-Boc-*N′*-methyl piperazine **151** and trapping with certain electrophiles, for example methyl chloroformate, fragmentation product **271** was observed. However, when using larger protecting groups such as *N*-benzyl, *N*-*t*-butyl, *N*-PhFl or *N*-cumyl, ring fragmentation was not observed and *α*-substituted *N*-Boc piperazines **208**, **245**, **255** and **259** were isolated (Scheme 3.47).



Scheme 3.47

A preliminary investigation into the lithiation/arylation of *N*-Boc piperazines has been performed. The methodology was complicated by a proclivity for formation of a mixture of *α*- and *β*-arylated piperazine regioisomers when using *N*-Boc-*N′*-benzyl piperazine **117**. A wide screen of ligands was undertaken and almost complete selectivity (95:5) for the formation of *β*-phenyl piperazine **295** was achieved using the *N*-heterocyclic carbene ligated palladium catalyst PEPPSI-*i*-Pr. However, the mixture of **295** and **294** was obtained in only 38% yield (Scheme 3.48). Additionally, use of *N*-Boc-*N′*-cumyl piperazine **241** under the same lithiation/arylation conditions resulted in a reversal in regioselectivity with selective formation of the *α*-phenyl piperazine **300** in 12% yield.



Scheme 3.48

It is possible that with future work these reactions may be optimised to give high yielding, selective methods for the synthesis of either *α*- or *β*-arylated piperazines. Further investigations into the catalyst system, reaction conditions and nature of the aryl halide could be fruitful. Specifically, the use of Badoin's phosphine ligands may facilitate the selective formation of *β*-arylated piperazines. Additionally, it may be possible to optimise the lithiation/arylation of *N*-Boc-*N′*-cumyl piperazine **241** to give solely *α*-arylated piperazines in good yield. To this end, the lithiation could be improved by employing *s*-BuLi/TMEDA in Et_2O and the arylation may be improved by using an alternative PEPPSI derivative, solvent or by altering the electronics of the aryl halide.

To expand the electrophile scope further, future work could investigate the application of Fu's enantioselective ligand controlled nickel catalysed lithiation/Negishi coupling to *N*-Boc piperazines.[105]

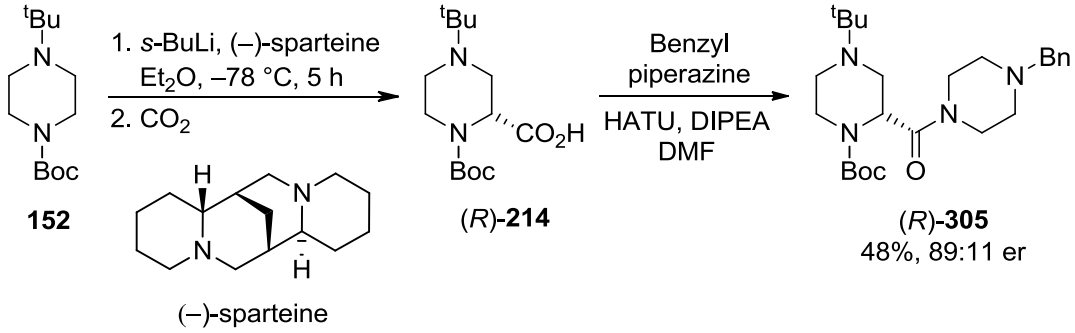
Chapter Four: Asymmetric Lithiation/Trapping of *N*-Boc Piperazines

N-Boc pyrolidine **12** and *N*-Boc piperidine **10** have been extensively studied as substrates for the *s*-BuLi/diamine mediated asymmetric lithiation/trapping methodologies. However, the equally important *N*-Boc piperazine systems have been comparatively neglected. At the start of this project, there was only one example of the asymmetric lithiation/trapping of *N*-Boc piperazines using *s*-BuLi and a chiral diamine.

This chapter details a thorough investigation of the asymmetric lithiation/trapping of *N*-Boc piperazines. The role of the piperazine protecting group on the reaction outcome is explored in detail, with a range of side-reactions being encountered, investigated and overcome. The use of a chiral auxiliary protecting group for the asymmetric lithiation/trapping of *N*-Boc piperazines, facilitating the synthesis of enantiopure α-substituted piperazines is detailed. A formal synthesis of the anti-retroviral Indinavir and the synthesis of disubstituted piperazines are disclosed.

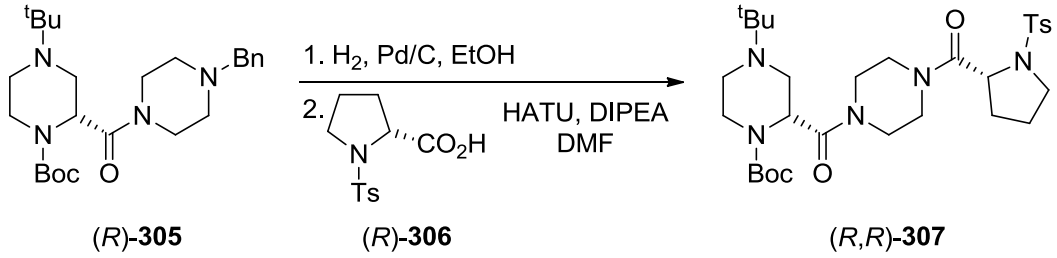
4.1 Previous Asymmetric Lithiation/Trapping of *N*-Boc Piperazines

To date, there has been only one reported example of *s*-BuLi/chiral diamine-induced asymmetric deprotonation of *N*-Boc piperazines. McDermott's group at AstraZeneca used *N*-Boc-*N'*-*t*-butyl piperazine **152** as a substrate.[108] Lithiation using *s*-BuLi/(–)-sparteine under standard conditions (Et_2O, –78 °C, 5 h) was followed by trapping with CO_2 to give carboxylic acid (*R*)-**214**, which was not purified. The crude carboxylic acid underwent amidation with benzyl piperazine in the presence of HATU to give amide (*R*)-**305** in 48% yield and 89:11 er (Scheme 4.1). Only one example of this supposedly unoptimised asymmetric deprotonation was reported. As shown by the ReactIR™ study using *N*-Boc-*N'*-*t*-butyl piperazine **152** in Chapter 2, the lithiation of **152** with *s*-BuLi/(–)-sparteine was incomplete after 5 h, possibly accounting for the moderate yield of (*R*)-**305** (see Scheme 2.20b)



Scheme 4.1

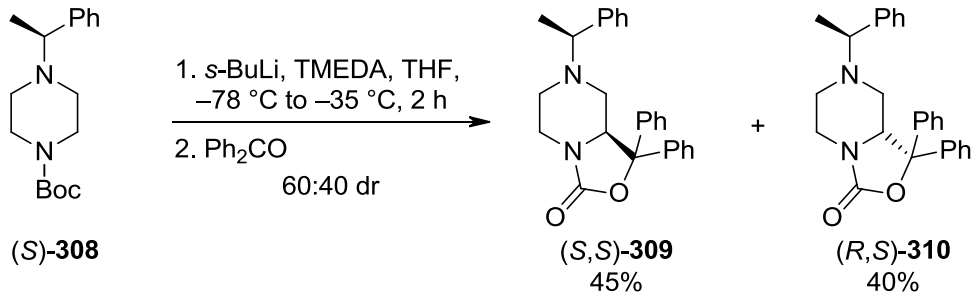
It was suspected that the absolute stereochemical configuration of (*R*)-**214** was the same as the products obtained from the *s*-BuLi/(–)-sparteine mediated lithiation/trapping of *N*-Boc pyrrolidine **12** and *N*-Boc piperidine **10**. This was confirmed by X-ray crystallography of a derivative (*R*,*R*)-**307**, which was prepared by debenzylation of (*R*)-**305** followed by amidation with (*R*)-*N*-tosyl proline (*R*)-**306** (Scheme 4.2).



Scheme 4.2

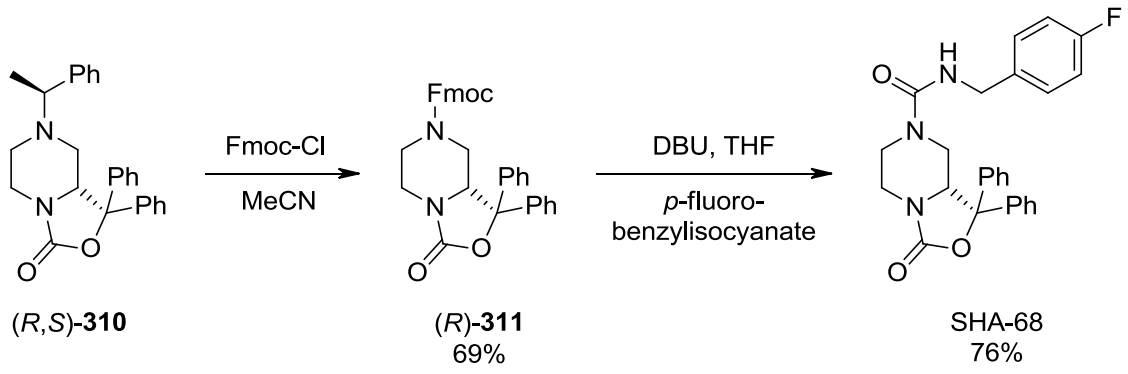
Workers at AstraZeneca showed that the asymmetric lithiation could be performed on a multi-gram scale. Lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** was performed on a 10 g scale giving (*R*)-**305** in slightly lower er (83:17).[182]

An interesting concept for the synthesis of enantioenriched *α*-substituted *N*-Boc piperazines was briefly explored by Guerrini and co-workers for the synthesis of the biologically active enantiomer of SHA-68, a neuropeptide S receptor (NPSR) antagonist.[183] Enantiopure *α*-methylbenzyl-substituted *N*-Boc piperazine (*S*)-**308** was deprotonated using *s*-BuLi/TMEDA in THF and trapped with benzophenone. A 60:40 mixture of separable diastereomeric oxazolidinones (*S*,*S*)-**309** and (*R*,*S*)-**310** was formed and after isolation, (*S*,*S*)-**309** and (*R*,*S*)-**310** were attained in 45% and 40% yield respectively (Scheme 4.3). The (*S*)-*α*-methylbenzyl group acts as a chiral auxiliary, inducing a slight preference for removal of the pro-(*S*) proton. The poor diastereoselectivity is understandable considering the large distance between the chiral auxiliary and the site of deprotonation. Nevertheless, this use of a chiral auxiliary facilitated the isolation of enantiomerically pure *α*-substituted piperazines. The major disadvantage of this approach is that the synthesis of the starting *N*-Boc piperazine (*S*)-**308** took five steps and proceeded in only 20% yield.



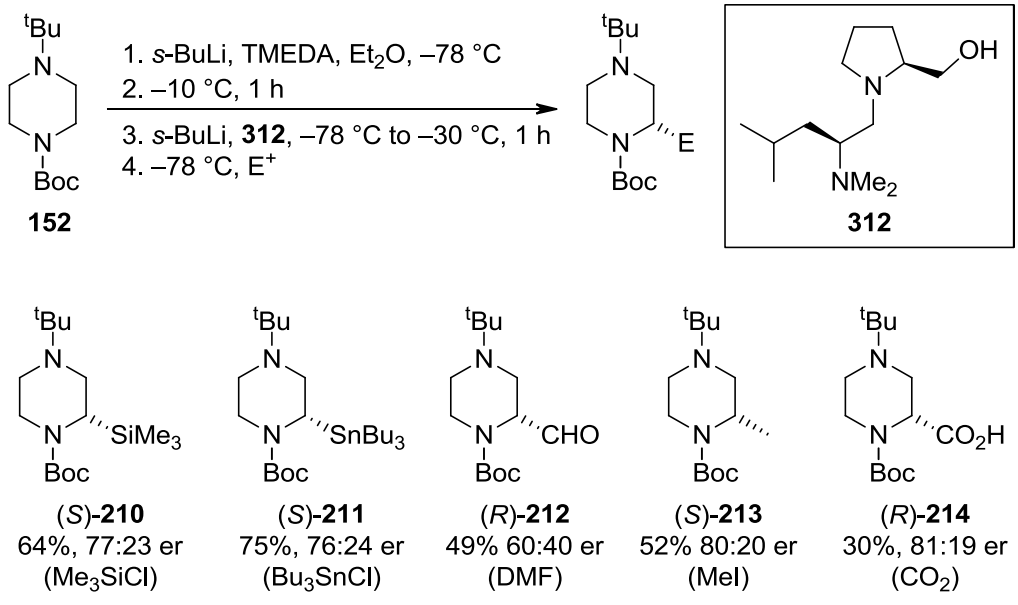
Scheme 4.3

The relative stereochemistry of the minor diastereomer (*R*,*S*)-**310** was determined by X-ray crystallography. The target, neuropeptide S receptor antagonist SHA-68, was synthesised from (*R*,*S*)-**310** in two steps. The chiral auxiliary was removed using Fmoc-Cl to give enantiomerically pure (*R*)-**311** in 69% yield. Fmoc deprotection using DBU and subsequent *in situ* urea formation gave SHA-68 in 76% yield (Scheme 4.4).



Scheme 4.4

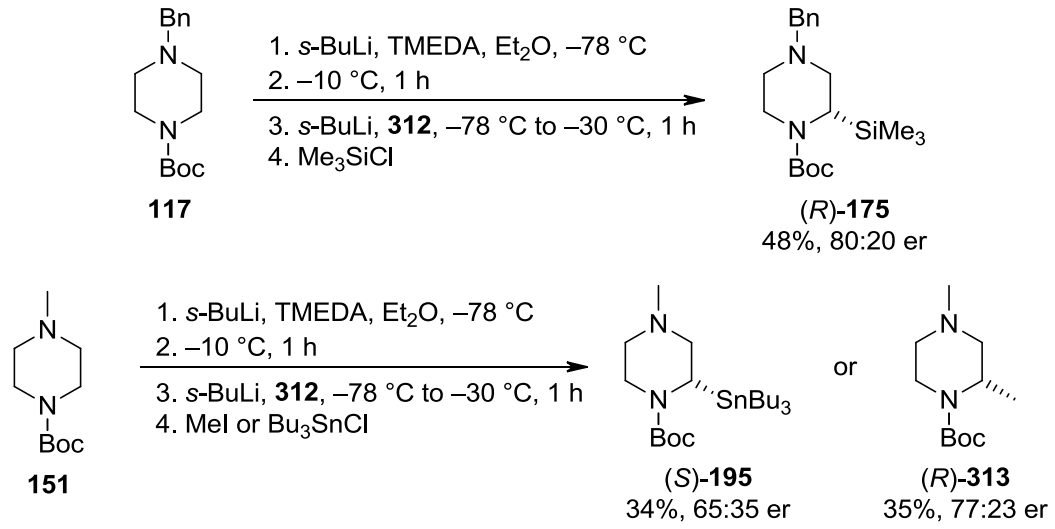
In related work, Coldham has described a dynamic thermodynamic resolution (DTR) process for the synthesis of enantioenriched *α*-substituted *N*-Boc piperazines.[147] Deprotonation was performed using *s*-BuLi/TMEDA, initially at –78 °C then at –10 °C for 1 h. Then, the reaction was cooled to –78 °C before lithiated ligand **312** was added and the reaction warmed to –30 °C and aged for 1 h to establish the thermodynamic ratio of diastereomeric organolithium complexes. The reaction was cooled to –78 °C to prevent further interconversion of organolithiums, prior to addition of the electrophile. When using *N*-Boc-*N′*-*t*-butyl piperazine **152** as a substrate, *α*-substituted piperazines **210**-**214** were isolated in 30-75% yield and 60:40-80:20 er (Scheme 4.5).



Scheme 4.5 Dynamic thermodynamic resolution of *N*-Boc-*N′*-*t*-butyl piperazine **152**

Other piperazines were used as substrates for the DTR methodology. When using *N*-Boc-*N′*-benzyl piperazine **117**, silane (*R*)-**175** was isolated in 48% yield and 80:20 er

(Scheme 4.6). *N*-Methyl piperazines (*R*)-**195** and (*S*)-**313** were obtained in 34% yield (65:35 er) and 35% yield (77:23 er) when using and *N*-Boc-*N′*-methyl piperazine **151**. It is possible that the low yields of (*S*)-**195** and (*R*)-**313** might be due to ring fragmentation side-reactions occurring, but no information on this was reported.



Scheme 4.6 Dynamic thermodynamic resolution of **117** and **151**

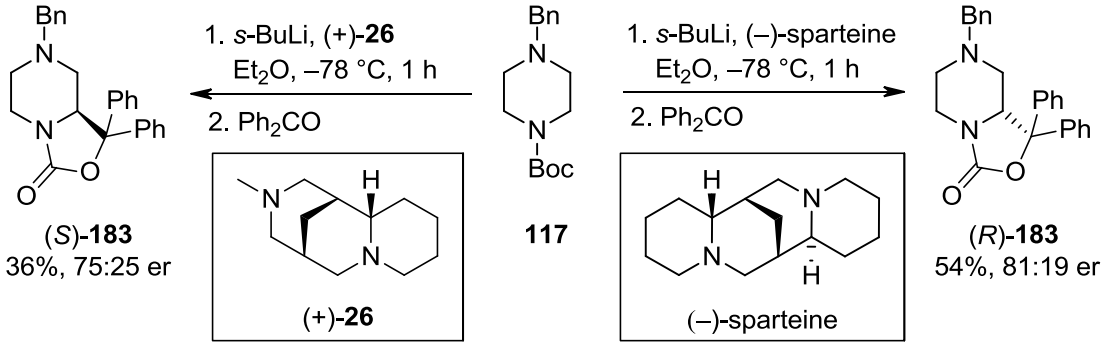
The reported studies into the asymmetric lithiation/trapping of *N*-Boc piperazines were promising. However, a systematic study of the substrate and electrophile scope was not performed. Additionally, products were generally isolated in moderate yields and enantioselectivities.

4.2 Asymmetric Lithiation/Trapping of *N*-Boc Piperazines

4.2.1 Asymmetric Lithiation/Trapping of *N*-Boc-*N′*-Benzyl Piperazines

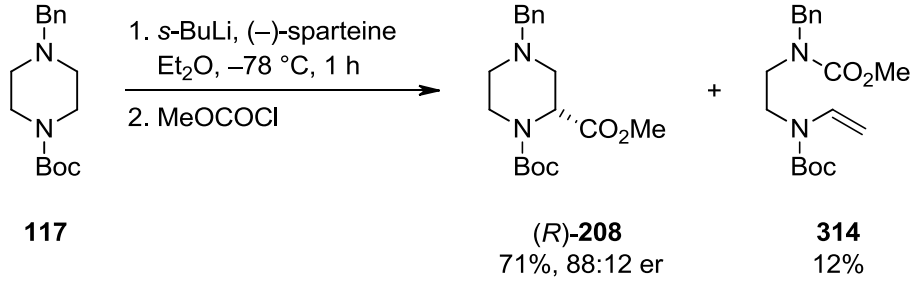
As described in Chapter 3, the racemic lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** was highly fruitful; trapping with a wide range of electrophiles gave *α*-substituted products in 44-90% yields (see Scheme 3.20) and the enantiomers of most of these products were separated using CSP-HPLC. With the success of the racemic lithiation/trapping with *N*-Boc-*N′*-benzyl piperazine **117**, the study into the asymmetric variant began with this substrate.

The ReactIR™ spectroscopic studies reported in Chapter 2 were used to determine the optimum lithiation times. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was achieved using *s*-BuLi/(–)-sparteine in Et_2O at –78 °C for 1 h. Subsequent trapping with benzophenone gave oxazolidinone (*R*)-**183** in 54% yield and 81:19 er (Scheme 4.7). The configuration of (*R*)-**183** was assigned by analogy with McDermott's work[108] and the er was determined by CSP-HPLC. Use of the (+)-sparteine surrogate (+)-**26** resulted in oxazolidinone (*S*)-**183** being isolated in a disappointing 36% yield and 75:25 er.



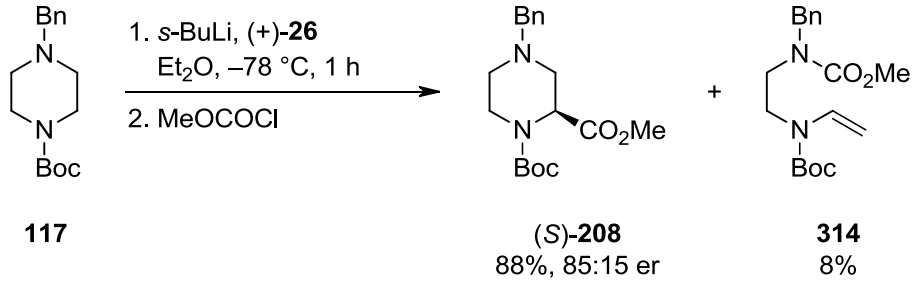
Scheme 4.7

In an attempt to develop the methodology into a general procedure for the synthesis of a wide range of enantioenriched *α*-substituted *N*-Boc piperazines, the electrophile scope was examined. Asymmetric lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(–)-sparteine followed by trapping with methyl chloroformate gave the desired substituted *N*-Boc piperazine (*R*)-**208** in 71% yield and 88:12 er. However, ring fragmented by-product, vinyl carbamate **314**, was also isolated, in 12% yield (Scheme 4.8).



Scheme 4.8

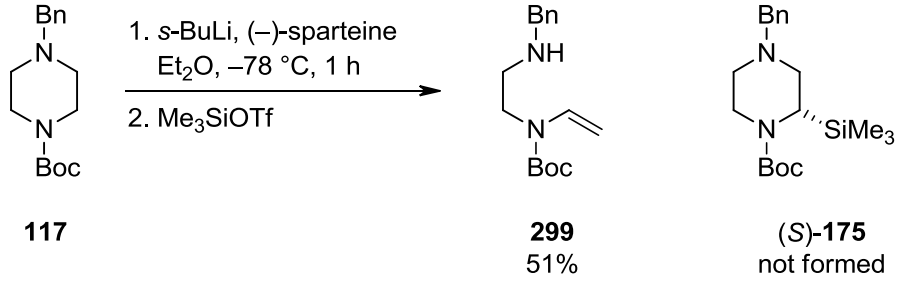
A similar outcome was found when the (+)-sparteine surrogate (+)-**26** was used. The desired substituted *N*-Boc piperazine (*S*)-**208** was obtained in an excellent 88% yield and 85:15 er, along with vinyl carbamate **314** in 8% yield (Scheme 4.9).



Scheme 4.9

As outlined in Chapter 3, it is proposed that ring fragmentation occurs *via* the nitrogen lone pair of lithiated piperazine **285** reacting with the electrophile preferentially (see Scheme 3.37). Although ring fragmentation was observed with *N*-Boc-*N′*-methyl piperazine **151** and *N*-Boc-*N′*-allyl piperazine **239** when using diamine-free conditions (see Chapter 3.2), there was no evidence for the formation of vinyl carbamate **314** when using *N*-Boc-*N′*-benzyl piperazine **117** (see Scheme 3.20). Clearly, the use of a chiral diamine has an effect on the reaction outcome.

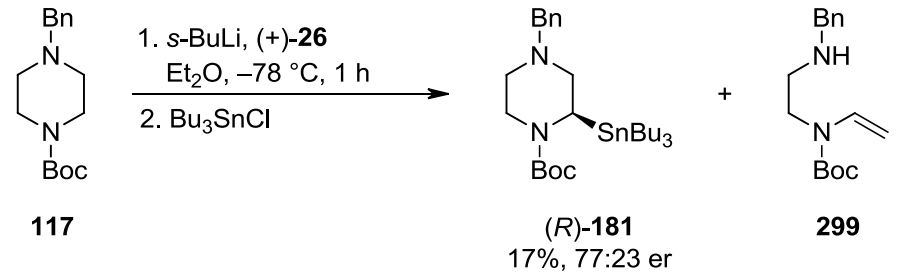
Ring fragmentation side-reactions did not only occur when using methyl chloroformate as the electrophile. Lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(–)-sparteine and trapping with Me_3SiOTf gave none of the desired *α*-silyl *N*-Boc piperazine **175**. Fragmentation product **299** was the only product, isolated in 51% yield (Scheme 4.10).



117 **299** 51% (*S*)-**175** not formed

Scheme 4.10

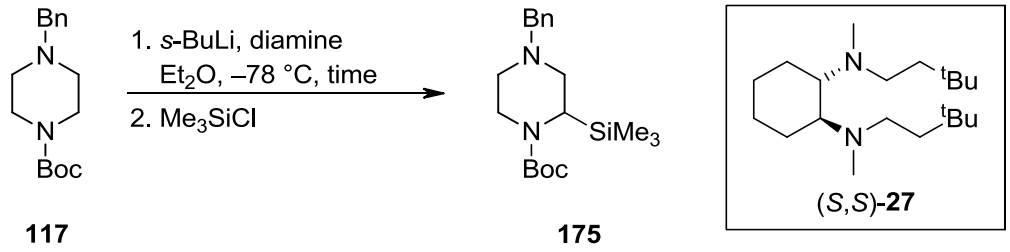
In a further example, lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(+)-sparteine surrogate (+)-**26** and trapping with Bu_3SnCl resulted in only 17% of the desired stannane (*R*)-**181** in 77:23 er (Scheme 4.11). Ring fragmentation product **299** was the major product, as confirmed by the ^1H NMR spectrum of the crude mixture, although it could not be isolated cleanly from the reaction mixture.



117 (*R*)-**181** 17%, 77:23 er **299**

Scheme 4.11

Ring fragmentation was a serious hurdle to the development of a general method for the asymmetric lithiation/trapping of *N*-Boc piperazines. Furthermore, it was not the only major obstacle encountered in the early stages of this project. Previous work within the group had shown that asymmetric lithiation of *N*-Boc-*N′*-benzyl piperazine **117** using *s*-BuLi/(–)-sparteine and trapping with Me_3SiCl gave *α*-silyl piperazine **175** in 38% yield and only 52:48 er (Table 4.1, entry 1).[184] During this investigation, the use of alternative diamines gave similar results. Using *s*-BuLi/(+)-sparteine surrogate (+)-**26**, *α*-silyl piperazine **175** was obtained in 53% yield and 50:50 er (entry 2). With the Alexakis diamine (*S*,*S*)-**27**, *α*-substituted *N*-Boc piperazine **175** was obtained in a poor 9% yield and 52:48 er (entry 3).



117 **175**

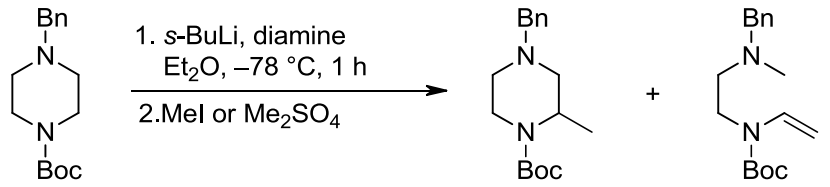
Entry	Diamine	Time (h)	Yield 175 (%)[a]	er 175 (*S*:*R*)[b]
1	(–)-sparteine	5	38	52:48[c]
2	(+)-**26**	1	53	50:50
3	(*S*,*S*)-**27**	1	9	48:52

[a] Yield after flash column chromatography. [b] Er determined by CSP-HPLC. [c] See reference 184.

Table 4.1 Attempted asymmetric lithiation/trapping of **117** with Me_3SiCl

The poor levels of enantioselectivity can be explained by the rate of trapping of the intermediate organolithium with Me_3SiCl. The use of *in situ* ReactIR™ spectroscopy has shown that trapping of lithiated *N*-Boc-*N′*-benzyl piperazine **117** with some electrophiles, particularly with Me_3SiCl, is exceptionally slow at –78 °C (see Scheme 2.27). As the reaction is warmed to room temperature the lithiated intermediate becomes configurationally unstable.[61] Importantly, epimerisation occurs before trapping, resulting in essentially racemic **175** being isolated. No ring fragmentation by-products were observed when using Me_3SiCl, unlike when using the more reactive Me_3SiOTf (see Scheme 4.10). It is noteworthy that lithiated *N*-Boc-*N′*-benzyl piperazine **117** reacts less rapidly with 'slow' electrophiles than lithiated *N*-Boc pyrrolidine **12** or 4-phenyl *N*-Boc piperidine **66**. This is an intrinsic limitation of the lithiation/trapping of *N*-Boc piperazines.

Further investigation of the use of slow trapping electrophiles in the asymmetric lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** was undertaken. Lithiation was performed using *s*-BuLi and chiral diamines and trapping was accomplished through the addition of either methyl iodide or dimethyl sulfate. The results of this investigation are presented in Table 4.2.



117 **176** **315**

Entry	E^+	Diamine	Yield (%)[a], er (*S*:*R*)[b] 176	Yield 315 (%)[a]
1	Me_2SO_4	TMEDA	65	-
2	MeI	(*S*,*S*)-**27**	45 (55:45 er)	-
3	Me_2SO_4	(*S*,*S*)-**27**	-	51
4	MeI	(–)-sparteine	33 (61:39 er)	13
5	Me_2SO_4	(–)-sparteine	11 (58:42 er)	43
6	Me_2SO_4	(+)-**26**	-	50

[a] Yield after flash column chromatography. [b] Er determined by CSP-HPLC.

Table 4.2 Effect of electrophile and diamine on the α-methylation of *N*-Boc-*N′*-benzyl piperazine **117**

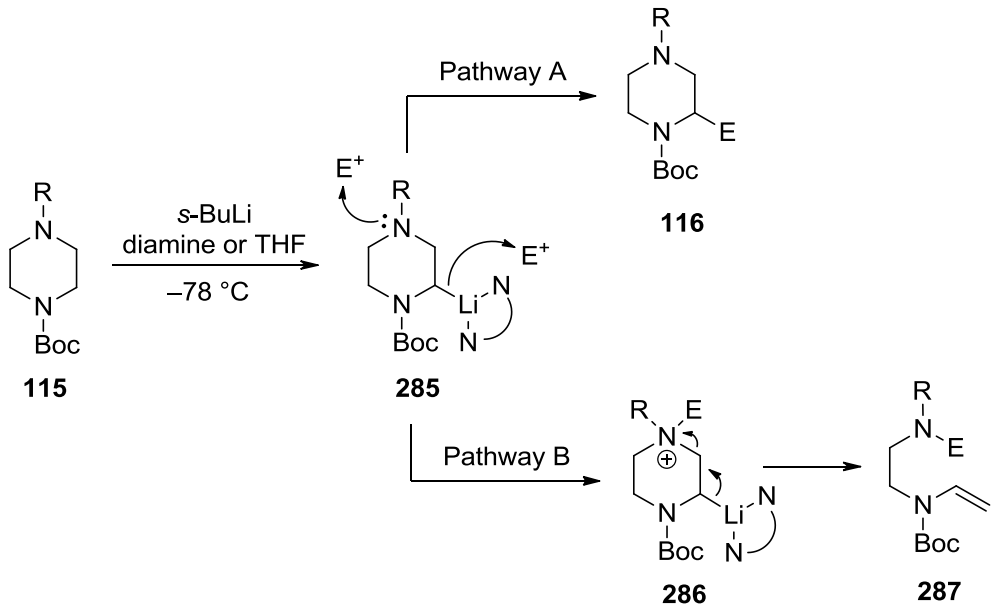
It was shown in Chapter 3 that racemic lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/THF and trapping with methyl iodide or dimethyl sulfate gave **176** in 74% and 69% yields respectively; no ring-fragmented product **315** was seen (see Scheme 3.20). As a control, the effect of TMEDA on the reaction outcome was performed. Racemic lithiation using *s*-BuLi/TMEDA in Et_2O at –78 °C and trapping with dimethyl sulfate gave **176** in 65% yield with no ring-fragmented product **315** (Table 4.2, entry 1).

The asymmetric lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(*S*,*S*)-**27** followed by trapping with methyl iodide gave (*S*)-**176** in 45% yield and 55:45 er (entry 2). The expected enantiomer, (*R*)-**176**, was determined to be the minor component by comparison of the measured optical rotation ($[\alpha]_D$ +4.8 (*c* 1.0 in EtOH)) with that reported in the literature ($[\alpha]_D$ +56 (*c* 0.44 in EtOH for a sample of >99:1 er)).[150] This unexpected sense of enantioinduction could be due to a dynamic thermodynamic resolution process occurring as the reaction warmed up.

Surprisingly, when asymmetric lithiation was performed under identical conditions (*s*-BuLi/(*S*,*S*)-**27**, Et_2O) and dimethyl sulfate was used as the electrophile, no *α*-methyl *N*-

Boc piperazine **176** was observed (by analysis of the ^{1}H NMR spectrum of the crude product) and ring-fragmented product **315** was isolated in 51% yield (entry 3). These result shows that both the diamine and the electrophile have an effect on the reaction outcome. Next, the effect of alternative chiral diamines was investigated. Lithiation of **117** with *s*-BuLi/(–)-sparteine and trapping with methyl iodide gave a mixture of products (entry 4). *α*-Methyl *N*-Boc piperazine **176** was isolated in 33% yield (61:19 er) and ring-fragmented product **315** was isolated in 13% yield. This result highlights the effect of the diamine on the product distribution. In comparison, when (*S*,*S*)-**27** was used, only by-product **315** was observed (entry 3). The low er (61:39 er) of (*S*)-**176** implies that, as expected, slow trapping was occurring and that the reaction was warming to a temperature at which the lithiated intermediate was configurationally unstable before any significant amount of trapping took place. When (–)-sparteine was used with dimethyl sulfate, the substituted *N*-Boc piperazine (*S*)-**176** was isolated in 11% yield (58:42 er) and by-product **315** was obtained in 43% yield (entry 5). Whereas the use of methyl iodide favoured formation of *α*-methyl piperazine (*S*)-**176**, the use of dimethyl sulfate favoured the formation of fragmentation product **315** (entries 4 and 5). Finally, when lithiation was performed using *s*-BuLi/(+)-sparteine surrogate (+)-**26** and trapped with dimethyl sulfate, only vinyl carbamate **315** was isolated, in 50% yield (entry 6).

To explain the dramatic effects of altering both the diamine and electrophile, the mechanism of fragmentation must be considered. The extent to which fragmentation occurred can be rationalised by a competition between two pathways (Scheme 4.12). In pathway A, trapping of the lithiated intermediate **285** by the electrophile gives the desired *α*-substituted piperazines **116**. Pathway B involves the nitrogen lone pair attacking the electrophile, giving quaternary ammonium species **286** which undergoes *β*-elimination to give vinyl carbamate **287**. The ReactIR™ spectroscopic studies presented in Chapter 2 show that for *N*-Boc pyrrolidine **12** the presence of a bulky diamine retarded electrophilic trapping with slow electrophiles (see Scheme 2.31). This is highly likely to be the case with *N*-Boc-*N′*-benzyl piperazine **117** as well. It is proposed that this decrease in the rate of electrophilic trapping in the presence of bulky chiral diamines allows the reaction to proceed (either partially or fully) through pathway B.



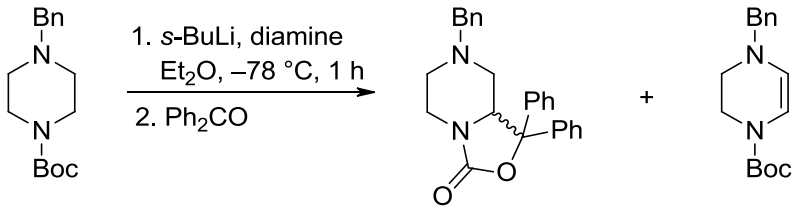
Scheme 4.12 Competing electrophile trapping pathways

In situ ReactIR™ studies showed that trapping of the organolithium with methyl iodide is faster than trapping with dimethyl sulfate (when using TMEDA as a ligand). This observation and the mechanism in Scheme 4.12 can explain the different reaction outcomes with the two electrophiles. For example, when utilising *s*-BuLi/(*S*,*S*)-**27** to effect lithiation, trapping with methyl iodide favoured formation of *α*-methyl piperazine **176**, whereas with dimethyl sulfate, the formation of fragmentation product **315** was favoured (Table 4.2, entries 2 and 3). As trapping with methyl iodide is faster, the reaction can proceed along pathway A. With dimethyl sulfate trapping of the organolithium is slower, resulting in predomination of pathway B. The same effect can be seen with (–)-sparteine (entries 4 and 5).

The product ratio of *α*-substituted piperazines **116** to vinyl carbamates **287** is dependent upon the relative rates of pathways A and B. The structure of the *N*-Boc piperazines and diamines, and the reactivity of the electrophiles all exert an influence on these rates, as highlighted by the results disclosed in this section and by the *in situ* ReactIR™ studies presented in Chapter 2.

Not only does the use of a bulky chiral diamine exacerbate the problems of slow trapping and the fragmentation side-reaction, a further complication was observed when trapping with benzophenone. Racemic lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** using diamine-free conditions and benzophenone resulted in the desired

oxazolidinone **183** being isolated in 90% yield (see Scheme 3.20). However, for lithiation with *s*-BuLi in the presence of bulky chiral diamines the reaction was more complex. Trapping with benzophenone gave alkene containing by-product **186** formed along with the desired product **183** (Table 4.3). Unfortunately, the isolation of pure alkene **186** from the crude reaction mixtures was not successful. However, unambiguous structural assignment was accomplished by mass spectrometry and ^{1}H NMR spectroscopy, and by analogy to known compounds.[185] Table 4.3 shows the effect of the diamine on the ratio of desired oxazolidinone **183** and alkene **186** (determined by analysis of ^{1}H NMR spectra of the crude mixtures) and the er of oxazolidinone **183**. Small, but significant, amounts of alkene **186** were formed (relative to the desired product) when (*S*,*S*)-**27** (entry 1) or (–)-sparteine (entry 2) were used, and the desired oxazolidinone **183** were isolated in 60% and 54% respectively. However, when (+)-sparteine surrogate (+)-**26** was used, alkene **186** was the major product of the reaction, with (*S*)-**183** isolated in only 35% yield (entry 3).



117 **183** **186**

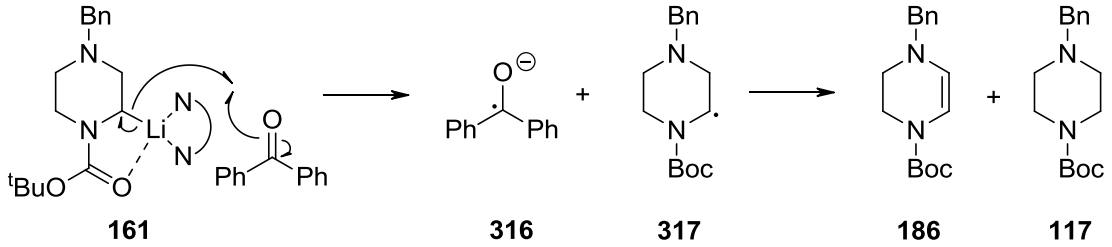
Entry	Diamine	Yield 183 (%)[a]	er 183 (*R*:*S*)[b]	183:186[c]
1	(*S*,*S*)-**27**	60	14:86	87:13
2	(–)-sparteine	54	81:19	78:22
3	(+)-**26**	35	25:75	41:59

[a] Yield after flash column chromatography. [b] Er determined by CSP-HPLC. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude product.

Table 4.3 Effect of the diamine on lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** with benzophenone

It is hypothesised that alkene **186** was formed through a radical process. The presence of benzophenone ketyl radical in the reaction mixture was evident from the persistent deep green colour observed when the benzophenone was added to the lithiated piperazine. Single electron transfer (SET) from the organolithium **161** to the benzophenone resulted in piperazine radical **317** and benzophenone ketyl radical **316**

(Scheme 4.13), as described by Gawley for pyrrolidine and piperidine based systems with benzophenone or alkyl halides.[86,186-188] Disproportionation of the piperazine radical **317** gave alkene **186** and starting material **117**.



Scheme 4.13 Mechanism of formation of alkene **186** *via* radical **317**

The reduction in er of oxazolidinone **183** (relative to results with methyl chloroformate under comparable conditions, see Scheme 4.8) can be attributed to some SET-mediated trapping. Radical trapping of the planar *N*-Boc piperazine radical **317** and benzophenone ketyl **316** would give the desired product, but without control over the newly formed stereocentre. This mechanism presumably resulted in a lower er of oxazolidinone **183**; SET trapping is well precedented with benzophenone.[186,189] In the lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(*S*,*S*)-**27**, oxazolidinone (*S*)-**183** was formed in 60% yield and a respectable 86:14 er (Table 4.3 entry 1), indicating a low level of radical trapping. However, lithiation with the (+)-sparteine surrogate (+)-**26** generated (*S*)-**183** in 35% yield and a poorer 75:25 er (entry 3). This suggests that radical trapping was more prevalent in this case. Notably, these side-reactions did not occur in the racemic, diamine-free lithiation. It was hypothesised that the use of a bulky diamine reduced the rate of anionic trapping with benzophenone thus allowing SET side-reactions to become competitive processes. Investigation by *in situ* ReactIR™ spectroscopy could not confirm or contradict this hypothesis. Complete trapping was shown to occur within 1 min at –78 °C, regardless of the route of trapping (see Scheme 2.38). However, the relative time scales of anionic trapping and SET trapping in the presence or absence of bulky diamines could not be determined due to the resolution of the ReactIR™ equipment. The reason for variable levels of SET side-reaction in the presence of different ligands is unknown.

Fragmentation of the piperazine ring and slow trapping by certain electrophiles were the two most significant problems encountered with *N*-Boc-*N′*-benzyl piperazine **117**. These problems, along with the SET side-reactions encountered with benzophenone, conferred

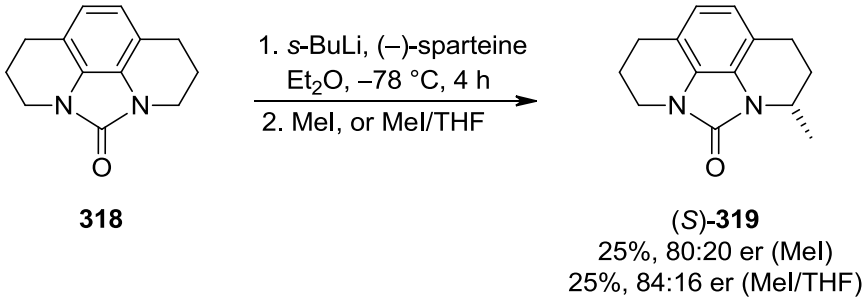
a poor electrophile scope on the lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117**. In the presence of chiral diamines, all electrophiles tested resulted in at least partial fragmentation, near-racemic products or single electron transfer side-products.

4.2.2 Diamine Displacement Strategy

Racemic lithiation of *N*-Boc-*N′*-benzyl piperazine **117** and trapping with either methyl iodide or dimethyl sulfate proceeded without issue to give 2-methyl piperazine **176** (see Scheme 3.20 and Table 4.2, entry 1). However, ring-fragmentation was generally observed when the analogous asymmetric reaction was performed (see Table 4.2, entries 3-6). This was due to slower electrophile trapping in the presence of a bulky diamine, as observed with *N*-Boc pyrrolidine **12** through *in situ* ReactIR™ monitoring (see Scheme 2.31). To circumvent the ring-fragmentation problem it was envisaged that reducing the steric bulk around the newly formed stereogenic centre would allow faster rates of trapping with 'slow' electrophiles. Two approaches were conceivable, Sn/Li exchange and a diamine displacement strategy. Previously, a Sn/Li exchange process was successfully used by O'Brien and co-workers to improve the yield and er of *α*-substituted *N*-Boc piperidines with slow trapping electrophiles.[95] Unfortunately, for *N*-Boc-*N′*-benzyl piperazine **117** this strategy was unfeasible as the requisite enantioenriched stannane could not be synthesised in a useful yield due to ring-fragmentation side reactions (see Scheme 4.11).

A diamine displacement method was therefore investigated with a view to reducing the steric bulk around the organolithium centre. It was hypothesised that asymmetric deprotonation of *N*-Boc-*N′*-benzyl piperazine **117** could be performed with *s*-BuLi and a chiral diamine to generate an enantioenriched organolithium intermediate. Then, displacement of the bulky chiral diamine from the organolithium intermediate could possibly be achieved with either a coordinating solvent, such as THF, or a smaller diamine such as TMEDA. This would reduce the steric bulk around the enantioenriched organolithium, allowing faster trapping with problematic electrophiles. ReactIR™ spectroscopic monitoring had shown that the trapping of lithiated *N*-Boc-*N′*-benzyl piperazine **117** with methyl iodide, in the presence of THF or TMEDA proceeded sufficiently quickly at –78 °C.

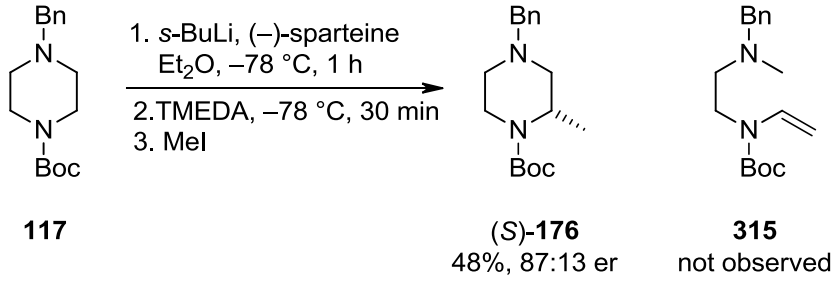
Diamine displacement of enantioenriched organolithium species is precedented from the catalytic two-ligand approach developed by O'Brien (see Scheme 1.19).[63] A further example was reported by Metallinos whist investigating the asymmetric lithiation/trapping of urea **318**.[29] Lithiation with *s*-BuLi/(–)-sparteine followed by trapping with methyl iodide gave (*S*)-**319** in 25% yield and 80:20 er (Scheme 4.14). However, when the lithiated intermediate was transferred to a solution of methyl iodide in THF at –78 °C, (*S*)-**319** was isolated in 25% yield and 84:16 er. This slight improvement in enantioinduction was attributed to the THF displacing (–)-sparteine from the organolithium.



Scheme 4.14

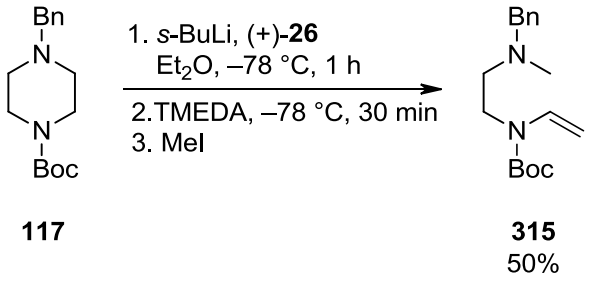
When lithiation of *N*-Boc-*N′*-benzyl piperazine **117** was performed using s-BuLi/(–)-sparteine followed by trapping with methyl iodide, 2-methyl *N*-Boc piperazine (*S*)-**176** was isolated in 33% yield (61:39 er) along with ring-fragmented product **315** in 13% yield (see Table 4.2, entry 4). This was the most promising result obtained for the asymmetric lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** with methylating agents, and so the diamine displacement strategy was applied to this system. Once lithiation of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(–)-sparteine was complete (1 h at –78 °C in Et_2O), TMEDA (5 eq.) was added and the reaction was stirred for 30 min before addition of methyl iodide. The desired product, 2-methyl *N*-Boc piperazine (*S*)-**176** was isolated in 43% yield and 87:13 er (Scheme 4.15). Ring-fragmented by-product **315** was not observed (by analysis of the ^{1}H NMR spectrum of the crude product). Although the yield of (*S*)-**176** was moderate, the enantiomeric ratio was greatly improved using the diamine displacement strategy. In fact, the enantiomeric ratio of (*S*)-**176** (87:13 er) probably reflects the ratio of organolithium intermediates. It is known that lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** with *s*-BuLi/(–)-sparteine and the 'fast' electrophile, methyl chloroformate, gave ester (*R*)-**208** in 88:12 er (see

Scheme 4.8). Clearly, diamine exchange was occurring, reducing the steric hindrance around the organolithium centre and facilitating faster trapping with methyl iodide. This also indicated that the lithiated piperazine coordinated to TMEDA is configurationally stable at –78 °C for the duration of the reaction.



Scheme 4.15

With the success of the diamine displacement strategy using *s*-BuLi/(–)-sparteine, the analogous reaction with *s*-BuLi/(+)-sparteine surrogate (+)-**26** was investigated. Previous results showed that lithiation of *N*-Boc-*N′*-benzyl piperazine **117** under these conditions and trapping with dimethyl sulfate resulted in formation of only ring-fragmented by-product **315** in 50% yield (see Table 4.2, entry 6). The use of the diamine displacement protocol gave no improvement. By-product **315** was the sole product and was isolated in 50% yield (Scheme 4.16). Clearly, TMEDA was unable to displace (+)-**26** from the lithiated intermediate.



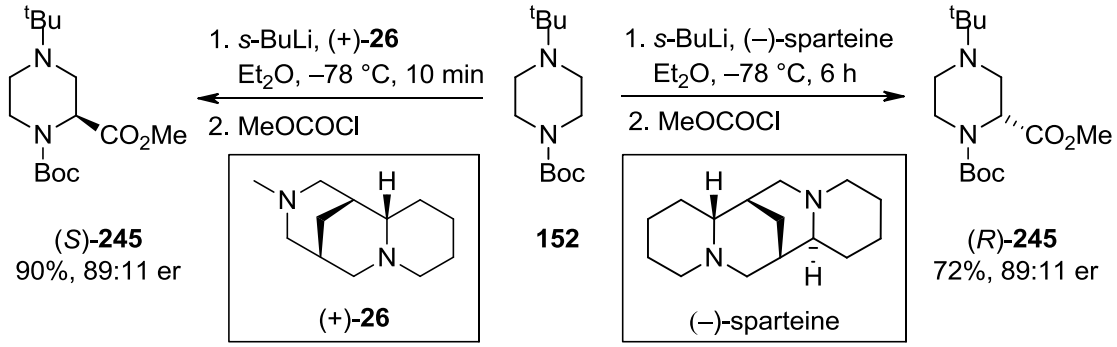
Scheme 4.16

Although this lack of improvement when using (+)-**26** was disappointing, the result was not a surprise. It is known through NMR spectroscopy studies that the (+)-sparteine surrogate (+)-**26** binds more tightly to organolithiums than (–)-sparteine.[57]

4.2.3 Investigation of the Asymmetric Lithiation/Trapping *N*-Boc Piperazines with Sterically Hindered Protecting Groups

By far the most serious problem encountered in the asymmetric lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** was ring fragmentation, which occurred with the vast majority of electrophiles investigated. It was envisaged that replacing the benzyl protecting group with a more sterically hindered group would prevent the lone pair from attacking susceptible electrophiles and thus prevent the unwanted ring fragmentation by-products, as was noticed first in the racemic lithiation/trapping reactions.

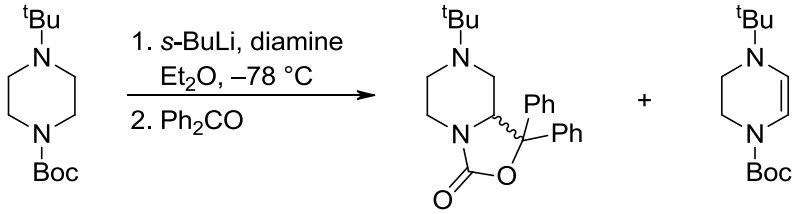
Asymmetric lithiation/trapping of *N*-Boc-*N′*-*t*-butyl piperazine **152** was investigated as this was the substrate used in McDermott's study.[108] Lithiation of **152** using *s*-BuLi/(–)-sparteine in Et_2O at –78 °C for 6 h (optimised lithiation time determined by ReactIR™ spectroscopy, see Scheme 2.20b), followed by trapping with methyl chloroformate gave ester (*R*)-**245** in 72% and 89:11 er (Scheme 4.17). Importantly, no ring fragmented by-products were observed in the ^{1}H NMR spectrum of the crude product. The opposite enantiomer (*S*)-**245** was synthesised in 90% yield and 89:11 er by deprotonation of **12** with *s*-BuLi/(+)-sparteine surrogate (+)-**26** for only 10 min at –78 °C, followed by trapping with methyl chloroformate.



Scheme 4.17

Next, an investigation into the use of benzophenone as an electrophile was conducted to assess the degree of SET side-reactions compared with the desired anionic electrophile trapping. Lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** with *s*-BuLi and a chiral diamine was performed followed by trapping with benzophenone. When (*S*,*S*)-**27** was used, oxazolidinone (*R*)-**246** was isolated in 36% yield and 85:15 er (Table 4.4, entry 1). Although the yield was relatively low, alkene **320** was not observed in the ^{1}H NMR

spectrum of the crude product. The use of (–)-sparteine resulted in the isolation of (*R*)-**246** in 74% yield and a respectable 90:10 er with alkene by-product not being observed (entry 2). When using the (+)-sparteine surrogate (+)-**26**, a small amount of alkene by-product **320** was observed (entry 3). Nevertheless, the desired oxazolidinone (*S*)-**246** was isolated in 76% yield and 86:14 er. Compared with the reaction using *N*-Boc-*N′*-benzyl piperazine **117** as a substrate (see Table 4.3), the SET side-reactions appear to be much less of a problem with *N*-Boc-*N′*-*t*-butyl piperazine **152** with higher enantiomeric ratios and lower amounts of alkene by-products being observed. It is unknown why this might be the case. As with *N*-Boc-*N′*-benzyl piperazine **117**, the use of (+)-sparteine surrogate (+)-**26** resulted in a greater degree of SET side-reactions.



152 **246** **320**

Entry	Diamine	Time	Yield 246 (%)[a]	er 246 (*R*:*S*)[b]	246:320[c]
1	(*S*,*S*)-**27**	1 h	36	15:85	100:0
2	(–)-sparteine	6 h	74	90:10	100:0
3	(+)-**26**	1 h	76	14:86	85:15

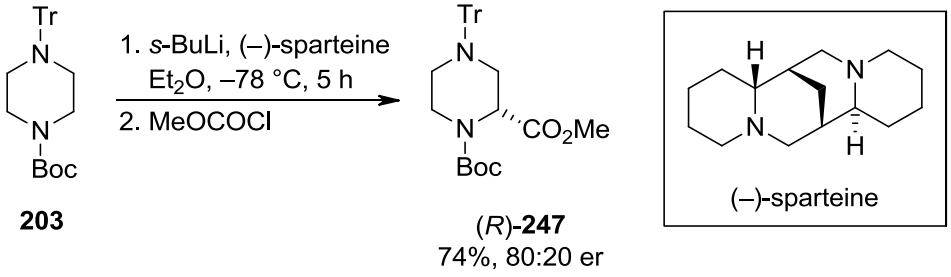
[a] Yield after flash column chromatography. [b] Er determined by CSP-HPLC. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude product.

Table 4.4 Effect of the diamine on lithiation/trapping of *N*-Boc-*N′*-*t*-butyl piperazine **152** with benzophenone

The use of the bulky *t*-butyl protecting group prevented ring fragmentation side-reactions and decreased the degree of SET side-reactions. However, the use of *N*-Boc-*N′*-*t*-butyl piperazine **152** had some drawbacks. The major limitation was that the *t*-butyl group cannot easily be removed once it has fulfilled its role as a protecting group.[147] This limits the synthetic utility of the methodology. A minor, but nonetheless frustrating limitation was that the substrate does not contain a UV chromophore. This makes CSP-HPLC method development more complex in cases where the electrophile itself does not introduce a chromophore into the product. To by-pass these problems, substrates

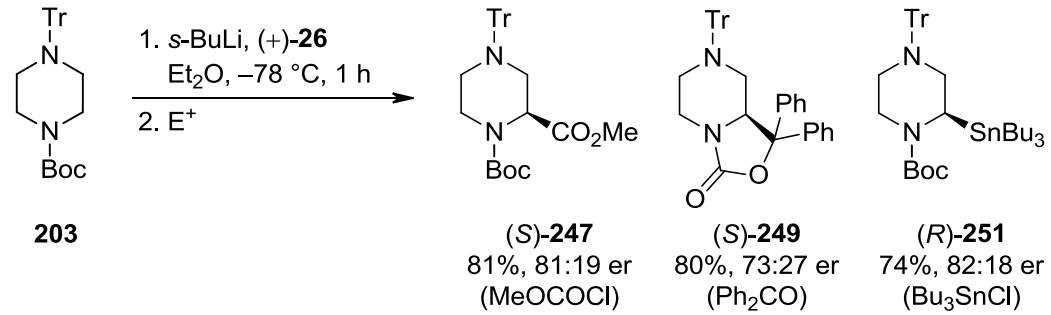
with large, sterically hindered and UV chromophore containing, but easily removable, protecting groups were investigated.

Previous work within the O'Brien group briefly explored the use of *N*-Boc-*N′*-trityl piperazine **203** as a substrate for asymmetric lithiation/trapping reactions.[184] Asymmetric lithiation using *s*-BuLi/(–)-sparteine for 5 h at –78 °C in Et_2O followed by trapping with methyl chloroformate gave (*R*)-**247** in 74% yield and 80:20 er (Scheme 4.18).



Scheme 4.18

To explore the scope of the lithiation/trapping of *N*-Boc-*N′*-trityl piperazine **203** lithiation was accomplished using *s*-BuLi/(+)-sparteine surrogate (+)-**26** before trapping with a small range of electrophiles. The desired enantioenriched *α*-substituted *N*-Boc piperazines (*S*)-**247**, (*S*)-**249** and (*R*)-**251** were obtained in good yield (74-81%) (Scheme 4.19). Importantly, ring fragmentation by-products were not observed in the ^{1}H NMR spectra of the crude reaction mixtures. Methyl ester (*S*)-**247** was isolated in a good 81% yield and 81:19 er when trapping with methyl chloroformate. This result is comparable with that obtained using (–)-sparteine (74% yield and 80:20 er). Unlike with racemic *s*-BuLi/TMEDA mediated lithiation/trapping (see Scheme 2.22) none of the disubstituted *N*-Boc piperazine **248** was formed during the reaction. Oxazolidinone (*S*)-**249** was isolated in 80% yield in a lower 73:27 er and stannane (*R*)-**251** was obtained in 74% yield and 82:18 er. The lower er seen benzophenone is probably due to a small amount of racemic SET trapping.



203

(*S*)-**247**
81%, 81:19 er
($MeOCOCl$)

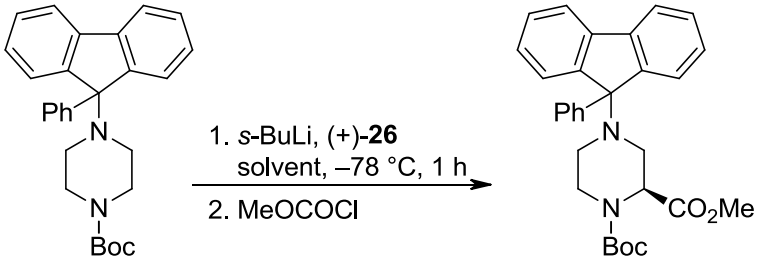
(*S*)-**249**
80%, 73:27 er
(Ph_2CO)

(*R*)-**251**
74%, 82:18 er
(Bu_3SnCl)

Scheme 4.19 Asymmetric lithiation/trapping of **203** with *s*-BuLi/(+)-**26**

Although the yields obtained were promising, the enantiomeric ratios were disappointing when compared to those with either *N*-Boc-*N′*-benzyl piperazine **117** (see Scheme 4.8) or *N*-Boc-*N′*-*t*-butyl piperazine **152** (see Scheme 4.17). For this reason, further investigation into the use of *N*-Boc-*N′*-trityl piperazine **203** was abandoned.

In an attempt to improve the enantioselectivity, the lithiation/trapping of phenyl fluorenyl protected piperazine **240** was studied using *s*-BuLi and the (+)-sparteine surrogate (+)-**26** at –78 °C (Table 4.5). When using Et_2O as solvent, ester (*S*)-**255** was isolated in an acceptable 68% yield and 86:14 er (Table 4.5, entry 1). It was envisaged that changing the solvent to either MTBE or toluene would improve the yield due to better solubility of the starting material **240**, as seen with the racemic variant (see Table 3.1). However, this was not the case: when using MTBE, (*S*)-**255** was isolated in a reduced 59% yield and 85:15 er (entry 2); with toluene, the yield of (*S*)-**255** was a disappointing 40% (81:19 er) (entry 3).



240 (*S*)-**255**

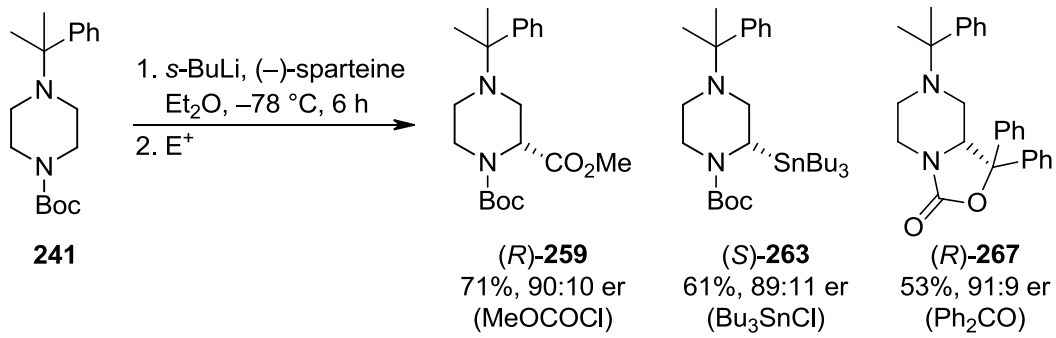
Entry	Solvent	Yield (*S*)-255 (%)[a]	er (*S*)-255[b]
1	Et_2O	68	86:14
2	MTBE	59	85:15
3	Toluene	40	81:19

[a] Yield after flash column chromatography. [b] Er determined by CSP-HPLC.

Table 4.5 Effect of solvent on the asymmetric lithiation of **240** with *s*-BuLi/(+)-**26**

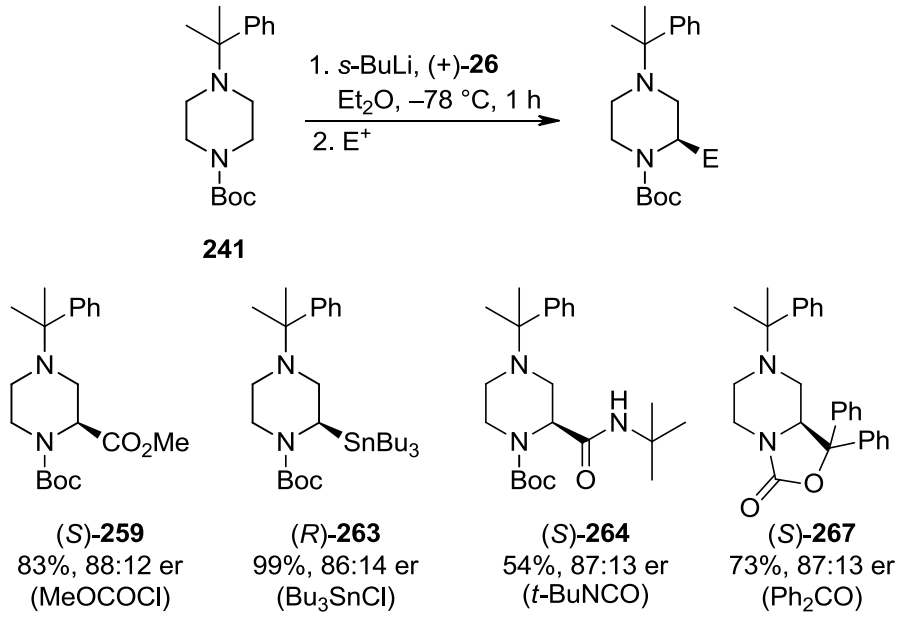
Although the yield and er of (*S*)-**255** attained when using Et_2O as a solvent were acceptable, the low solubility of the substrate was a problem and no further investigation into the lithiation of *N*-Boc-*N′*-PhFl piperazine **240** was undertaken.

The racemic lithiation/trapping of *N*-Boc-*N′*-cumyl piperazine **241** gave high yields of *α*-substituted *N*-Boc piperazines with a range of electrophiles (see Chapter 3.2). Therefore, the asymmetric lithiation/trapping methodology was investigated. The length of time required for complete lithiation of *N*-Boc-*N′*-cumyl piperazine **241** using *s*-BuLi and chiral diamines had not been established by ReactIR™ spectroscopy. Therefore, by analogy with *N*-Boc-*N′*-*t*-butyl piperazine **152**, deprotonation with *s*-BuLi/(–)-sparteine was performed for 6 h before addition of the electrophiles. Trapping with methyl chloroformate gave (*R*)-**259** in 71% yield and 90:10 er (Scheme 4.20). The yield and er is comparable to that obtained with *N*-Boc-*N′*-benzyl piperazine **117** (see Scheme 4.8) and *N*-Boc-*N′*-*t*-butyl piperazine **152** (see Scheme 4.17). Crucially, no ring fragmented by-products were observed with **241**. The use of Bu_3SnCl resulted in (*S*)-**263** being isolated in 61% yield and 89:11 er. In order to determine the enantiomeric ratio of stannane (*S*)-**263**, Sn/Li exchange using *n*-BuLi at –78 °C in THF followed by trapping with methyl chloroformate to give ester (*R*)-**259** was performed. When using benzophenone, (*R*)-**267** was obtained in 53% yield. The corresponding alkene by-product was observed by ^{1}H NMR spectroscopy of the crude mixture, but unfortunately could not be isolated cleanly. However, a surprisingly high 91:9 er was achieved.



Scheme 4.20 Asymmetric lithiation/trapping of **241** with *s*-BuLi/(–)-sparteine

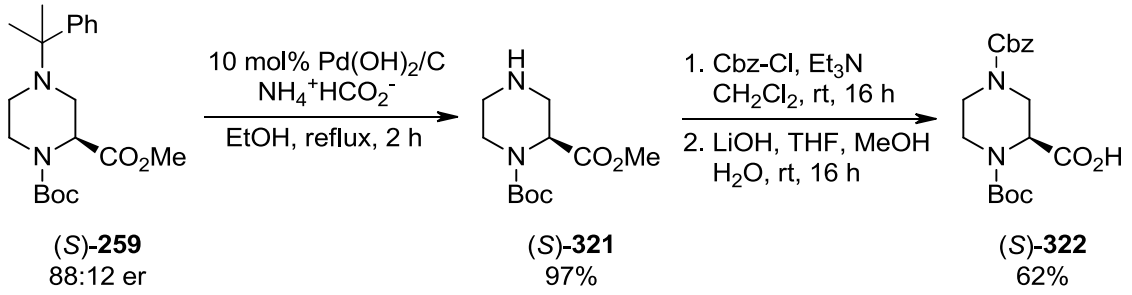
Synthesis of the opposite enantiomeric series of compounds through the asymmetric lithiation of *N*-Boc-*N′*-cumyl piperazine **241** was undertaken (using *s*-BuLi and the (+)-sparteine surrogate (+)-**26** at –78 °C for 1 h). Trapping with a range of electrophiles gave (*S*)-**259**, (*R*)-**263**, (*S*)-**264** and (*S*)-**267** in 54-99% yield and 86:14-88:12 er (Scheme 4.21). Oxazolidinone (*S*)-**267** was isolated in 73% yield; a small amount of the SET alkene by-product was formed. As seen with *N*-Boc-*N′*-*t*-butyl piperazine **152** it appears that increasing the steric bulk of the protecting group decreases the problematic SET side-reactions. The yield of amide (*S*)-**264** was only 54%, due to the formation of cyclised products that could not be isolated cleanly.



Scheme 4.21 Asymmetric lithiation/trapping of **241** with *s*-BuLi/(+)-**26**

The absolute stereochemistry of methyl ester (*S*)-**259** was determined by conversion to known carboxylic derivate (*S*)-**322**. Direct displacement of the cumyl group with benzyl

chloroformate was unsuccessful and so a two-step procedure to convert cumyl piperazine (*S*)-**259** into Cbz protected piperazine (*S*)-**322** was undertaken (Scheme 4.22). Removal of the cumyl group was achieved using transfer hydrogenolysis with $Pd(OH)_2/C$ and ammonium formate at reflux for 2 h, giving secondary amine (*S*)-**321** in 97% yield. Then, acylation with benzyl chloroformate was accomplished and following saponification of the methyl ester, carboxylic acid (*S*)-**322** was isolated in 62% yield over two steps. The absolute stereochemistry was confirmed by comparison of the optical rotation of (*S*)-**322** ($[\alpha]_D$ −14.9 (*c* 0.7 in $CHCl_3$)) with a known sample synthesised from serine ($[\alpha]_D$ −17.5 (*c* 1.0 in $CHCl_3$ for a sample of >99:1 er)).[190]



Scheme 4.22

The use of *N*-Boc-*N′*-cumyl piperazine **241** prevented the ring fragmentation side-reaction. Crucially, lithiation/trapping methodology applied to **241** allowed the synthesis of both enantiomeric series of *α*-substituted piperazines in high yield and good enantiomeric ratios, unlike when using other protected *N*-Boc piperazines. Additionally, the cumyl group could be easily removed by hydrogenolysis (see Scheme 3.27) or transfer hydrogenolysis, allowing further derivatisation of the substituted piperazines to interesting target molecules.

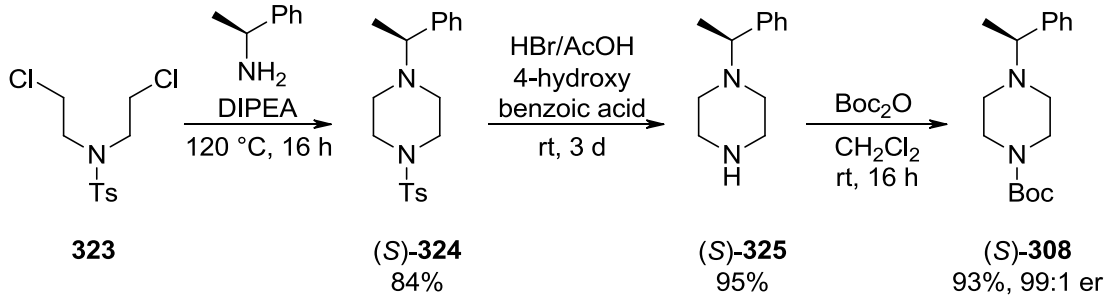
4.3 Chiral Auxiliary Approach to Enantiopure *N*-Boc Piperazines

4.3.1 Synthesis of Enantiopure Monosubstituted *N*-Boc Piperazines

The use of *N*-Boc-*N′*-cumyl piperazine **241** as a substrate allowed access to both enantiomeric series of *α*-substituted *N*-Boc piperazines in 86:14-91:9 er. These levels of enantioselectivity are in line with results published by McDermott[108] and with earlier research carried out within the O'Brien group.[184] However, with *N*-Boc pyrrolidine **12**, enantioselectivity was as high as 98:2 er.[42] Unfortunately, with *N*-Boc piperazines stereoselectivities at this level are difficult to achieve though enantioselective deprotonation using the currently available chiral diamines.

The chiral auxiliary approach pioneered by Guerrini and co-workers allowed access to single enantiomers of *α*-substituted piperazines (see Scheme 4.3).[183] It was envisaged that this methodology could be developed further by using chiral diamines to affect an asymmetric deprotonation. If the auxiliary and diamine both favour the removal of the same proton, high yields of enantiomerically pure *α*-substituted *N*-Boc piperazines could be achieved.

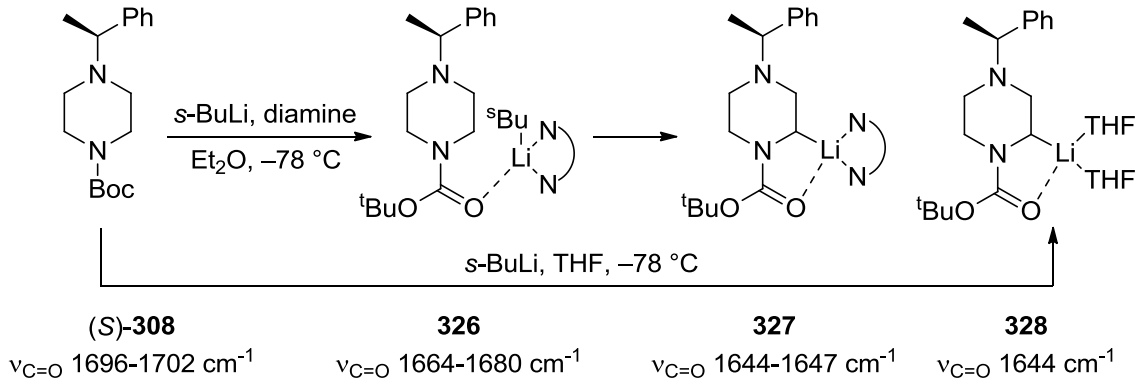
The first challenge was to develop a practical multi-gram scale synthesis of *N*-Boc-*N′*-(*S*)-*α*-methyl benzyl piperazine (*S*)-**308**. A method for the synthesis of piperazines from primary amines developed by D'Ambra and co-workers was used.[191,192] Reaction between commercially available *N*-tosyl amine **323** and enantiomerically pure (*S*)-(−)-*α*-methylbenzylamine in DIPEA gave tosyl piperazine (*S*)-**324** in 84% yield (Scheme 4.23). Removal of the tosyl group with HBr in the presence of 4-hydroxy benzoic acid gave secondary amine (*S*)-**325** in 95% yield without the need for purification. Boc protection under standard conditions gave the desired substrate (*S*)-**308** in 93% yield as a single enantiomer. Overall, synthesis of 13.4 g of (*S*)-**308** was achieved in 74% total yield over three steps, a significant improvement on the literature method (20% over 5 steps).[183] Importantly, only one purification operation was required; (*S*)-**308** was purified by flash column chromatography.

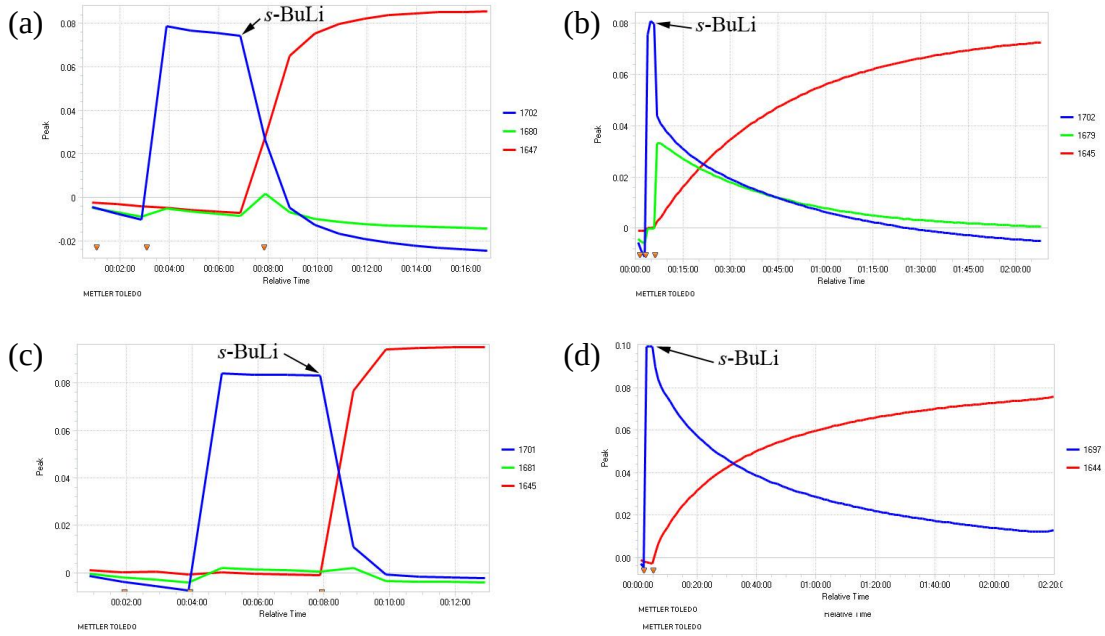


323 (*S*)-**324** 84% (*S*)-**325** 95% (*S*)-**308** 93%, 99:1 er

Scheme 4.23

In order to facilitate the development of asymmetric lithiation/trapping methodology, the length of time required for the complete lithiation of (*S*)-**308** with *s*-BuLi and a range of ligands was ascertained by *in situ* ReactIR™ spectroscopic studies (Scheme 4.24). As expected, complete lithiation of (*S*)-**308** with *s*-BuLi and TMEDA was rapid, proceeding *via* pre-lithiation complex **326** to give lithiated intermediate **327** within 7 min (Scheme 4.24a). Lithiation in the presence of the (+)-sparteine surrogate (+)-**26** was also fast, reaching completion within 2 min (Scheme 4.24c). Lithiation in the presence of (–)-sparteine was nearing completion after 2 h (Scheme 4.24b), as was diamine-free lithiation in THF to **328** (Scheme 4.24d). The lithiation of *N*-Boc-*N′*-(*S*)-*α*-methyl benzyl piperazine (*S*)-**308** took longer to reach completion than lithiations of *N*-Boc-*N′*-benzyl piperazine **117**, but was faster than the lithiation of *N*-Boc-*N′*-*t*-butyl piperazine **152** (see Table 2.1). This supports the idea that increasing the steric bulk of the protecting group increases the time required for complete lithiation of the substrate to occur.

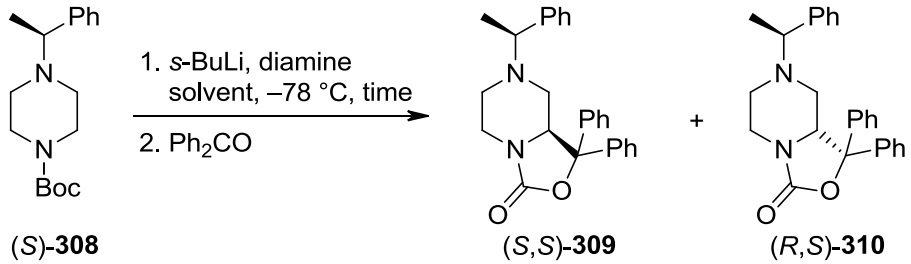




Scheme 4.24 Lithiation of *N*-Boc-*N*′-(*S*)-*α*-methylbenzyl piperazine (*S*)-**308** with *s*-BuLi and ligands, (a) TMEDA, (b) (–)-sparteine, (c) (+)-**26**, (d) THF

These ReactIR™ spectroscopic studies showed that the lithiation conditions employed by Guerrini, specifically the warming of the reaction mixture (*s*-BuLi, TMEDA, THF, –78 °C then –35 °C for 2 h), were overly complicated and unnecessary. Therefore, the investigation began by optimising the racemic lithiation and trapping with benzophenone (Table 4.6). Diamine-free lithiation of *N*-Boc-*N*′-(*S*)-*α*-methyl benzyl piperazine (*S*)-**308** with *s*-BuLi in THF at –78 °C for 3 h resulted in a slight preference for the removal of the pro-(*S*) proton, a 60:40 dr in favour of (*S*,*S*)-**309** was observed. Products (*S*,*S*)-**309** and (*R*,*S*)-**310** were isolated in 52% and 32% yield respectively (Table 4.6, entry 1). The same degree of diastereoselectivity was observed by Guerrini when performing the lithiation using *s*-BuLi/TMEDA in THF. Interestingly, when using TMEDA in Et_2O, (*S*,*S*)-**309** and (*R*,*S*)-**310** were formed with improved

diastereoselectivity (70:30 dr) (entry 2). The yields of the isolated oxazolidinones were good, with (*S*,*S*)-**309** being obtained in 58% yield and (*R*,*S*)-**310** in 15% yield. Changing the solvent to MTBE gave similar results to those with Et_2O, products (*S*,*S*)-**309** and (*R*,*S*)-**310** formed in 70:30 dr and with yields of 56% and 20% yield respectively (entry 3).



(*S*)-**308** (*S*,*S*)-**309** (*R*,*S*)-**310**

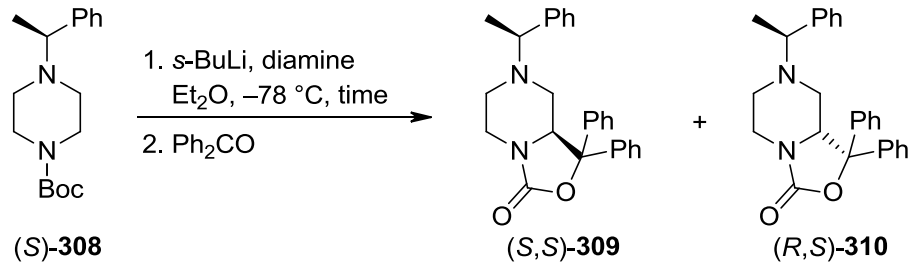
Entry	Diamine	Solvent	Time (h)	dr (309:310)[a]	Yield 309 (%)[b]	Yield 310 (%)[b]
1	-	THF	3	60:40	52	32
2	TMEDA	Et_2O	1	70:30	58	15
3	TMEDA	MTBE	1	70:30	56	20

[a] Dr determined by analysis of ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after flash column chromatography.

Table 4.6 Effect of solvent and diamine on the lithiation of *N*-Boc-*N′*-(*S*)-*α*-methylbenzyl piperazine (*S*)-**308**

Lithiation of (*S*)-**308** using *s*-BuLi and TMEDA in ethereal solvents provided a good combined yield of oxazolidinones (*S*,*S*)-**309** and (*R*,*S*)-**310** (73-84%). Knowing that the chiral auxiliary could induce modest levels of diastereoselectivity, the compounded effect of chiral diamines on the reaction was investigated. Since the chiral auxiliary induces a preference for the removal of the pro-(*S*) proton, a chiral diamine that also favoured the removal of the pro-(*S*) proton should give a 'matched' case. It was anticipated that upon trapping, oxazolidinones (*S*,*S*)-**309** and (*R*,*S*)-**310** would be formed with a high diastereomeric ratio, and hence (*S*,*S*)-**309** could be isolated as a single stereoisomer in high yield. The effects of chiral diamines on the lithiation/trapping of *α*-methylbenzyl-substituted *N*-Boc piperazine (*S*)-**308** with benzophenone are detailed in Table 4.7. It has been observed that the *s*-BuLi/(+)-sparteine surrogate (+)-**26** complex preferentially removed the pro-(*S*) proton of *N*-Boc heterocycles. Therefore, lithiation of (*S*)-**308** under these conditions resulted in the formation of (*S*,*S*)-**309** and (*R*,*S*)-**310** in a

90:10 dr (Table 4.7, entry 1). Gratifyingly, this increase in diastereoselectivity shows that the diamine and auxiliary are matched, in that they both favour removal of the pro-(*S*) proton. However, an even higher diastereomeric ratio was expected. Disappointingly, the yields of (*S*,*S*)-**309** and (*R*,*S*)-**310** were low (31% and 4% respectively). When (–)-sparteine was used, a mismatch between the diamine and auxiliary was observed with (*R*,*S*)-**310** and (*S*,*S*)-**309** formed in 60:40 dr (entry 2). Similarly, the isolated yields of (*R*,*S*)-**310** (29%) and (*S*,*S*)-**309** (16%) were disappointing. The use of the Alexakis diamine (*S*,*S*)-**27** led to the formation of the products (*S*,*S*)-**309** and (*R*,*S*)-**310** in 90:10 dr and 32% and 2% isolated yields (entry 3). The mismatched enantiomer (*R*,*R*)-**27** gave the products (*R*,*S*)-**310** and (*S*,*S*)-**309** in 70:30 dr and 15% and 6% isolated yields (entry 4).



(*S*)-**308** (*S*,*S*)-**309** (*R*,*S*)-**310**

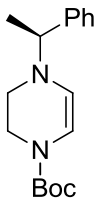
Entry	Diamine	Time (h)	dr (309:310)[a]	Yield 309 (%)[b]	Yield 310 (%)[b]
1	(+)-**26**	1	90:10	31	4
2	(–)-sparteine	3	40:60	16	29
3	(*S*,*S*)-**27**	1	90:10	32	2
4	(*R*,*R*)-**27**	1	30:70	6	15

[a] Dr determined by analysis of ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after flash column chromatography.

Table 4.7 Effect of chiral diamines on the lithiation of *N*-Boc-*N′*-(*S*)-*α*-methylbenzyl piperazine (*S*)-**308**

Although the matched/mis-matched effect was clearly demonstrated, both the yields and diastereomeric ratios were disappointing. This was probably due to competing SET processes, as is often observed with benzophenone. The yields are poor due to the formation of alkene (*S*)-**329** (Figure 4.1), present in significant quantities in all cases (by analysis of ^{1}H NMR spectra of the crude reaction mixtures). A small portion of (*S*)-**329** was isolated cleanly in the reaction with (–)-sparteine and the structure confirmed (entry

2). Additionally, it is possible that the observed diastereomeric ratio of the products is lower than the diastereomeric ratio of lithiated intermediates. Planar radical formation on the piperazine and subsequent single electron transfer mediated electrophile trapping could cause erosion of dr post-lithiation.

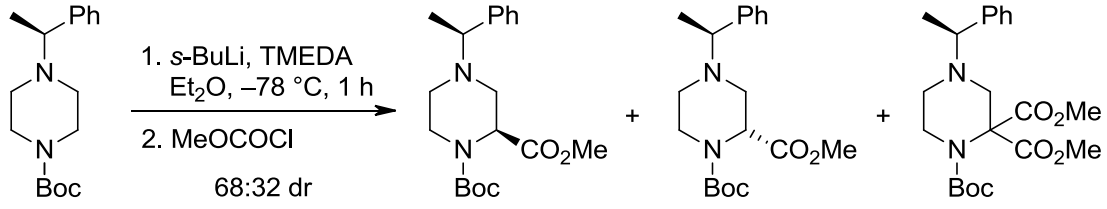


(*S*)-**329**

Figure 4.1

With the benefit of hindsight, the decision to use benzophenone as an electrophile for the development of this chiral auxiliary/chiral diamine methodology was misguided. Although there was precedent for using benzophenone from Guerrini's work, and the absolute and relative stereochemistry of the products were known, the single electron transfer problems complicated the initial development of this methodology.

To by-pass these problems, trapping with methyl chloroformate was investigated. Lithiation with *s*-BuLi/TMEDA in Et_2O followed by trapping formed esters (*S*,*S*)-**330** and (*R*,*S*)-**331** in 68:32 dr (Scheme 4.25). Isolated yields of 19% and 8% respectively were low due to the formation of diester (*S*)-**332** (24%). The relative stereochemistry of (*S*,*S*)-**330** was confirmed using the same method as detailed for the cumyl protected analogue (see Scheme 4.22).

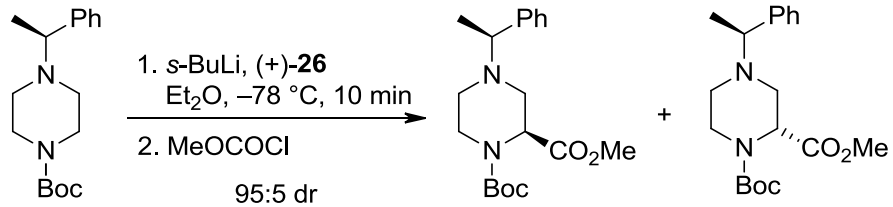


(*S*)-**308** (*S*,*S*)-**330** 19% (*R*,*S*)-**331** 8% (*S*)-**332** 24%

Scheme 4.25

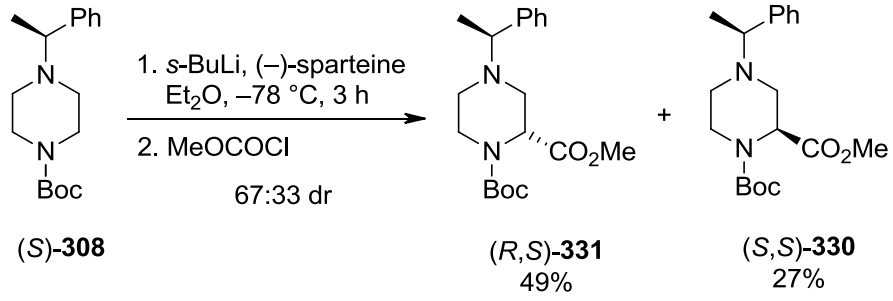
As reported earlier (Scheme 3.22 and Table 3.1, entry 1), the formation of diester by-products occurs frequently when using *s*-BuLi/TMEDA. Due to the fact that these by-

products are generally not observed when using chiral diamines, the investigation of the matched chiral auxiliary/chiral diamine system was investigated. Pleasingly, lithiation of *N*-Boc-*N′*-(*S*)-*α*-methyl benzyl piperazine (*S*)-**308** with *s*-BuLi/(+)-sparteine surrogate (+)-**26** for 10 min at –78 °C followed by trapping with methyl chloroformate formed (*S*,*S*)-**330** and (*R*,*S*)-**331** in 95:5 dr. The major diastereomer, (*S*,*S*)-**330**, was isolated in 90% yield and the minor diastereomer (*R*,*S*)-**331** in 4% yield (Scheme 4.26). Additionally, no ring fragmentation by-products or diester (*S*)-**332** were observed. Analysis of (*S*,*S*)-**330** by CSP-HPLC, in comparison with a racemic sample, showed that no racemisation had occurred and that (*S*,*S*)-**330** had been formed in 99:1 er.



Scheme 4.26

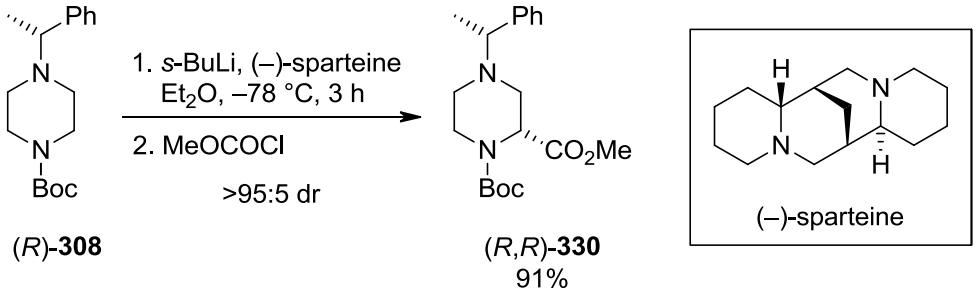
Lithiation of (*S*)-**308** using *s*-BuLi/(–)-sparteine results in a mismatch between the chiral auxiliary and the chiral diamine. When trapping with methyl chloroformate (*R*,*S*)-**331** and (*S*,*S*)-**330** were formed in a 63:37 dr with yields of 49% and 27% respectively (Scheme 4.27).



Scheme 4.27

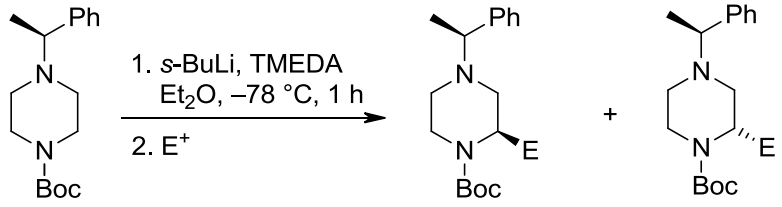
In order to access the opposite enantiomeric series of *α*-substituted piperazines in high yield, the opposite enantiomer of the substrate was required. *N*-Boc-*N′*-(*R*)-*α*-methyl benzyl piperazine (*R*)-**308** was synthesised in an analogous fashion to the (*S*) enantiomer. Subsequent lithiation of *N*-Boc-*N′*-(*R*)-*α*-methyl benzyl piperazine (*R*)-**308**

with *s*-BuLi/(–)-sparteine for 3 h at –78 °C followed by trapping with methyl chloroformate formed (*R*,*R*)-**330** and (*S*,*R*)-**331** in >95:5 dr; ester (*R*,*R*)-**330** was isolated 91% yield (Scheme 4.28).

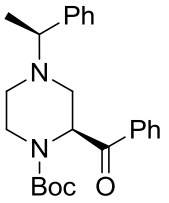
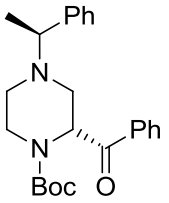
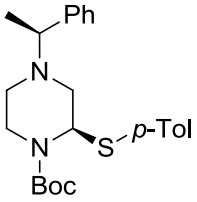
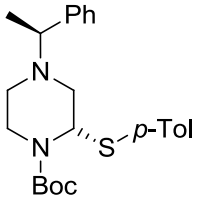
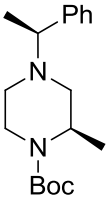
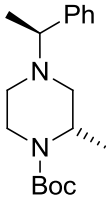
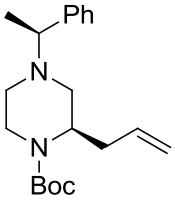
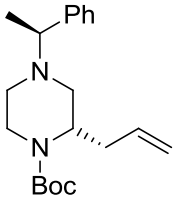


Scheme 4.28

To demonstrate the scope of this matched chiral auxiliary/chiral diamine methodology, a small selection of electrophiles were investigated. Initially, racemic lithiation of (*S*)-**308** was performed using *s*-BuLi/TMEDA in Et_2O at –78 °C followed by trapping with electrophiles and the results are presented in Table 4.8. In all but one case, diastereoselectivities (68:32-71:29 dr) were similar to that obtained with methyl chloroformate (68:32 dr, see Scheme 4.25). However, the dr obtained with methyl iodide (63:27 dr) was marginally lower, possibly due to slow trapping of the lithiated intermediate at low temperatures (Table 4.8, entry 3). Overall total yields were good, ranging from 79-98%.



(*S*)-**308**

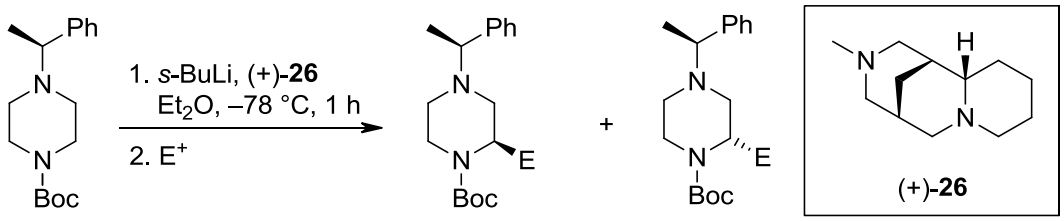
Entry	E^+	Products	dr[a]	Yields (%)[b]
1	PhCONMe(OMe)	 (*S*,*S*)-**333**  (*R*,*S*)-**334**	71:29	62, 17
2	$(p\text{-TolS})_2$	 (*R*,*S*)-**335**  (*S*,*S*)-**336**	69:31	67, 27
3	MeI	 (*R*,*S*)-**337**  (*S*,*S*)-**338**	63:37	62, 35
4	AllylBr[c]	 (*R*,*S*)-**339**  (*S*,*S*)-**340**	68:32	56, 23

[a] Dr determined by analysis of ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after flash column chromatography. [c] *via* Li/Cu transmetallation using CuCN.2LiCl.

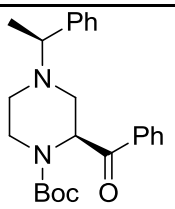
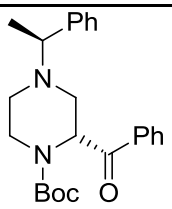
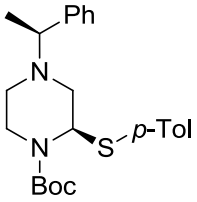
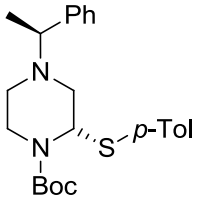
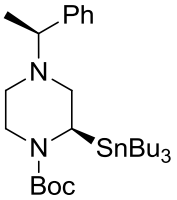
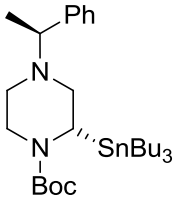
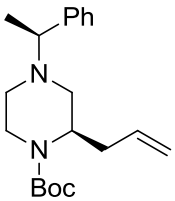
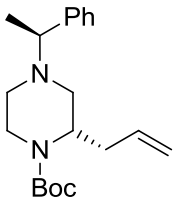
Table 4.8 Racemic lithiation/trapping of (*S*)-**308** with *s*-BuLi/TMEDA and a range of electrophiles

Next, lithiation of (*S*)-**308** was performed using *s*-BuLi/(+)-sparteine surrogate (+)-**26** followed by trapping with a similar set of electrophiles, the results are presented in

Table 4.9. In all cases the reactions proceeded with good diastereoselectivity (>92:8 dr). Importantly, no ring-fragmentation by-products were observed.



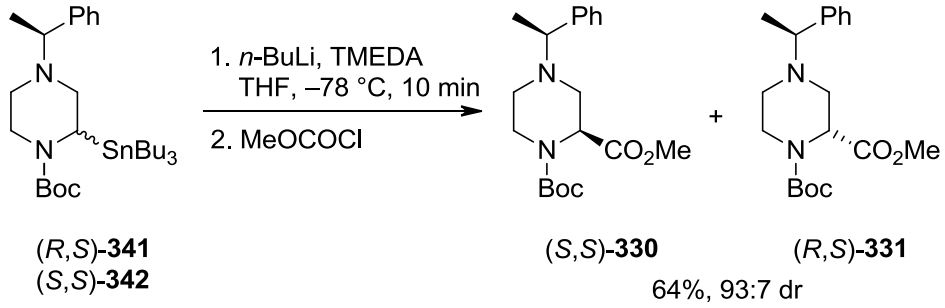
(*S*)-**308**

Entry	E^+	Products	dr[a]	Yields (%)[b]
1	PhCONMe(OMe)	 (*S*,*S*)-**333**  (*R*,*S*)-**334**	93:7	86, 6
2	$(p\text{-TolS})_2$	 (*R*,*S*)-**335**  (*S*,*S*)-**336**	95:5	86, 4
3	Bu_3SnCl	 (*R*,*S*)-**341**  (*S*,*S*)-**342**	93:7[d]	94[e]
4	AllylBr[c]	 (*R*,*S*)-**339**  (*S*,*S*)-**340**	95:5	79, 5

[a] Dr determined by analysis of ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after flash column chromatography. [c] *via* Li/Cu transmetallation using CuCN.2LiCl. [d] Determined by conversion into (*S*,*S*)-**330** and (*S*,*R*)-**331**. [e] Combined yield.

Table 4.9 Asymmetric lithiation/trapping of (*S*)-**308** with *s*-BuLi/(+)-**26** and a range of electrophiles

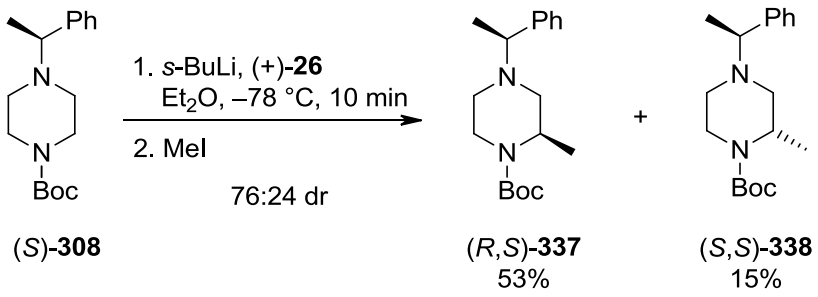
Diastereoselective lithiation followed by trapping with the Weinreb amide *N*-methoxy-*N*-methylbenzamide gave (*S*,*S*)-**333** and (*R*,*S*)-**334** in 93:7 dr. The major diastereomer (*S*,*S*)-**333** was isolated in 86% yield (Table 4.9, entry 1). Trapping with *p*-tolyl disulfide resulted in the diastereomers (*R*,*S*)-**335** and (*R*,*S*)-**336** being formed in 95:5 dr (entry 2). The major diastereomer, thioether (*R*,*S*)-**335** was isolated in 86% yield. When trapping with Bu_3SnCl, an inseparable mixture of diastereomers (*R*,*S*)-**341** and (*S*,*S*)-**342** was formed in 94% combined yield and 93:7 dr (entry 3). Due to the complexity of the ^1H NMR spectrum of the mixture of stannanes, the diastereomeric ratio of (*R*,*S*)-**341** and (*S*,*S*)-**342** had to be determined by conversion into a mixture of diastereomeric esters (*S*,*S*)-**330** and (*S*,*R*)-**331**. Sn/Li exchange was accomplished using *n*-BuLi and TMEDA in THF at –78 °C for 10 min before trapping with methyl chloroformate (Scheme 4.29). Esters (*S*,*S*)-**330** and (*S*,*R*)-**331** were obtained in a combined 64% yield and 93:7 dr, thus giving the diastereomeric ratio of stannanes (*R*,*S*)-**341** and (*S*,*S*)-**342**.



Scheme 4.29

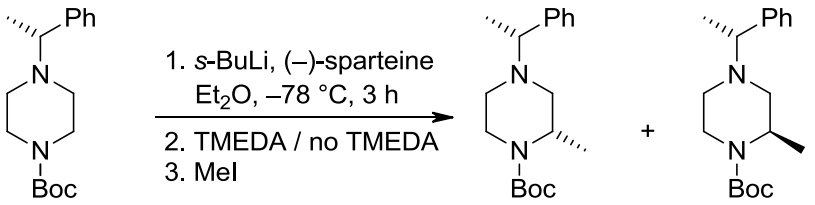
Allyl piperazines (*R*,*S*)-**339** and (*S*,*S*)-**340** were formed in 95:5 dr when using Dieter's Li/Cu transmetalation[93] method followed by trapping with allyl bromide (Table 4.9, entry 4). Major diastereomer (*R*,*S*)-**339** was isolated in 79% yield.

Lithiation/trapping of (*S*)-**308** with a range of electrophiles allowed the synthesis of a variety of enantiopure *α*-substituted *N*-Boc piperazines with excellent levels of diastereoselectivity and high isolated yields. However, when trapping with methyl iodide, (*R*,*S*)-**337** and (*S*,*S*)-**338** were formed in a relatively poor 76:24 dr, with yields of 53% and 15% respectively (Scheme 4.30).



Scheme 4.30

The low dr is attributed to slow trapping by methyl iodide at low temperatures and the initially high dr is thus compromised. The diamine displacement strategy (see Chapter 4.2.3) was employed to improve the diastereoselectivity of trapping with methyl iodide. As it is known that TMEDA cannot displace the (+)-sparteine surrogate (+)-**26** from the lithiated intermediates but it can displace (–)-sparteine, the strategy was applied to the antipode of the starting material (*R*)-**308**. Lithiation was initially accomplished using *s*-BuLi/(–)-sparteine at –78 °C. Without using an excess of TMEDA to effect a diamine displacement, (*S*,*R*)-**337** and (*R*,*R*)-**338** were formed in a 55:45 dr and 32% and 27% isolated yields (Table 4.10, entry 1). This showed that warming of the reaction to a temperature at which the organolithium was configurationally unstable was occurring, before a significant degree of trapping occurred. Interestingly, the dr is lower than the enantiomeric reaction using (+)-sparteine surrogate (+)-**26**. When the diamine displacement method was employed (entry 2), a marked improvement was observed. *α*-Methyl piperazines (*S*,*R*)-**337** and (*R*,*R*)-**338** were formed in a 90:10 dr and isolated in 70% and 3% yield respectively.



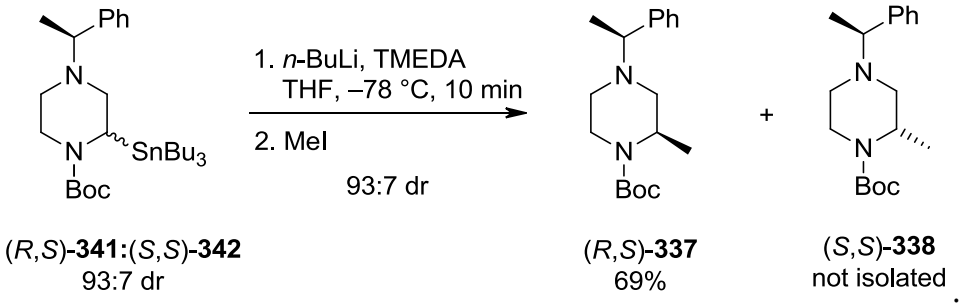
(*R*)-**308** (*S*,*R*)-**337** (*R*,*R*)-**338**

Entry	Diamines	dr 337:338[a]	Yield 337 (%)[b]	Yield 338 (%)[b]
1	(–)-sparteine	55:45	32	27
2	(–)-sparteine then TMEDA	90:10	70	3

[a] Dr determined by analysis of ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield after flash column chromatography.

Table 4.10 Effect of diamine displacement on the lithiation/trapping of *N*-Boc-*N′*-(*R*)-*α*-methylbenzyl piperazine (*R*)-**308**

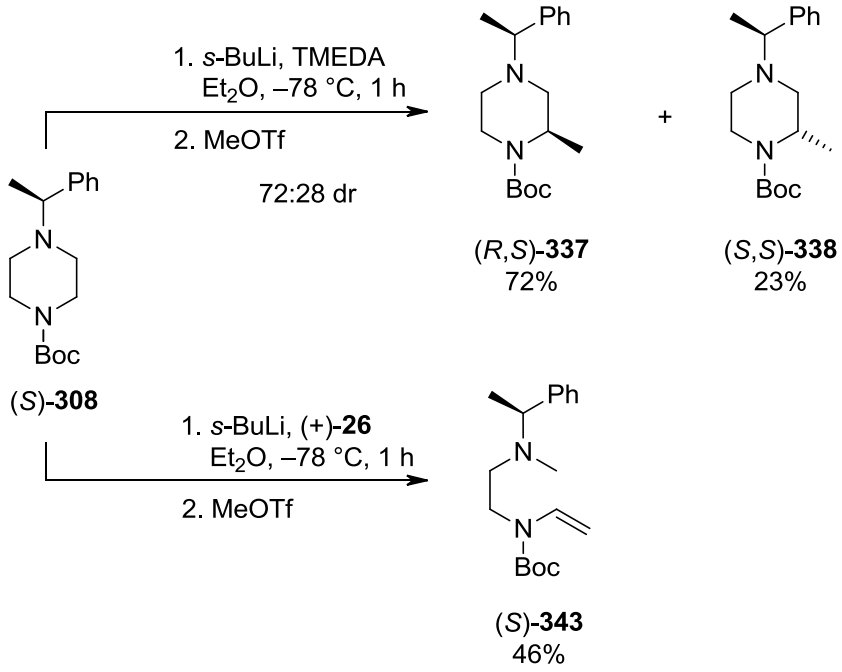
An alternative strategy was investigated to improve the yield of methylated piperazine (*R*,*S*)-**337**. A Sn/Li exchange procedure from the diastereomeric mixture of stannanes (*R*,*S*)-**341** and (*S*,*S*)-**342** was performed. As with the diamine displacement strategy, this procedure removes the requirement for a bulky chiral diamine in the trapping with methyl iodide, thus speeding up trapping at low temperatures and allowing (*R*,*S*)-**337** and (*S*,*S*)-**338** to be formed without loss of diastereoselectivity. Transmetalation was achieved using *n*-BuLi/TMEDA in THF at –78 °C for 10 min before addition of methyl iodide. 2-Methyl piperazines (*R*,*S*)-**337** and (*S*,*S*)-**338** were formed without loss of diastereoselectivity in 93:7 dr. Major isomer (*R*,*S*)-**337** was isolated in 69% yield (Scheme 4.31). The minor diastereomer was observed by analysis of the ^{1}H NMR of the crude mixture but was not isolated due to the small scale of the reaction.



(*R*,*S*)-**341**:(*S*,*S*)-**342** 93:7 dr (*R*,*S*)-**337** 69% (*S*,*S*)-**338** not isolated

Scheme 4.31

Although the diamine displacement and Sn/Li exchange strategies led to an improvement in the yield of major diastereomer (*R*,*S*)-**337**, a more direct method was desired. Therefore, the use of methyl triflate as an electrophile was investigated. It is know than methyl triflate is 10^4 times more reactive then methyl iodide in the alkylation of pyridines.[193] It was envisaged that trapping with methyl triflate would be much quicker than with methyl iodide at low temperatures, thus trapping would occur without epimerisation of the organolithium intermediate. When lithiation of (*S*)-**308** with *s*-BuLi/TMEDA in Et_2O was followed by trapping with methyl triflate, (*R*,*S*)-**337** and (*S*,*S*)-**338** were formed in 72:28 dr and isolated in 72% and 23% yield respectively (Scheme 4.32).

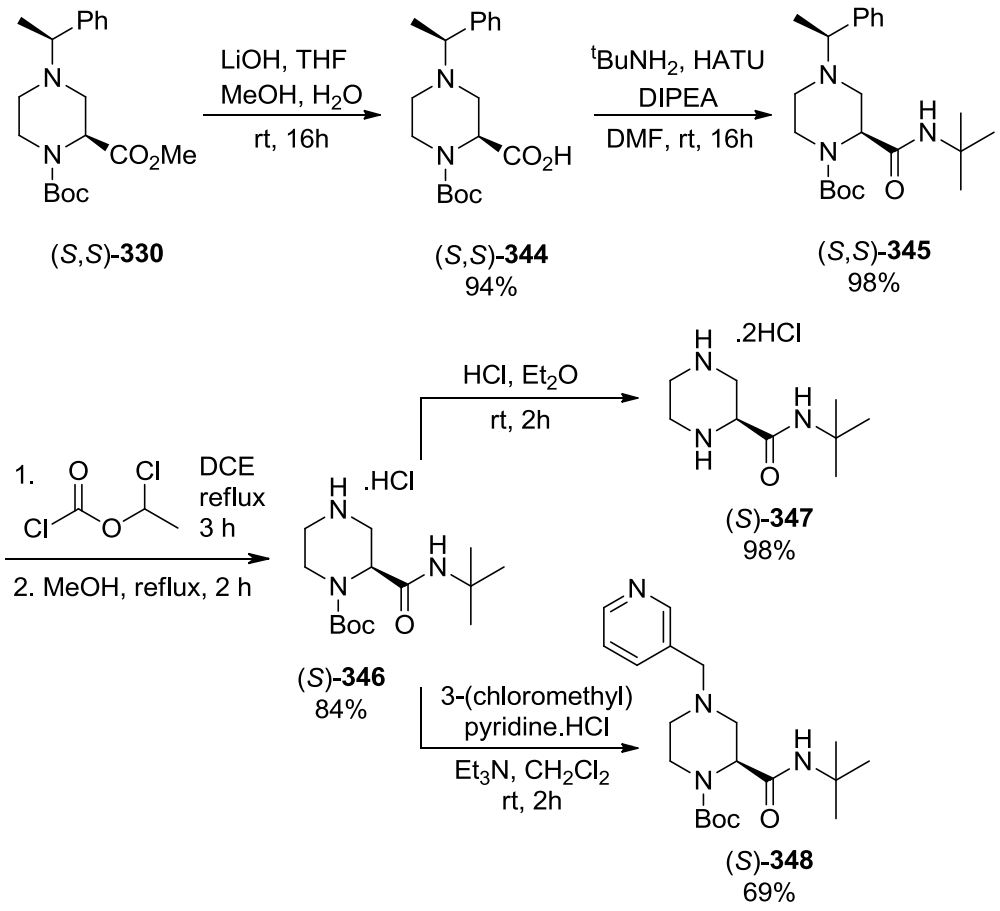


Scheme 4.32 Lithiation/trapping of (*S*)-**308** with methyl triflate

In contrast, when lithiation of (*S*)-**308** was carried out with *s*-BuLi/(+)-sparteine surrogate (+)-**26** followed by trapping with methyl triflate, the desired *α*-methyl piperazines were not formed. Ring-fragmented by-product (*S*)-**343** was isolated in 46% yield (Scheme 4.32). This is the only electrophile investigated that caused the ring fragmentation of *N*-Boc-*N′*-(*S*)-*α*-methyl benzyl piperazine (*S*)-**308**. The speed of trapping of the organolithium intermediate is slowed in the presence of a bulky diamine thus allowing the fragmentation pathway to predominate. Assuming that the lone pair of the nitrogen attacks methyl triflate in an S_N2 process, the small size of the electrophile coupled with its high reactivity could explain the observed fragmentation. Despite the

ring fragmentation encountered with methyl triflate when using *s*-BuLi/(+)-**26**, (*R*,*S*)-**337** can still be isolated in 72% yield as a single enantiomer when using *s*-BuLi/TMEDA to effect lithiation.

To demonstrate the applicability of the chiral auxiliary/chiral diamine methodology, a formal synthesis of the antiretroviral drug Indinavir (see Figure 3.1) was undertaken. Lithiation of (*S*)-**308** using *s*-BuLi/(+)-**26** followed by trapping with *t*-butyl isocyanate was performed in an attempt introduce the *t*-butyl amide functionality. However, the reaction resulted in a complex mixture of cyclised and uncyclised products that could not be separated. Since the amide functionality could not be introduced directly, manipulation of ester (*S*,*S*)-**330** was carried out. Saponification of the ester proceeded smoothly to give acid (*S*,*S*)-**344** in 94% yield (Scheme 4.33). Synthesis of the *t*-butyl amide moiety of (*S*,*S*)-**345** was completed in 98% yield through amidation with *t*-butylamine, using HATU as the coupling agent. Hydrogenolysis of the cumyl protecting group was unsuccessful, presumably due to the presence of the amide functionality. Therefore, protecting group removal was achieved by reaction with 1-chloroethyl chloroformate, followed by MeOH, to give piperazine hydrochloride (*S*)-**346** in 84% yield. The formal synthesis was completed by removal of the Boc group using HCl in Et_2O, giving piperazine dihydrochloride (*S*)-**347** in 98% yield.[194] Alternatively, a partial synthesis of Indinavir was achieved by alkylating (*S*)-**346** with 3-(chloromethyl)pyridine in the presence of Et_3N to give (*S*)-**348** in 69% yield.



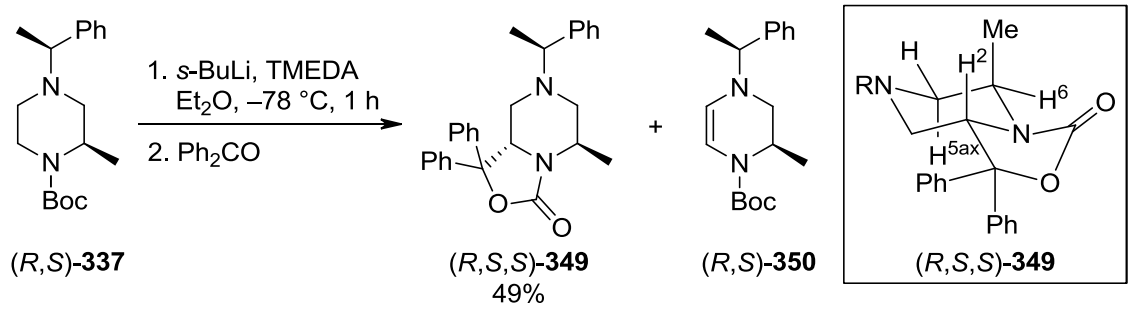
Scheme 4.33 Formal synthesis of Indinavir

4.3.2 Synthesis of Enantiopure Disubstituted *N*-Boc Piperazines

With methodology developed to construct enantiopure α-substituted piperazines, further elaboration of these products to synthesise 2,6- and 2,5-disubstituted piperazines was investigated. The synthesis of disubstituted piperidines through two consecutive lithiation/trapping reactions was pioneered by Beak[74,75] and examples were provided Chapter 1.2.5.

2-Methyl *N*-Boc piperazine (*R*,*S*)-**337** was initially chosen due to the lack of reactive functional groups. Lithiation with *s*-BuLi/TMEDA in Et_2O at –78 °C for 1 h before trapping with benzophenone gave (*R*,*S*,*S*)-**349** in 49% as a single diastereomer (Scheme 4.34). Based on the analysis of the ^{1}H NMR spectrum of the crude product a 77:23 mixture of (*R*,*S*,*S*)-**349** and alkene by-product (*R*,*S*)-**350** was formed, thus accounting for the moderate yield of (*R*,*S*,*S*)-**349**. Interestingly, this is the only encounter of the

formation of SET by-products when using *s*-BuLi/TMEDA in the work disclosed within this thesis.

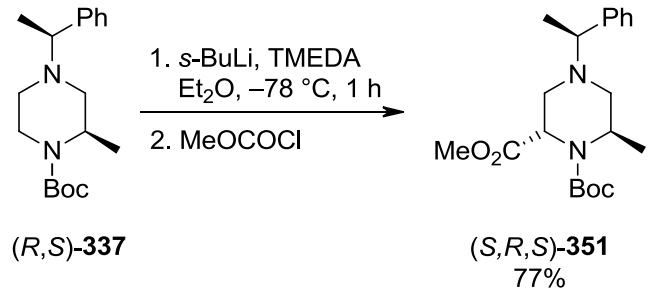


(*R*,*S*)-**337** (*R*,*S*,*S*)-**349** 49% (*R*,*S*)-**350** (*R*,*S*,*S*)-**349**

Scheme 4.34

Benzophenone was chosen as the electrophile because the product (oxazolidinone (*R*,*S*,*S*)-**349**) does not have the Boc group. This eliminated rotamers from the ^{1}H NMR spectrum, allowing structural assignment by evaluation of the coupling constants. A large vicinal axial-axial coupling of 11.0 Hz is evident between H^{2} the adjacent axial proton, placing the oxazolidinone group in an equatorial orientation as expected. Coupling constants could not be resolved for H^{6} but a 2D COSY experiment showed that H^{6} and H^{5ax} were coupled. Analysis of the coupling constants for H^{5ax} showed a 4.0 Hz axial-equatorial coupling to H^{6}, indicating that H^{6} is in an equatorial orientation and hence the methyl substituent is in an axial orientation. The observed diastereoselectivity arises due to the fact that the 2-methyl substituent adopts an axial conformation to avoid $A^{1,3}$-type strain with the Boc group. Subsequent Boc-directed equatorial lithiation and retentive trapping results in a 2,6-*trans*-relationship (see Scheme 1.40).

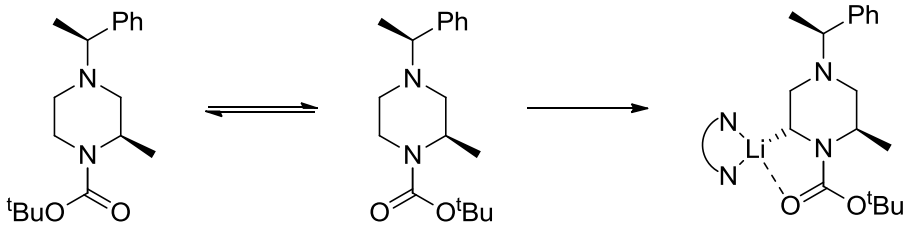
In an analogous reaction, lithiation of 2-methyl *N*-Boc piperazine (*R*,*S*)-**337** and trapping with methyl chloroformate gave (*S*,*R*,*S*)-**351** in 77% as a single diastereomer (Scheme 4.35). The relative stereochemistry was assigned by analogy with (*R*,*S*,*S*)-**349** as it was not possible to fully analyse the ^{1}H NMR spectrum due to the presence of rotamers.



(*R*,*S*)-**337** (*S*,*R*,*S*)-**351** 77%

Scheme 4.35

Unsymmetrical *N*-Boc heterocycles can possibly exist as two different rotameric forms. As shown previously with 2-phenyl *N*-Boc pyrrolidine **39** (see Scheme 2.7), *N*-Boc tetrahydroisoquinoline **135** (see Scheme 2.10) and *N*-Boc imidazolidine **154** (see Scheme 2.23) the barrier to rotation of the *N*-Boc group is often high at low temperatures, resulting in low yields of substituted products. However the relatively high yield of (*S*,*R*,*S*)-**351** (77%) suggests that rotamers (*R*,*S*)-**337a** and (*R*,*S*)-**337b** readily interconvert at low temperatures (Scheme 4.36). Similarly, it is known that the rotamers of 2-phenyl *N*-Boc piperidine convert rapidly at –78 °C in THF.[115] Lithiation would only be expected at the least hindered position of (*R*,*S*)-**337b** to give lithiated intermediate (*R*,*R*,*S*)-**352**. However, closer inspection of the lithiation event using ReactIR™ or variable temperature NMR would be necessary to definitively prove that rotamers (*R*,*S*)-**337a** and (*R*,*S*)-**337b** readily interconvert at low temperatures on the reaction timescale.

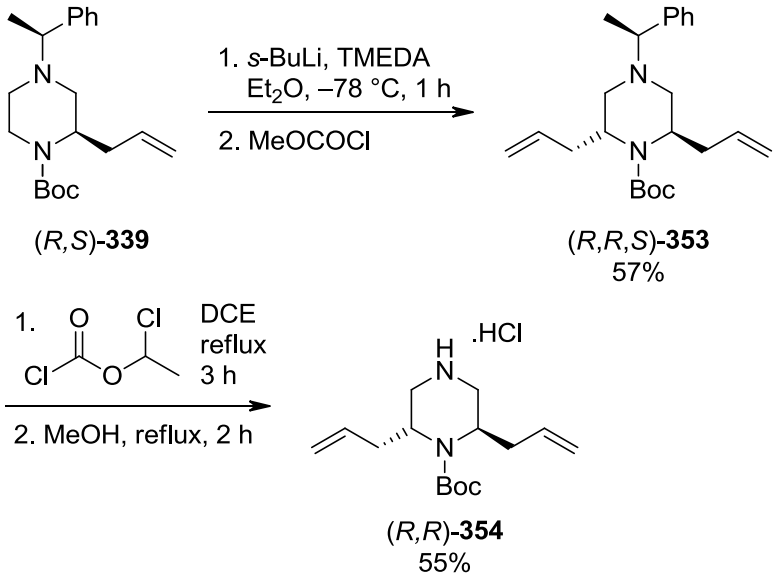


(*R*,*S*)-**337a** (*R*,*S*)-**337b** (*R*,*R*,*S*)-**352**

Scheme 4.36 Lithiation of rotameric forms of (*R*,*S*)-**337**

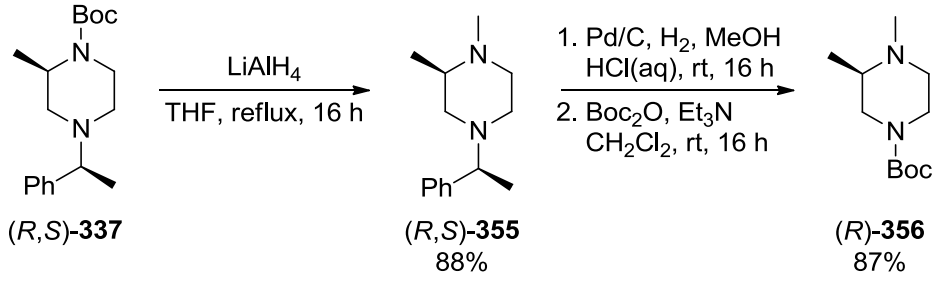
van Maarseveen and co-workers assigned a *cis*-relationship between the allyl groups of racemic 2,6-diallyl piperazine **200** (see Scheme 3.6), but this assignment is at odds with previous work on 2,6-disubstitited *N*-Boc piperidines and the work disclosed within this section. In order to investigate the stereochemical relationship between two allyl groups, enantiopure diallyl piperazine (*R*,*R*,*S*)-**353** was synthesised. Lithiation of allyl

piperazine (*R*,*S*)-**339** was accomplished using *s*-BuLi/TMEDA. After transmetallation to copper (using CuCN.2LiCl) and trapping with allyl bromide, diallyl piperazine (*R*,*R*,*S*)-**353** was isolated in 57% yield (Scheme 4.37). Removal of the α-methyl benzyl protecting group was accomplished using 1-chloroethyl chloroformate followed by MeOH to give (*R*,*R*)-**354** in 55% yield. The optical rotation of (*R*,*R*)-**354** was found to be $[\alpha]_D$ –34.9 (*c* 0.7 $CHCl_3$). The non-zero optical rotation proves the *trans*-relationship between the allyl groups; the *cis*-compound is meso (achiral) and would have an optical rotation of zero. It is still possible, although unlikely, that van Maarseveen's synthesis of the *N*-methyl diallyl derivative **200** did result in the formation of a *cis*-disubstituted piperazine.



Scheme 4.37

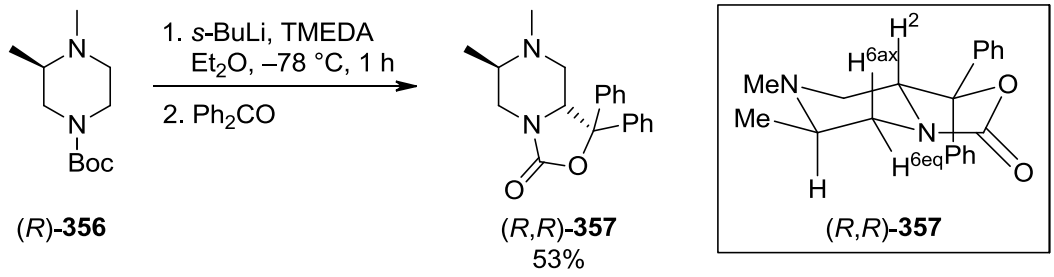
Next, the synthesis of 2,5-disubsituted piperazines was investigated. The requisite substrate, 3-methyl piperazine (*R*)-**356** was synthesised in three steps from enantiopure 2-methyl piperazine (*R*,*S*)-**337** (Scheme 4.38). Reduction of the Boc group with $LiAlH_4$ in THF at reflux gave tertiary amine (*R*,*S*)-**355** in 88% yield. Then, removal of the α-methyl benzyl protecting group was accomplished using hydrogenation with Pd/C in acidic MeOH. Following Boc protection of the resulting secondary amine, 3-methyl piperazine (*R*)-**356** was isolated in 87% yield.



(*R*,*S*)-**337** (*R*,*S*)-**355** 88% (*R*)-**356** 87%

Scheme 4.38

N-Boc-*N′*-methyl piperazine **151** was shown to undergo ring-fragmentation side-reactions with the majority of electrophiles (see Chapter 3.2). However, benzophenone reacted with the intermediate organolithium without fragmentation (see Scheme 3.33). Therefore, lithiation/trapping of 3-methyl piperazine (*R*)-**356** was performed with *s*-BuLi/TMEDA and benzophenone. Oxazolidinone (*R*,*R*)-**357** was isolated in 53% yield as a single diastereomer (Scheme 4.39). The *trans*-relationship between the substituents was determined by analysis of the coupling constants from the ^{1}H NMR spectrum of (*R*,*R*)-**357**. H^{2} shows a large axial coupling of 11.0 Hz, indicating that the oxazolidinone is in an equatorial orientation. H^{6eq} shows a large geminal coupling and an equatorial-axial coupling of 3.5 Hz. Additionally H^{6ax} shows a large axial-axial coupling of 11.5 Hz. The *trans*-relationship arises due to the methyl group adopting an equatorial orientation before equatorial deprotonation and retentive trapping (see Scheme 1.43).



(*R*)-**356** (*R*,*R*)-**357** 53% (*R*,*R*)-**357**

Scheme 4.39

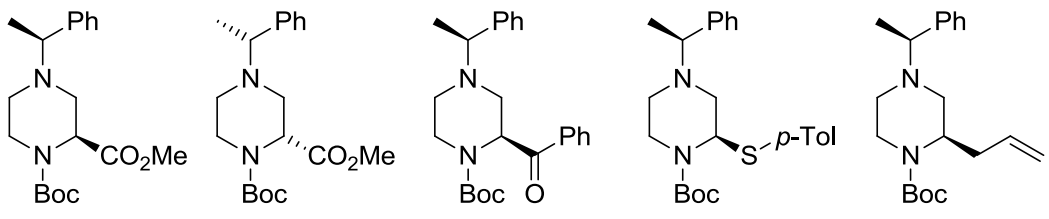
The work presented in this section shows the synthesis of enantiomerically pure *trans*-2,6- and *trans*-2,5-disubstitiuted *N*-Boc piperazines using the chiral auxiliary approach.

4.4 Conclusions and Future Work

Preliminary investigations into the asymmetric lithiation/trapping of *N*-Boc-*N′*-benzyl piperazine **117** revealed a series of problems. Specifically, ring fragmentation side-reactions were encountered with a range of electrophiles, whist other slow trapping electrophiles resulted in either ring fragmentation or near-racemic products being isolated, or both.

Increasing the steric bulk of the piperazine protecting group prevented the lone pair attacking electrophiles and thus minimised or eliminated the ring fragmentation side-reaction. Additionally, use of a large protecting group reduced the SET side-reactions with benzophenone. A range of piperazines protected with sterically large protecting groups were investigated. The use of *N*-Boc-*N′*-*t*-butyl piperazine **152**, *N*-Boc-*N′*-trityl piperazine **203** and *N*-Boc-*N′*-PhFl piperazine **240** was moderately successful. However, each of these substrates had drawbacks. Finally, the use of *N*-Boc-*N′*-cumyl piperazine **241** allowed the synthesis of a range of *α*-substituted *N*-Boc piperazines in good yields and er, in both enantiomeric series. As far as it can be known, this is the first report of the cumyl protecting group for the protection, manipulation and deprotection of amines.

The development of an asymmetric lithiation/trapping method using an *N*-Boc piperazine substrate protected with an *α*-methyl benzyl chiral auxiliary **308** allowed the synthesis of enantiopure *α*-substituted *N*-Boc piperazines in excellent yield. Both enantiomeric series are attainable in high yield by matching the sense of induction from the chiral auxiliary and the chiral diamine. A representative selection of piperazines synthesised is shown in Figure 4.2. Further work could focus on expanding the electrophile scope of this reaction.



(*S*,*S*)-**330** (*R*,*R*)-**330** (*S*,*S*)-**333** (*R*,*S*)-**335** (*R*,*S*)-**339**

Figure 4.2

The *α*-methyl benzyl protecting group could be removed using several different conditions allowing further derivatisation of the piperazine scaffold, with a formal synthesis of the antiretroviral drug Indinavir being completed.

The synthesis of enantiopure *trans*-disubstituted piperazines has been accomplished using two consecutive stereoselective lithiation/trapping reactions. The selection of compounds formed is shown in Figure 4.3.

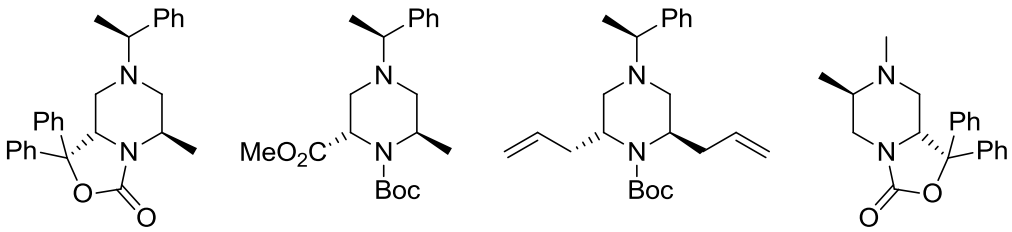
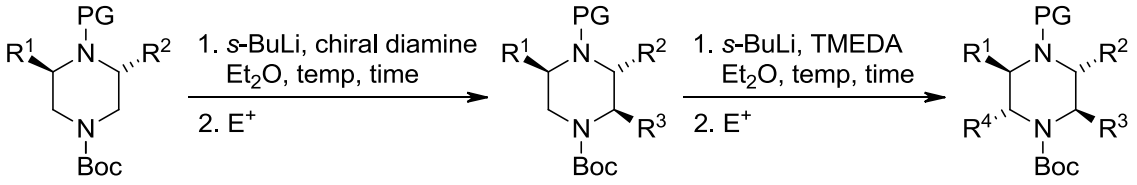


Figure 4.3

Further elaboration of the piperazine scaffold could be achieved using the methodology developed, with the synthesis of tri- and tetrasubstituted piperazines **358** and **359** being feasible (Scheme 4.40). The third lithiation would need to employ a chiral diamine to control the regioselectivity of the lithiation/trapping. Additionally, in order to obtain good yields, the reactions would need to be performed at a temperature at which *N*-Boc rotamers could interconvert readily.



358 **359**

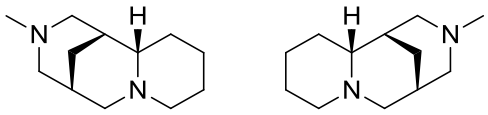
Scheme 4.40 Possible synthesis of tri- and tetrasubstituted piperazines **358** and **359**

Piperazines are ubiquitous within drug molecules, but very few examples exist with the piperazine substituted at carbon. The methodology developed within this chapter would allow medicinal chemists to synthesise a range of enantiopure mono- and disubstituted piperazines that are differentially protected, for incorporation into potential drug molecules.

Chapter Five: Synthesis of the (–)-Sparteine Surrogate

The (+)-sparteine surrogate (+)-**26** (Figure 5.1) has been used with great success in the *s*-BuLi-mediated asymmetric lithiation of *N*-Boc heterocycles.[48,57,60,63,68,95,195,196] It has found utility in the lithiation of other substrates including *O*-alkyl carbamates[48,197] as first reported by Hoppe,[41] the lithiation of phosphine boranes,[198,199] ferrocene derivatives,[200] and diaryl-methane derivatives.[201] Additionally, it has been employed as a ligand for transition metals with palladium catalysed oxidative kinetic resolution of secondary alcohols,[202] copper(II)-mediated resolution of BINOL,[203] and oxidative dearomatisation of benzaldehyde derivatives being reported.[204] A review of the chemistry of the (+)-sparteine surrogate (+)-**26** was published in 2008.[205]

As shown by previous work in the O'Brien group[53,95] and in Chapter 2, the lithiation times of *N*-Boc heterocycles are much shorter using *s*-BuLi and the (+)-sparteine surrogate (+)-**26** than with (–)-sparteine. This itself creates an opportunity for the (–)-sparteine surrogate (–)-**26** (Figure 5.1) in synthesis. Furthermore, the unreliable supply of naturally occurring (–)-sparteine,[206,207] makes access to the (–)-sparteine surrogate (–)-**26** critical. However, the reliance on (–)-cytisine, itself a natural product, as a starting material for the synthesis of (+)-**26** precludes the synthesis of the enantiomer in an analogous fashion.



(+)-**26** (–)-**26**

Figure 5.1

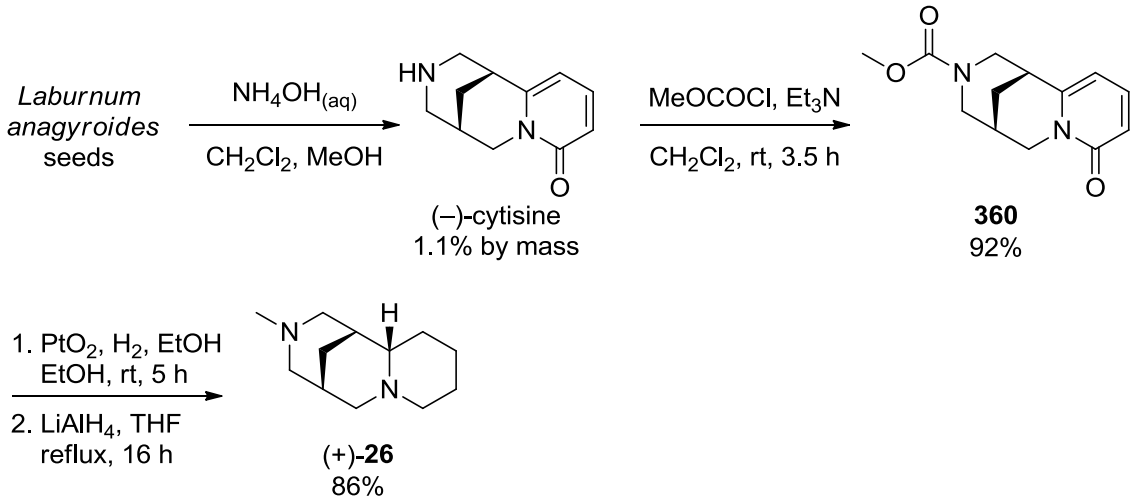
Thus, gram-scale synthetic routes to the (–)-sparteine surrogate (–)-**26** were explored. This chapter details two approaches for synthesis of the (–)-sparteine surrogate (–)-**26**. The first involved the synthesis and resolution of racemic **26**, and the second, aimed to develop a fully stereoselective synthesis wherein an enzymatic kinetic resolution of an early stage intermediate would give the required enantiopure building block.

5.1 Previous Syntheses of the Sparteine Surrogate

To date, all syntheses of enantioenriched sparteine surrogate **26** have relied on one of three strategies: use of an enantiopure starting material from the chiral pool, resolution of racemic surrogate **26** or asymmetric synthesis. This section reviews the current published methods for the synthesis of the sparteine surrogate **26**.

5.1.1 Use of Chiral Pool Starting Materials: Synthesis of the (+)-Sparteine Surrogate from (–)-Cytisine

The wide adoption of O'Brien's (+)-sparteine surrogate (+)-**26** is a testament to its success as a ligand. Its acceptance by the synthetic community has been facilitated by the fact that it is easy to synthesise in high yield from (–)-cytisine (Scheme 5.1) using a procedure developed in the O'Brien group.[48,51] This was made possible by Lasne's development of a straightforward and low cost procedure for the extraction of (–)-cytisine from *Laburnum anagyroides* seeds on a multi-gram scale.[208]



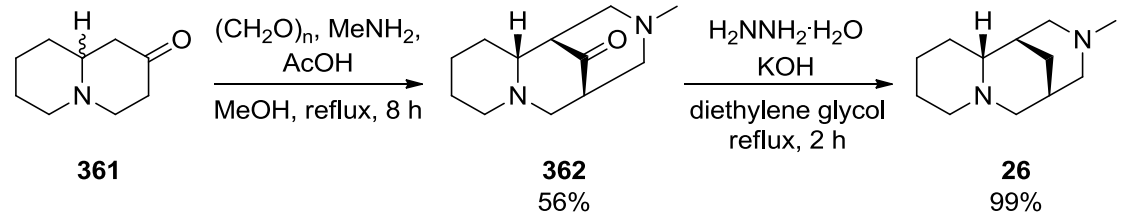
Scheme 5.1 Synthesis of (+)-**26** from (–)-cytisine

Using Lasne's method, workers in the O'Brien group extracted (–)-cytisine from *Laburnum anagyroides* seeds in 1.1% mass yield. With (–)-cytisine in hand, methyl carbamate **360** was formed in 92% yield by reaction with methyl chloroformate in the presence of triethylamine. Then, diastereoselective hydrogenation on the least hindered *exo*-face, employing Adams's catalyst, followed by global reduction with $LiAlH_4$ gave the (+)-sparteine surrogate (+)-**26** in 86% yield. Chiral shift ^1H NMR spectroscopy

showed (+)-**26** to be >98:2 er. Thus, an efficient multi-gram synthesis of (+)-**26** from (–)-cytisine was completed in three steps in 79% overall yield.

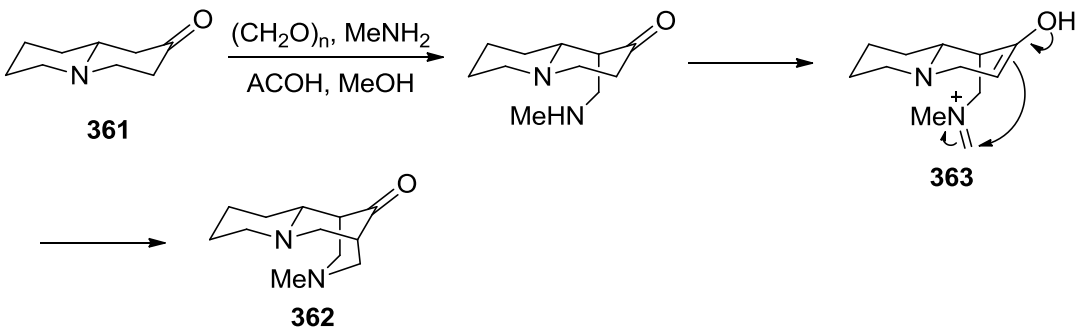
5.1.2 Synthesis and Resolution of Racemic Sparteine Surrogate

Scheiber and Nemes reported the first synthesis of racemic sparteine surrogate **26** in 1994 before its use as a sparteine-like diamine was even considered (Scheme 5.2).[209] 2-Quinolizinone **361** (synthesised using previously reported procedures[210,211]) was transformed into bispidone **362** as a single diastereomer *via* a double Mannich reaction in 56% yield. Reduction of the carbonyl group was accomplished using the Huang-Minlon modification of the Wolff-Kishner reduction to give **26** in 99% yield.



Scheme 5.2

The stereoselectivity in the double Mannich reaction can be explained as shown in Scheme 5.3. It is a result of a preferred double chair conformation of bicyclic ketone **361** and the fact that the second Mannich reaction can only occur when the iminium ion is orientated axially, as in **363**.

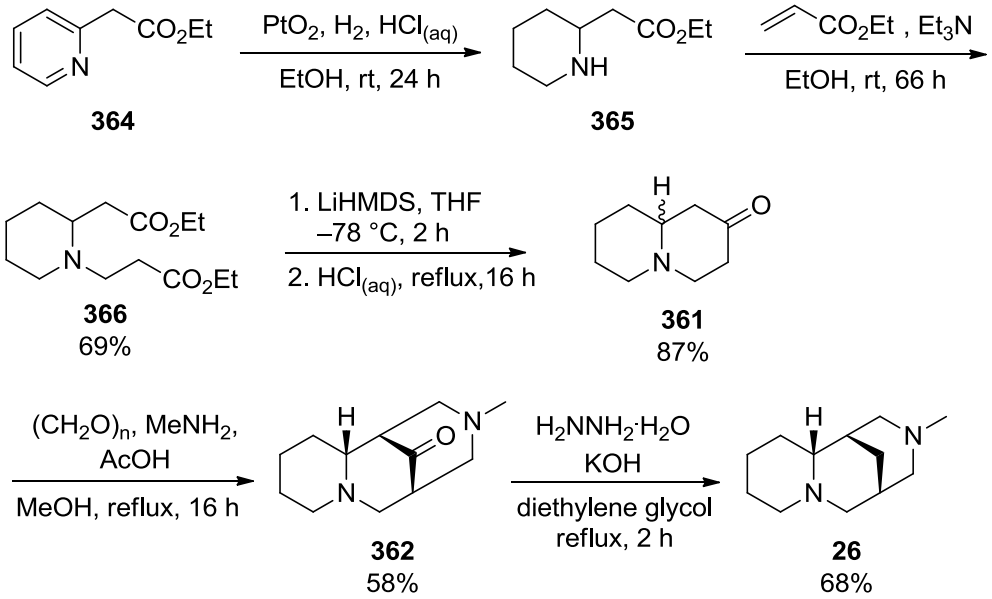


Scheme 5.3 Stereoselectivity in the double Mannich reaction of **361**

Work within the O'Brien group was initially focussed on accessing the (+)-sparteine surrogate (+)-**26** *via* Scheiber and Nemes' route using enantiopure bicyclic ketone (*R*)-

361.[212] Unfortunately, preliminary studies on related bicyclic amino ketones showed that racemisation occurred under the harsh acidic conditions required for the double Mannich reaction. This presumably occurred through either a retro-Mannich or retro-Michael reaction. Further experimentation did not identify racemisation free double Mannich conditions and attention was turned to the resolution of **26** for the attainment of (+)-**26**.

To facilitate this goal, an optimised synthesis of racemic sparteine surrogate **26** was developed (Scheme 5.4).[213] Hydrogenation of ethyl-2-pyridyl acetate **364** using Adams's catalyst under acidic conditions gave crude piperidine ester **365** which was reacted with ethyl acrylate in the presence of triethylamine to give di-ester **366** in 69% overall yield. A Dieckmann condensation was accomplished using LHMDS at –78 °C, followed by decarboxylation under acidic conditions to give bicyclic ketone **361** in 87% yield. The synthesis was completed using the double Mannich/Wolff-Kishnner protocol developed by Scheiber and Nemes, with bispidone **362** being isolated in 58% yield and **26** in 68% yield. In summary, the synthesis of racemic sparteine surrogate **26** was completed in 24% yield over five steps.



Scheme 5.4 O'Brien's synthesis of racemic sparteine surrogate **26**

Classical resolution of **26** was attempted using a range of chiral acids (Figure 5.2) as resolving agents in acetone.[214] Literature precedent suggested this was a viable strategy. Leonard had reported the total synthesis of racemic sparteine and resolution with (+)-

camphorsulfonic acid (+)-**367** in acetone in 1950.[215] Several other chiral acids that are often used in the resolution of amines were also investigated, including tartaric acid derivatives (–)-**368** and (–)-**369**,[216,217] (*S*)-malic acid (*S*)-**370** and (*S*)-mandelic acid (*S*)-**371**.

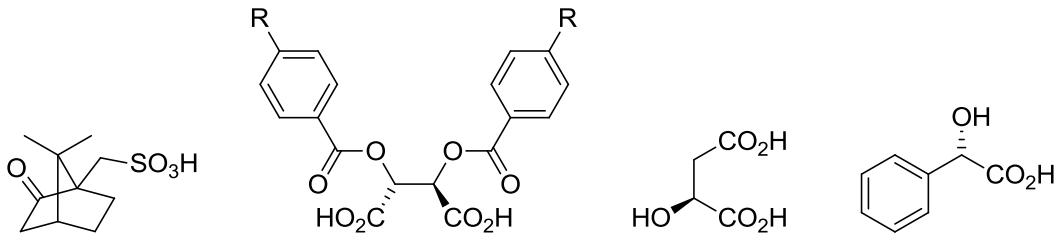
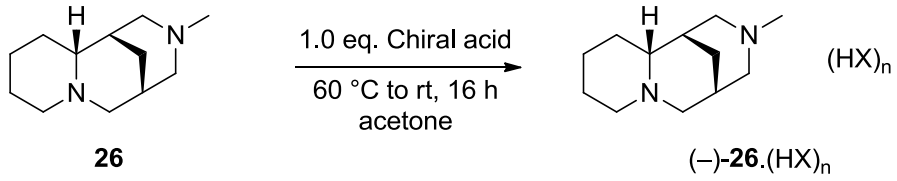


Figure 5.2

Acetone was chosen as the solvent due to the literature precedent of the resolution of sparteine, and 1.0 eq. of the resolving agent was employed. Mixtures of a chiral acid and sparteine surrogate **26** were formed at 60 °C and allowed to cool over 12 h. The results of this investigation are shown in Table 5.1.



Entry	Resolving agent	Yield (%)	er[a]
1	(+)-**367**	-	-
2	(–)-**368**	-	-
3	(–)-**369**	69	0
4	(*S*)-**370**	-	-
5	(*S*)-**371**	-	-

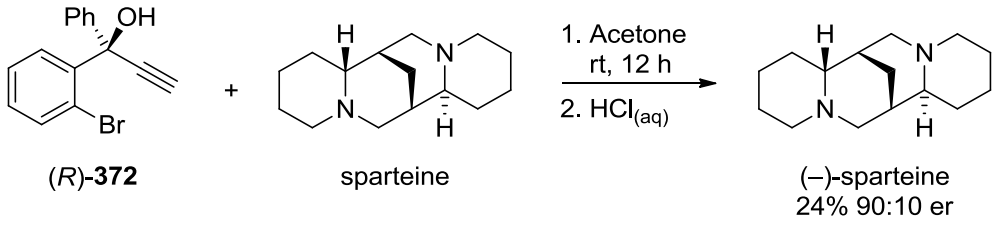
[a] Er of the free base, determined by ^{1}H NMR spectroscopy in the presence of a chiral shift reagent.

Table 5.1 Attempted resolution of racemic sparteine surrogate **26** using chiral acids

Crystals were observed in only one case, when (–)-**369** was employed as the resolving agent (Table 5.1, entry 3). No enantioenrichment was observed. It is possible that the

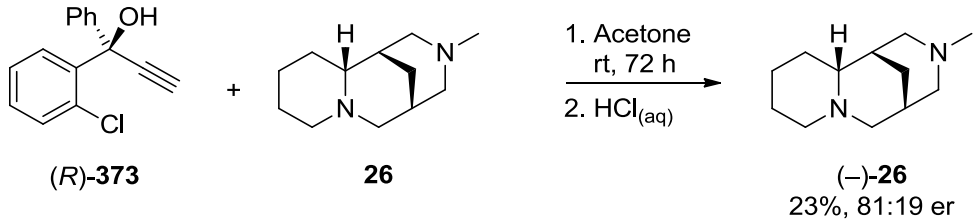
use of 1.0 equivalent of resolving agent (–)-**369** led to the high yield (69%) and racemic nature of the isolated material.

The O'Brien group then turned their attention to resolution *via* lattice inclusion, a technique pioneered by Schlenk.[218] In 1983, Toda and co-workers showed that racemic sparteine could be resolved using enantiopure acetylenic alcohols including (*R*)-**372** (Scheme 5.5).[219] An equimolar mixture of (*R*)-**372** and racemic sparteine in acetone gave crystals that, upon treatment with aqueous HCl, resulted in the isolation of (–)-sparteine in 24% yield and 90:10 er. Importantly, when complexation of 90:10 er (–)-sparteine and (*R*)-**372** was repeated, enantiopure (–)-sparteine was obtained.



Scheme 5.5

Due to the similarity in structure of (–)-sparteine and the sparteine surrogate **26** it was hypothesised by O'Brien and co-workers that resolution of the latter could be accomplished using enantiopure acetylenic alcohols.[213] To this end a sample of enantiopure (*R*)-**373** was prepared by resolution with (–)-sparteine using Toda's method. Treatment of racemic surrogate **26** with (*R*)-**373** in acetone gave crystals that, upon treatment with aqueous HCl, liberated enantioenriched (–)-**26** in 23% yield and 81:19 er (Scheme 5.6).

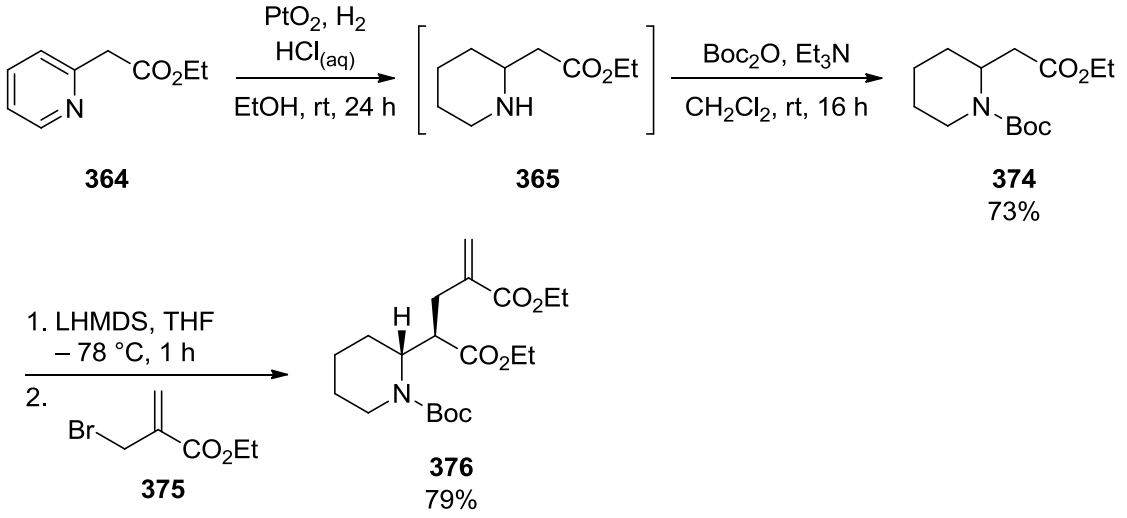


Scheme 5.6

To summarise, enantioenrichment of the sparteine surrogate **26** by resolution with acetylenic alcohol (*R*)-**373** was possible. However, since two resolutions would be required to produce (–)-**26** in high enantiomeric ratio the overall yield of the resolution

would be prohibitively low. Additionally, (–)-sparteine was required for the resolution of racemic **373**.

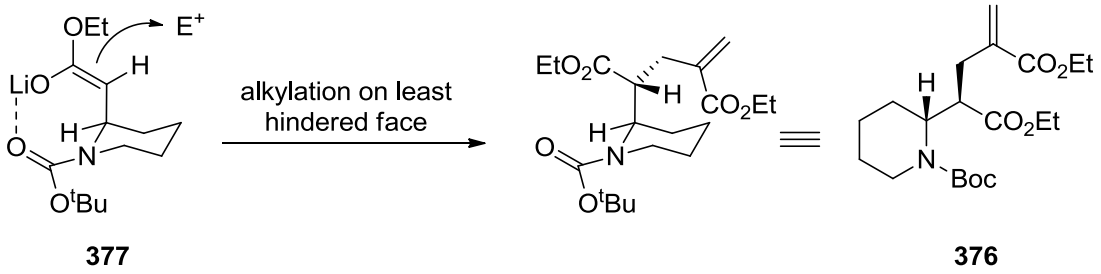
More recently, Canipa and O'Brien developed a novel synthesis of racemic sparteine surrogate **26**.[220] The route involved three key reactions: (i) the diastereoselective alkylation of cyclic *β*-amino esters, (ii) annulation *via* an intramolecular conjugate addition, followed by stereoselective protonation and (iii) formation of the bispidine framework *via* double displacement of a di-mesylate with methylamine. The first three steps of the synthetic route are shown in Scheme 5.7. As with the previous route to **26**, the synthesis began with hydrogenation of pyridine **364** to piperidine **365** using Adams's catalyst. The crude piperidine was then transformed into *N*-Boc ester **374** using Boc_2O in the presence of triethylamine in 73% overall yield.



Scheme 5.7

The next step was a diastereoselective alkylation of *N*-Boc ester **374**. Treatment of **374** with LHMDS in THF at –78 °C followed by addition of (*α*-bromomethyl)acrylate **375** (synthesised according to a known procedure[221]) gave di-ester **376** in 79% yield as a single diastereomer. Stereoselectivity in the alkylation of protected piperidine derived cyclic *β*-amino esters, such as **374**, is well precedented from the work of Knight,[222,223] Lhommet,[224] and others.[45,225-227] A rationale for the stereoselectivity observed in the alkylation has been proposed by Knight and is shown in Scheme 5.8. It is assumed that the enolate **377** adopts the *E* configuration shown, and that the lithium coordinates to the carbonyl of the Boc group. The electrophile then approaches from the least hindered

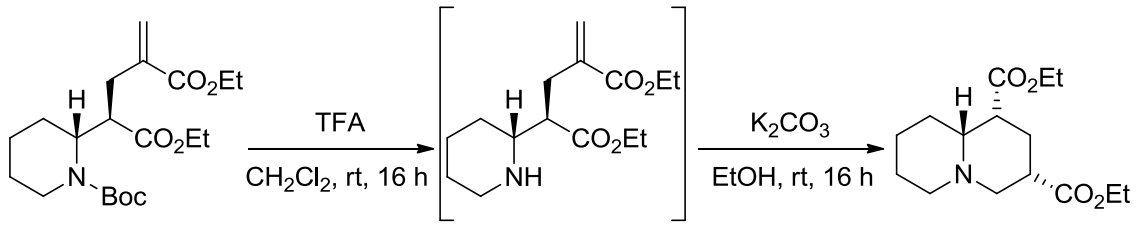
back face, avoiding interactions with the sterically demanding Boc group. This leads to formation of **376** as the major diastereomer.



377 **376**

Scheme 5.8 Rationale for stereoselectivity in the alkylation of **377**

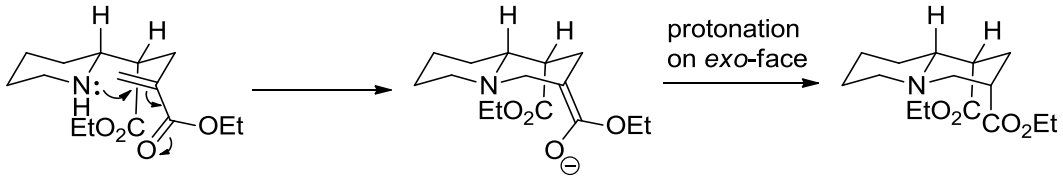
The next key step was a sequential Boc deprotection/intramolecular conjugate addition reaction. Removal of the *N*-Boc protecting group from di-ester **376** was accomplished using TFA under standard conditions. The crude secondary amine **378** was treated with K_2CO_3 in EtOH at room temperature for 16 h, resulting in intramolecular conjugate addition to give **379** as a single diastereomer in 90% yield (Scheme 5.9).



376 **378** **379**
90%

Scheme 5.9

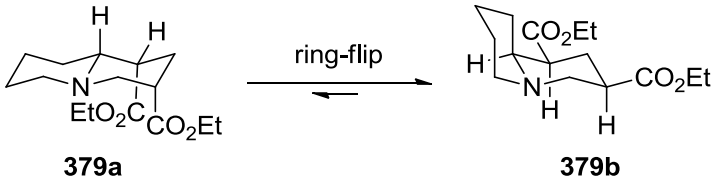
The ring-closing conjugate addition proceeded stereoselectively to give the *cis*-diastereomer of **379**. This can be rationalised as shown in Scheme 5.10. Intramolecular conjugate addition of the secondary amine of **378** onto the *α*,*β*-unsaturated ester gave intermediate enolate **380**. Protonation of the enolate by EtOH from the less hindered *exo*-face gave the desired *cis*-stereochemistry.



378 **380** **379**

Scheme 5.10 Rationale for stereoselectivity in the synthesis of **379**

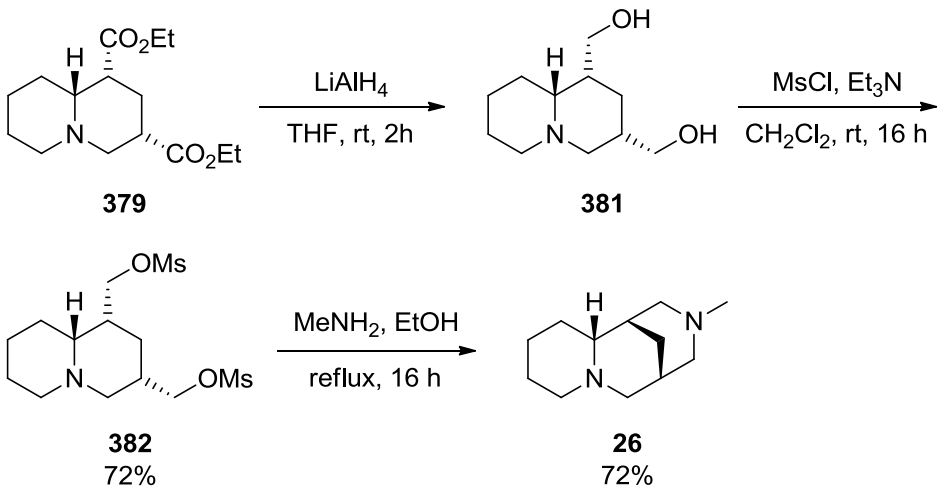
Analysis of the ^{1}H NMR spectrum of di-ester **379** suggested that the bicyclic compound adopted the conformation **379b** and not **379a** (Scheme 5.11). This conformation was favoured as it places the two ester groups in an equatorial positions, avoiding unfavourable 1,3 diaxial interactions, and the ring-flip was made possible by nitrogen inversion.



379a **379b**

Scheme 5.11

With the requisite stereocentres formed in two completely diastereoselective steps, the synthesis was completed in three problem free transformations (Scheme 5.12). Reduction of di-ester **379** to diol **381** using $LiAlH_4$ was followed by the application of standard sulfonylation conditions to give di-mesylate **382** in 72% yield over two steps. Finally, double displacement with methylamine in EtOH completed the synthesis of **26** in 72% yield. Precedent for this double displacement came from Breuning's work on the synthesis of oxa-bispidines *via* double displacement of a di-mesylate with methylamine.[228,229]



379 **381**

382
72%

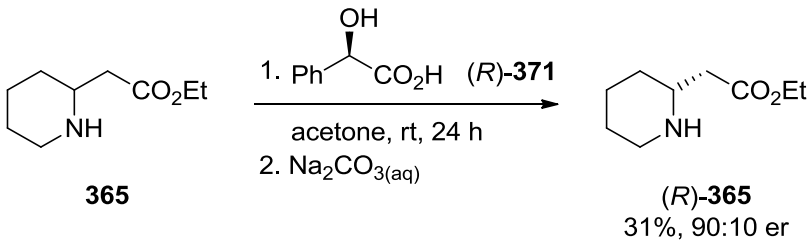
26
72%

Scheme 5.12

In summary, synthesis of racemic sparteine surrogate **26** was completed in eight steps (five isolation steps) in 27% overall yield. This route is unpublished to date. Importantly, the synthesis is completely diastereoselective and potentially scalable. The

major disadvantages of this route are that it starts with the relatively expensive ethyl-2-pyridyl acetate **364** and it is relatively labour intensive, requiring four chromatographic separations of intermediates and a final distillation of **26**.

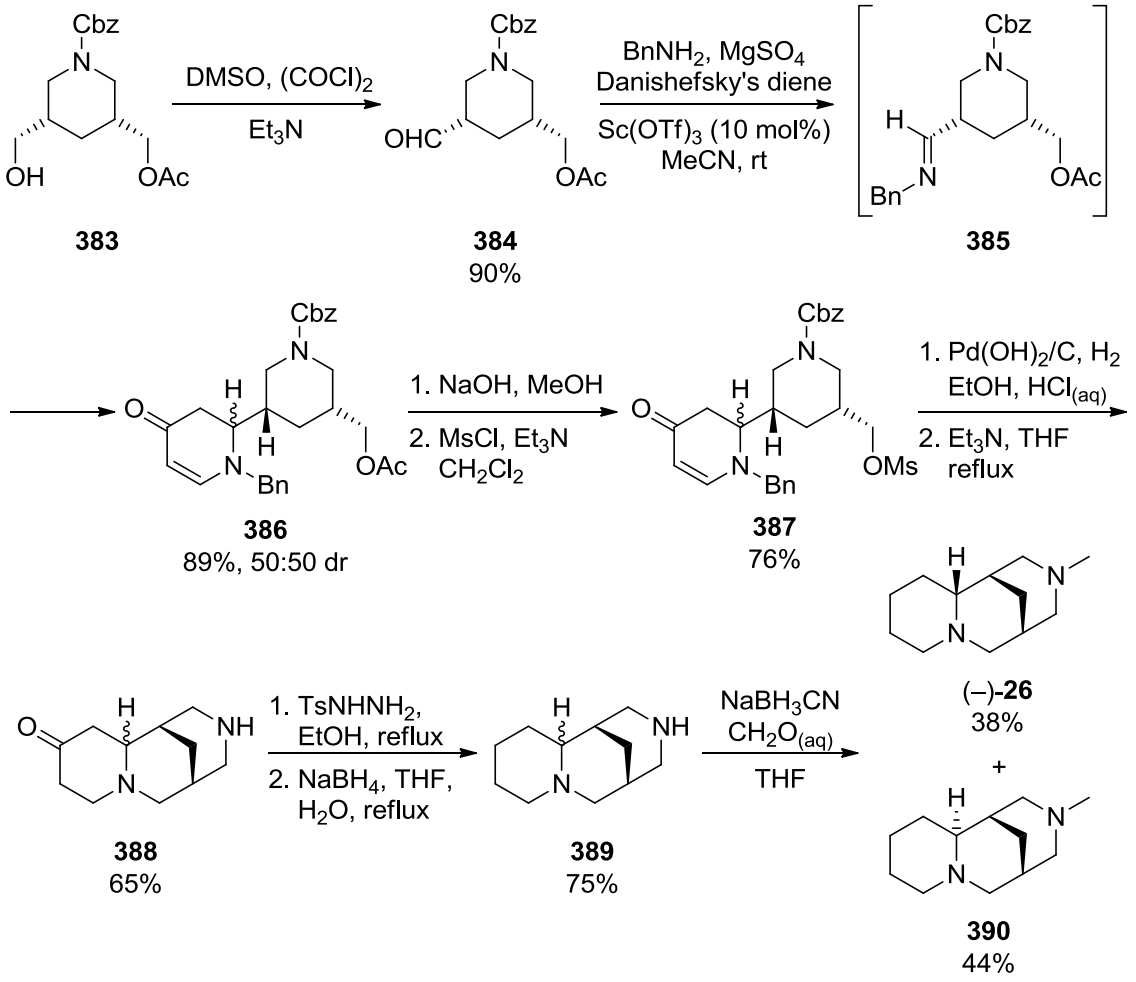
Although racemic sparteine surrogate **26** was synthesised using this route, it was identified that there was potential for this method to be used in the synthesis of enantioenriched sparteine surrogate **26**. This would require the preparation of enantioenriched *N*-Boc ester **374**. To this end, a preliminary investigation into the resolution of secondary amine **365** was undertaken (Scheme 5.13). *β*-Amino ester **365** was dissolved in acetone with (*R*)-mandelic acid (*R*)-**371** (1.0 eq.) and stirred for 24 h. The resulting white precipitate was filtered off and then treated with base to release (*R*)-**365**, in 31% yield and 90:10 er. Although this preliminary investigation was partially successful, (*R*)-**365** was not obtained with a sufficient degree of enantioenrichment to be of practical use in the preparation of (–)-sparteine surrogate (–)-**26**.



Scheme 5.13

5.1.3 Asymmetric Synthesis of the Sparteine Surrogate

To date, three syntheses of enantiopure sparteine surrogate **26** have been accomplished using asymmetric synthesis. In 2002, Lesma reported the synthesis of (–)-**26** starting from enantiopure piperidine mono-acetate **383** (both enantiomers of which are available by enzymatic desymmetrization of the corresponding *meso*-diol or *meso*-di-acetate[230]) (Scheme 5.14).[231]

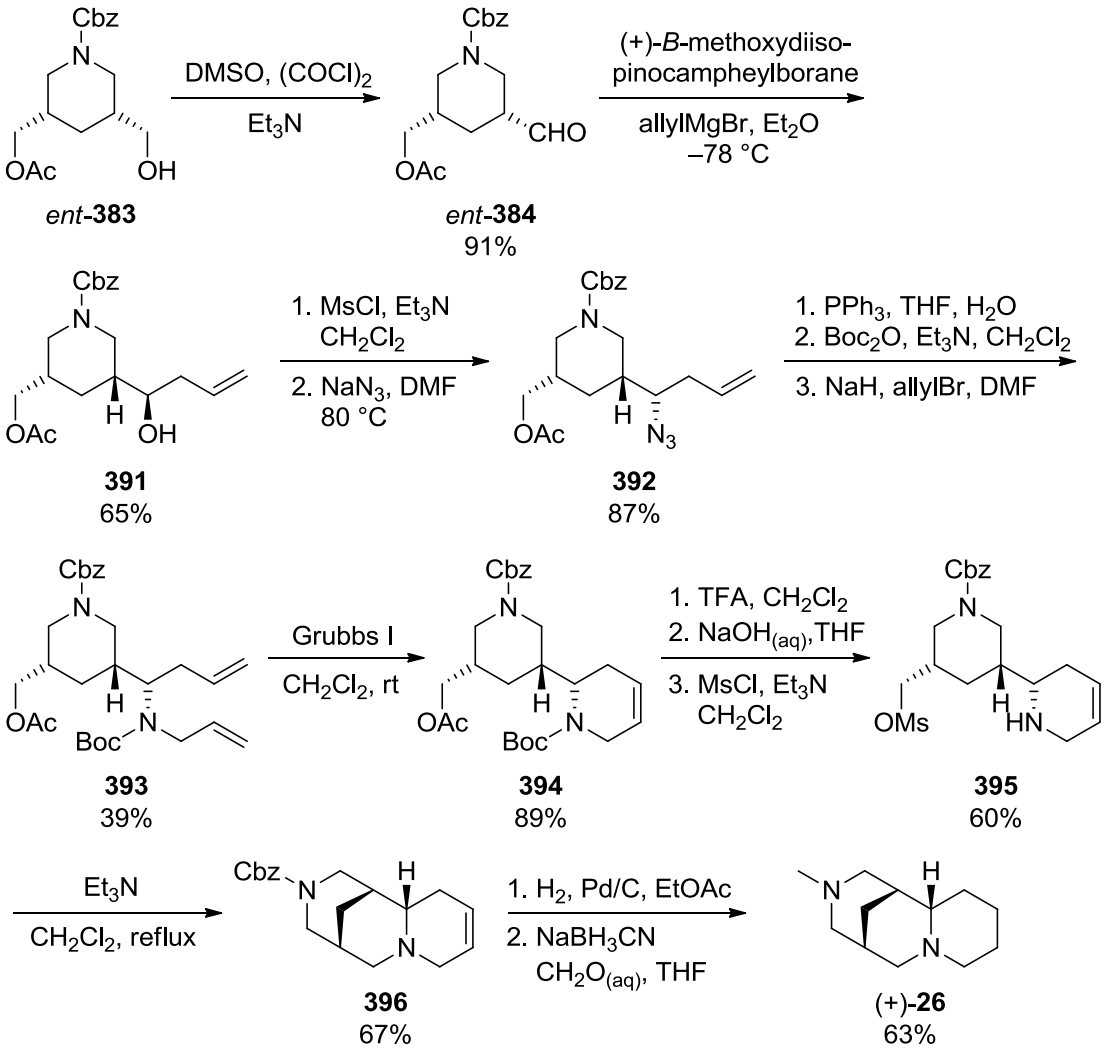


Scheme 5.14 Lesma's asymmetric synthesis of (–)-sparteine surrogate (–)-**26**

Swern oxidation of mono-alcohol **383** gave aldehyde **384** in 90% yield. Then, in the key step, benzyl imine **385** was formed *in situ* before a $Sc(OTf)_3$ catalysed hetero-Diels Alder reaction with Danishefsky's diene gave a 50:50 mixture of diastereomeric piperidines **386** in 89% yield. Saponification and mesylation gave a mixture of mesylates **387**. Subsequent hydrogenation of the alkene and concurrent hydrogenolysis of the benzyl and Cbz groups, followed by heating in basic media, completed the formation of the tricyclic core, giving **388** in 65% yield. Then, reduction of the ketone gave **389** in 75% yield. The synthesis was completed through reductive amination to methylate the secondary amine and then, finally, separation of the diastereomeric mixture. The sparteine surrogate (–)-**26** was obtained in 38% yield, and its epimer **390** in 44% yield. Although this synthetic route does allow for the preparation of both enantiomers of the sparteine surrogate **26**, the length of the route, the complete lack of diastereoselectivity in the Diels-Alder reaction and the need to separate the

diastereomeric tricycles (–)-**26** and **390** probably precludes this route from being used to generate useful quantities of sparteine surrogate (–)-**26**.

In 2005, Lesma reported a more efficient and selective synthesis of the (+)-sparteine surrogate (+)-**26**, starting from enantiopure piperidine mono-acetate *ent*-**383** (Scheme 5.15).[232]

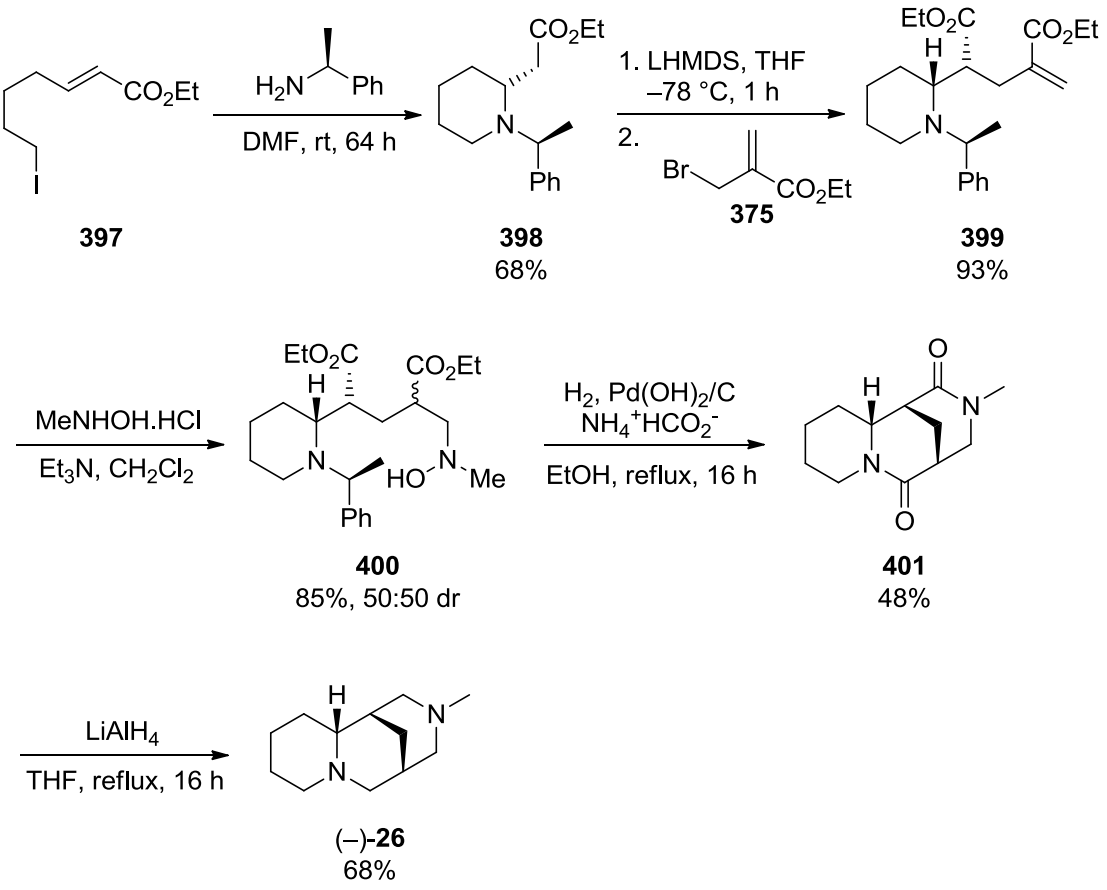


Scheme 5.15 Lesma's asymmetric synthesis of (+)-sparteine surrogate (+)-**26**

Using a previously reported procedure, azide **392** was prepared in four steps.[233] Swern oxidation of *ent*-**383** proceeded smoothly to give aldehyde *ent*-**384** in 91% yield. Stereoselective Brown allylation proceeded in 91:9 dr and upon separation of the diastereomers, allyl alcohol **391** was obtained in 65% yield. Azide **392** was formed in 87% yield by mesylation of the alcohol followed by displacement with NaN_3. Subsequent Staudinger reduction of the azide followed by Boc protection and *N*-

allylation gave the RCM precursor **393** in 39% yield over three steps. Diene **393** underwent RCM using Grubbs' first generation catalyst to form **394** in 89% yield. Then, Boc deprotection, ester saponification and mesylation of the resulting alcohol were completed to give **395** in 60% yield. Base promoted cyclisation formed the tricyclic core, with **396** being isolated in 67% yield. Finally, hydrogenation of the alkene and removal of the Cbz group was accomplished in the presence of Pd/C. Subsequent reductive amination affected *N*-methylation to give the (+)-sparteine surrogate (+)-**26** in 63% yield. In summary, enantiopure (+)-**26** was synthesised in 4% overall yield from *ent*-**383**. Although the Brown allylation resulted in good levels of diastereoselectivity, the route is too long to be used for the synthesis of (+)-**26** on a multi-gram scale.

More recently, a higher yielding synthesis of (–)-**26** has been reported by the O'Brien group starting from iodo ester **397**, itself synthesised in three steps from 5-chloropentanol (Scheme 5.16).[225] Piperidine **398** was formed by treatment of iodo ester **397** with (*S*)-*α*-methylbenzylamine. The amine first displaced the iodide in an S_N2 reaction then the resulting secondary amine added to the *α*,*β*-unsaturated ester moiety in a diastereoselective manner. Piperidine **397** was isolated in 68% yield after separation of a 75:25 diastereomeric mixture of products.



Scheme 5.16 O'Brien's asymmetric synthesis of (–)-sparteine surrogate (–)-**26**

Then, stereoselective alkylation of **398** by treatment with LHMDS and ethyl (*α*-bromomethyl)acrylate **375** gave di-ester **399** as a single diastereomer in 93% yield. Conjugate addition of *N*-methyl hydroxylamine to *α*,*β*-unsaturated ester of **399** resulted in a 50:50 mixture of diastereomeric hydroxylamines **400** in 85% yield. Subsequent cleavage of both the *N*-*α*-methylbenzyl and *N*-*O* bonds using transfer hydrogenolysis was performed, to give **401** in 48% yield. Since only one diastereomer of **400** has the correct stereochemistry to undergo bis-lactamisation, **401** was formed as a single diastereomer. The synthesis of (–)-**26** was completed by reduction with $LiAlH_4$ in 68% yield. Overall, enantiopure (–)-**26** was synthesised in 18% yield over only five steps, starting from iodo ester **397**. Unfortunately, the formation and separation of by-products in the conversion of diastereomeric hydroxylamines **400** to tricycle **401** precludes this route being used for the synthesis of multi-gram quantities of (–)-**26.**

5.1.4 Conclusions

To date, the most efficient, and hence useful synthesis of the sparteine surrogate **26** is O'Brien's synthesis of (+)-**26** from naturally occurring (–)-cytisine over three steps (see Scheme 5.1). This method allows the facile preparation of gram quantities of (+)-**26**. However, due to the reliance on (–)-cytisine as a starting material, only one enantiomer (+)-**26** can be made *via* this route. Although the antipode (–)-**26** has been synthesised by Lesma and by O'Brien, these routes are not amenable to the synthesis of enantiopure (–)-**26** on a multi-gram scale due to the number of steps involved, or problems encountered with purification.

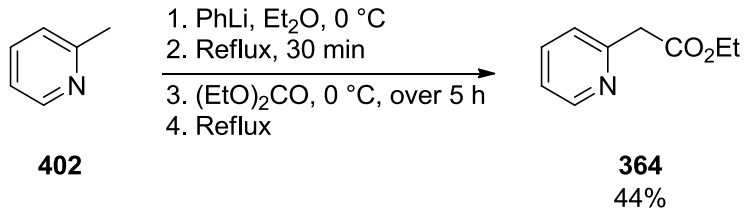
Recently, it has become apparent that the (+)-sparteine surrogate (+)-**26** out-performs (–)-sparteine in many aspects of asymmetric lithiation chemistry. For example, Chapter 2 shows several examples where the time required for lithiation of *N*-Boc heterocycles is an order of magnitude shorter with *s*-BuLi/(+)-**26** than with (–)-sparteine. This increase in the rate of deprotonation allows the asymmetric lithiation of *N*-Boc piperidine **10** with *s*-BuLi/(+)-**26** to give *α*-substituted products in good yield and er (see Scheme 1.32). The analogous reaction with *s*-BuLi/(–)-sparteine gives <10% yield due to the slow rate of lithiation. There are more subtle advantages to the use of **26** over (–)-sparteine. Recent work within the O'Brien group has shown that the (+)-sparteine surrogate (+)-**26** is compatible with THF as a solvent whereas when (–)-sparteine is employed in THF, racemic products were isolated.[57] Additionally, it has been shown that for the *s*-BuLi mediated lithiation at higher temperature (–30 °C) (+)-**26** outperforms (–)-sparteine in terms of yield and enantioselectivity.[60]

These reasons, coupled with the fact that (–)-sparteine is currently difficult to obtain, make the need for an efficient synthesis of (–)-**26** apparent. Thus, new methods for the gram-scale synthesis of enantiopure (–)-**26** were sought. The first approach was *via* a classical resolution of racemic sparteine surrogate **26** and secondly, *via* the formation of an enantiomerically pure intermediate and subsequent diastereoselective synthesis building on Canipa and O'Brien's unpublished route.[220]

5.2 Improved Synthesis and Classical Resolution of the Sparteine Surrogate

5.2.1 Synthesis of Racemic Sparteine Surrogate

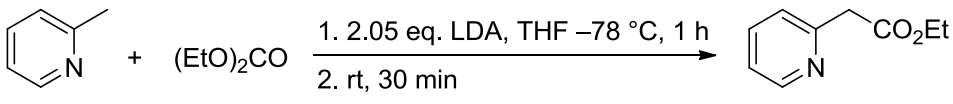
The moderate success enjoyed by O'Brien and co-workers in the synthesis and resolution of **26** (see Schemes 5.4 and 5.6)[214] inspired a re-investigation, with a view to improving the resolution procedure to allow the acquisition of either enantiomer of the sparteine surrogate **26** on gram-scale in >99:1 er. Due to the relatively high cost of the initial starting material used by O'Brien, ethyl-2-pyridyl acetate **364**, the first objective was to develop a synthesis of pyridine ester **364** using cheaper starting materials. In 1953, Goldberg *et al*. published a synthesis of **364** that involved the treatment of 2-picoline **402** with phenyllithium followed by subsequent trapping with diethyl carbonate (Scheme 5.17).[234] However, lengthy reaction times and awkward procedures were required and **364** was obtained in only 44% yield.



402 **364** 44%

Scheme 5.17

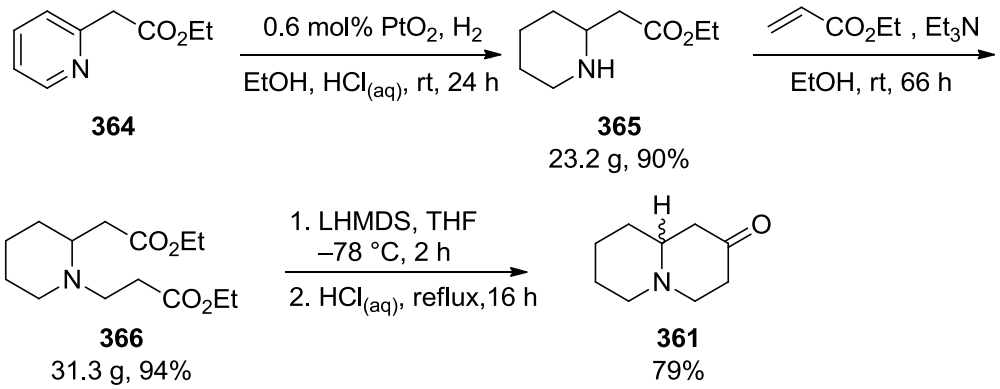
Building on work by Liu,[235] optimisation studies on the synthesis of **364** were focussed around replacing phenyllithium with LDA, resulting in a simplified procedure (Scheme 5.18). Lithiation of 2-picoline **402** with 2.05 eq. of LDA at –78 °C in the presence of diethyl carbonate gave **364** in 89% yield on a multi-gram scale after distillation. In this reaction 14.7 g of **364** was produced. 2 eq. of LDA are required due to **364** being deprotonated in preference to 2-picoloine **402** once it has formed.



402 **364** 89%, 14.7 g

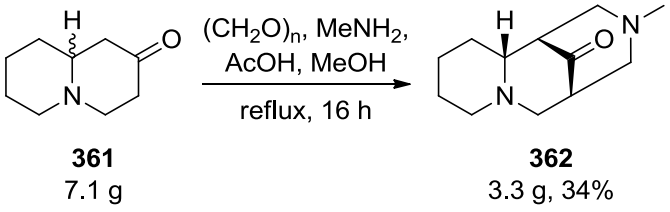
Scheme 5.18

With a simple, scalable synthesis of **364** developed, attention was turned to the synthesis of bicyclic ketone **361** using the method previously reported by O'Brien and co-workers.[213] Starting with 25 g (150 mmol) of ethyl-2-pyridyl acetate **364**, hydrogenation in the presence of Adams's catalyst gave piperidine **365** in 90% yield (pure by ^{1}H NMR spectroscopy) (Scheme 5.19). Subsequent treatment with ethyl acrylate in the presence of triethylamine gave 31.3 g of di-ester **366** in 94% yield. Dieckmann condensation effected by LHMDS followed by decarboxylation in aqueous acid gave bicyclic ketone **361** in 79% yield after distillation. Overall, 7.2 g of **361** was obtained, without the need for chromatography, in 59% yield over four steps from the cheap, commercially available starting material 2-picoline **402**.



Scheme 5.19

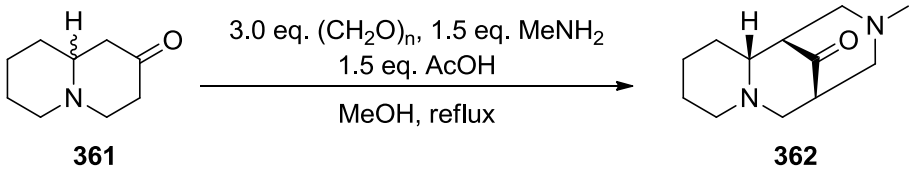
The next challenge was optimisation of the double Mannich reaction to generate bispidone **362** from bicyclic ketone **361**. Scheiber and Nemes originally reported a 58% yield for this reaction,[209] as did workers in the O'Brien group[213] using Beak's modified conditions for the preparation of bispidines.[46] However, in this study, scale-up to multi-gram quantities resulted in the yield dropping significantly (Scheme 5.20). Starting with 7.1 g of bicyclic ketone **361**, bispidone **362** was isolated in a disappointing 34% yield.



Scheme 5.20

The low yield was attributed to problems with purification by distillation of the high boiling product **362** on scale. In fact, ^{1}H NMR spectroscopy of the solid black residue remaining after distillation showed that significant amounts of **362** remained. In an attempt to remedy this situation, different methods of purification were attempted. Purification by forming a crystalline acid salt of **362** met with failure. A range of acids were trialled but crystalline solids failed to form in all cases. An attempt at purification by flash column chromatography was prohibitively labour intensive and the yield was still low.

In order to develop a cleaner reaction that might allow for easier purification of bispidone **362**, optimisation of the double Mannich reaction was investigated. Standard reaction conditions were applied (1.5 eq. of methylamine and AcOH, 3.0 eq. of paraformaldehyde in MeOH at reflux) and the reaction was monitored by GC (Scheme 5.21 and Figure 5.3). In Figure 5.3 reaction progress is depicted with the relative proportion of ketone **361** shown in blue and bispidone **362** in red. It was observed that half of the ketone **362** was consumed by the first time point, within the first 10 min. However, the reaction stalled at this point and took over 24 h (not shown) for complete consumption of **362**. Importantly, the relative proportion of bispidone **361** decreased after 4 h as the amount of by-products (not shown) increased.



361 **362**

Scheme 5.21

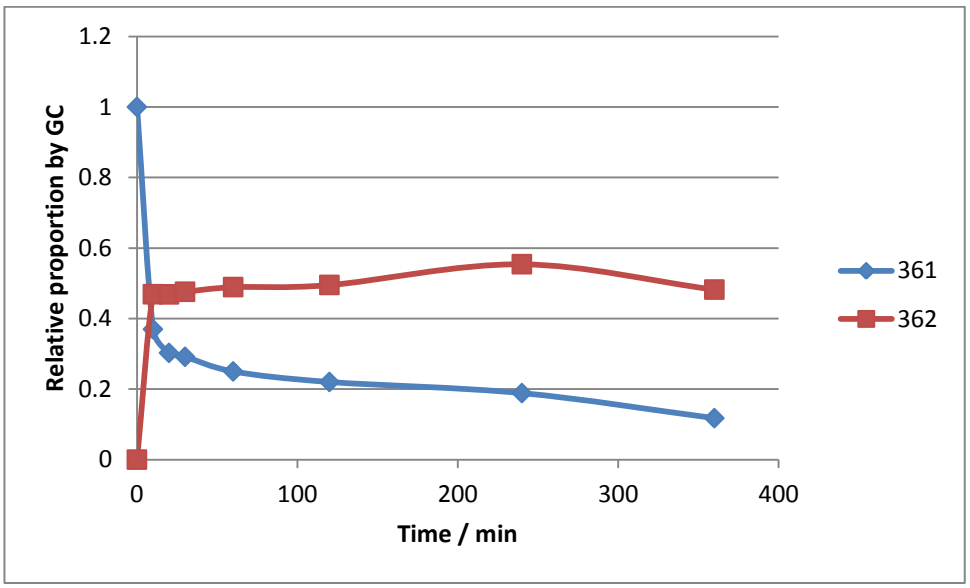
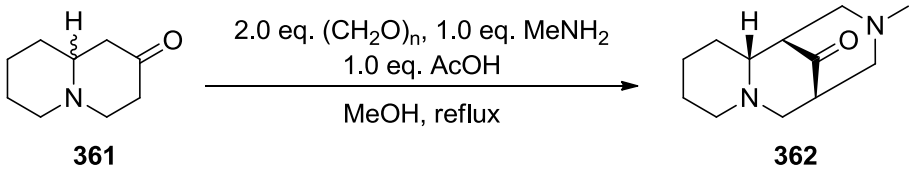


Figure 5.3 GC monitoring of the double Mannich reaction of **361** to **362**

A second experiment using a stoichiometric quantity of the reagents (1.0 eq. of methylamine and AcOH, 2.0 eq. of paraformaldehyde in MeOH at reflux) was studied using GC to investigate the hypothesis that excess reagents were adversely affecting the reaction (Scheme 5.22 and Figure 5.4). Similarly, it was observed that half of **361** was consumed within 10 min and that the reaction stalled, requiring 24 h for complete consumption of **362**. It is unknown why the formation of bispidone **362** is fast at the outset and then orders of magnitude slower thereafter. However, product inhibition of the reaction could have occurred.



361 **362**

Scheme 5.22

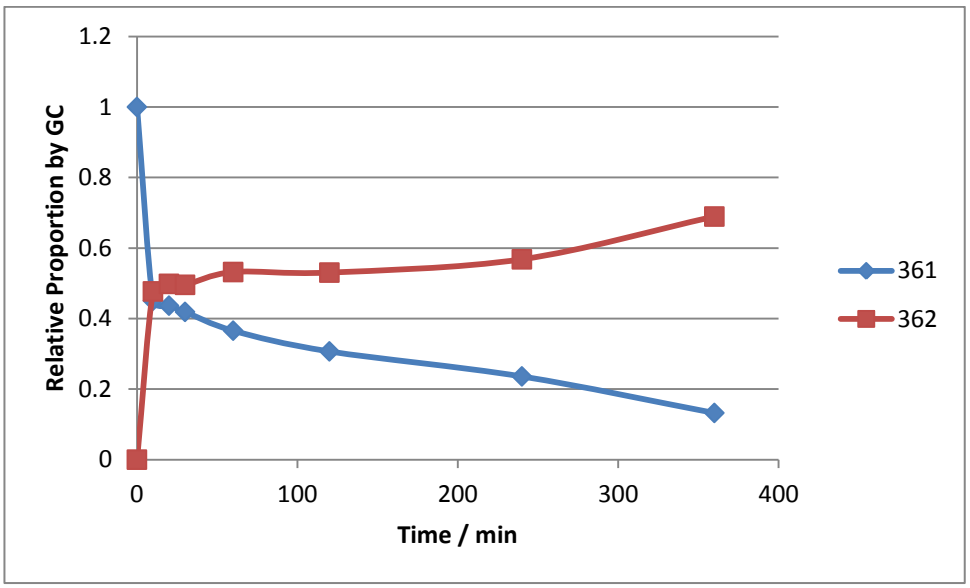
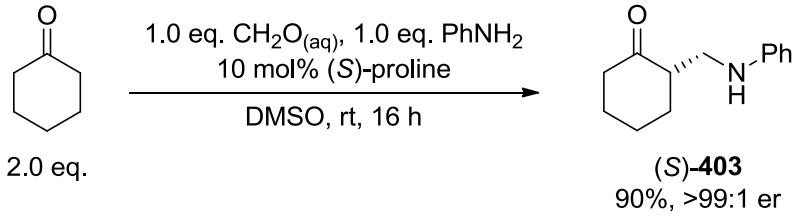


Figure 5.4 GC monitoring of the double Mannich reaction of **361** to **362**

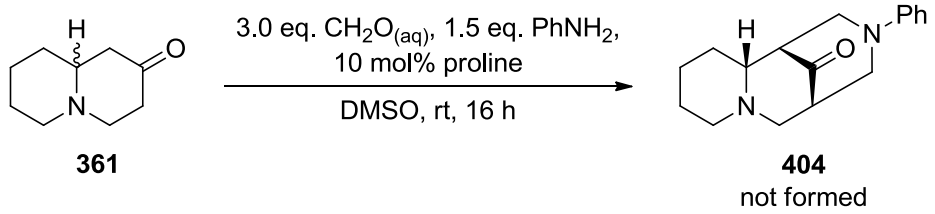
This study of the conversion of ketone **361** into bispidone **362** failed to provide a method for the generation of an easily separable crude mixture of **362** on scale. Despite this, it was observed that performing the double Mannich reaction using only 1.0 eq. of the reagents gave a marginally cleaner reaction profile than the use of Beak's conditions.

In an effort to improve the yield and operational simplicity of the double Mannich reaction, alternative conditions for the conversion of ketone **361** into bispidone **362** were sought. In 2004, Cordova reported the (*S*)-proline-catalysed enantioselective Mannich reaction between simple ketones, formaldehyde and aryl amines.[236] In one example, reaction using cyclohexanone, formaldehyde and aniline gave the *β*-amino ketone (*S*)-**403** in 90% yield with >99:1 er (Scheme 5.23).



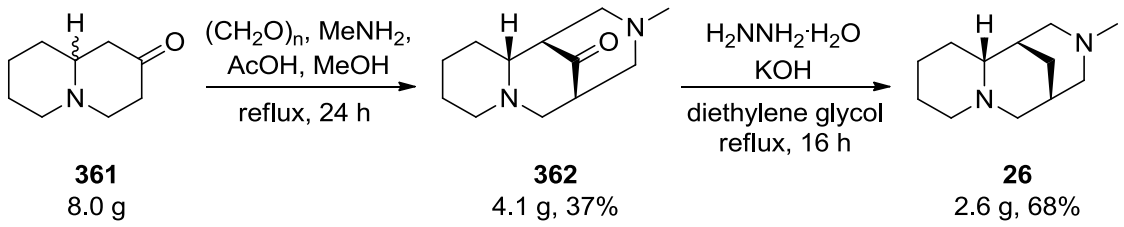
Scheme 5.23

It was envisaged that this type of methodology could be applied to the double Mannich reaction of bicyclic ketone **361** by altering the stoichiometry of the reaction. Additionally, it was foreseeable that the mild nature of this reaction may also have enabled the use of an enantioenriched bicyclic ketone **361** without racemisation occurring under the reaction conditions. To this end, bicyclic ketone **361** was subjected to modified Mannich conditions (Scheme 5.24). Disappointingly, a complex mixture of products was observed, with no bispidone **404** formed.



Scheme 5.24

With the failure of the organocatalytic double Mannich reaction, the synthesis of several grams of the racemic sparteine surrogate **26** was completed by resorting to the slightly modified acidic double Mannich conditions. Disappointingly, no real improvement in yield was seen on scale-up. Double Mannich reaction on 8.0 g of ketone **361** resulted in bispidone **362** being isolated in 37% yield (Scheme 5.25). Subsequent Wolff-Kishner reduction using hydrazine monohydrate and KOH proceeded in 68% yield completing the synthesis of **26**.



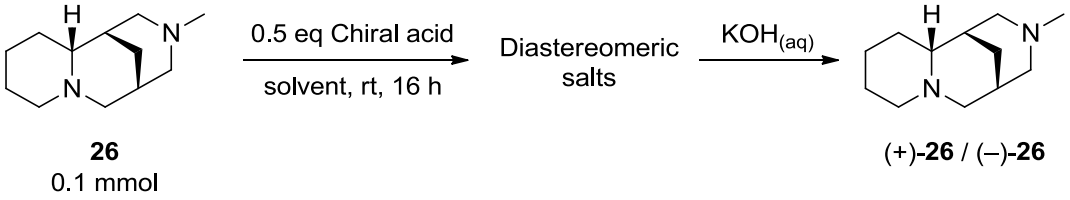
Scheme 5.25

To conclude, an optimised synthesis of intermediate bicyclic ketone **361** has been developed allowing access to multi-gram quantities of **361** in 59% yield over four steps from cheap materials. Attempts to improve the yield of isolated bispidone **362** obtained from the subsequent double Mannich reaction were less successful. Nevertheless, several grams of racemic **26** were synthesised in preparation for investigation into the classical resolution of the sparteine surrogate **26**.

5.2.2 Classical Resolution of the Sparteine Surrogate

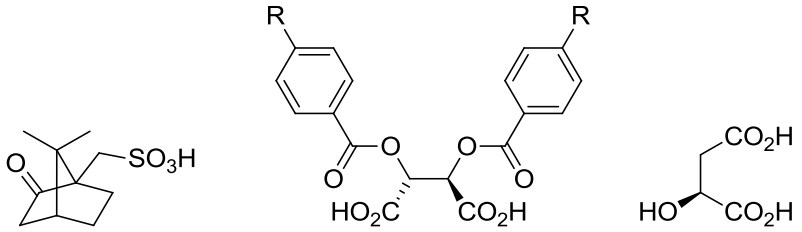
Previous work on the resolution of **26** within the O'Brien group used ^{1}H NMR spectroscopy in the presence of a chiral shift reagent to ascertain the enantiomeric ratio of the sparteine surrogate generated from the diastereomeric salts.[214] A more accurate and operationally simple procedure was desired. To this end, a CSP-GC method for the determination of the enantiomeric ratio of **26** was developed by the analytical team at AstraZeneca.[237] The CSP-GC method developed utilised a Cyclodex B column at oven temperatures of 110 °C to 140 °C (ramp rate 1 °C min^{-1}).

With an improved analytical method in hand, the resolution of **26** using chiral acids was re-investigated. Previous attempts in the O'Brien group had used 1.0 eq. of the chiral resolving agents (**367-371**) and only one solvent, acetone (see Table 5.1).[214] It was felt that the use of only one solvent limited the chance of obtaining crystalline salts, and that the use of greater than 0.5 eq. of the resolving agent could result in a poor resolution of **26**. To remedy these limitations, an initial screen of four resolving agents **367-370** (0.5 eq.) with 19 mg (0.1 mmol) of racemic sparteine surrogate **26** in four different solvents (acetone, MeCN, IPA and MTBE) was undertaken. The results are presented in Table 5.2 with yields of the diastereomeric salts given. The diastereomeric salts were treated with $KOH_{(aq)}$ to release sparteine surrogate **26**, the enantiomeric ratio of which was determined by CSP-GC. The absolute stereochemistry of the major enantiomer was determined by comparison with a pure sample of (+)-sparteine surrogate (+)-**26** synthesised from (–)-cytisine.



26
0.1 mmol

(+)-**26** / (–)-**26**



(+)-**367**

(–)-**368**: R = H
(–)-**369**: R = Me

(*S*)-**370**

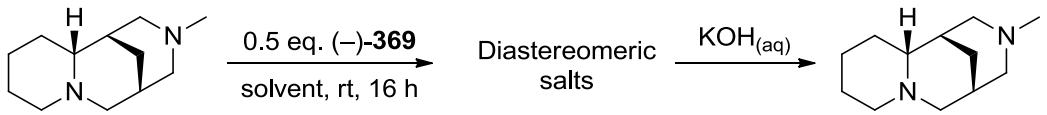
		Resolving agent			
Entry	**Solvent**	(+)-**367**	(–)-**368**	(–)-**369**	(*S*)-**370**
1	Acetone	-	20%[a], 73:27 er[b]	32%, 28:72 er	-
2	MeCN	-	-	12%, 2:98 er	-
3	IPA	-	-	-	-
4	MTBE	43%, 50:50 er	26%, 64:36 er	49%, 45:55 er	-

[a] Yield of the diastereomeric salts. [b] Er of the free base determined by CSP-GC [(+)-**26**:(–)-**26**].

Table 5.2 Classical resolution of racemic sparteine surrogate **26**

Whereas the successful resolution of racemic sparteine using (+)-camphorsulfonic acid (+)-**367** in acetone was reported by Leonard,[215] the use of (+)-**367** for the resolution of sparteine surrogate **26** was a resounding failure (entries 1–4). Of the four solvents used, only resolution in MTBE gave any crystals (43%) and the re-isolated surrogate **26** was determined to be racemic (entry 4). Use of (*S*)-malic acid (*S*)-**370** failed to give any isolatable solid (entries 1-4). Solids were formed in several solvents using tartaric acid derivatives (–)-**368** and (–)-**369**. It is noteworthy that the use of 0.5 eq. of (–)-*O*,*O*'-di-*p*-toluoyl-L-tartaric acid (–)-**369** in acetone gave a 32% yield of a diastereomeric salt which gave (–)-**26** in 72:28 er (entry 1). Previous work using 1.0 eq. of (–)-**369** in acetone gave the salt in 69% yield but the resulting diamine **26** was racemic (see Table 5.1). This observation lends weight to the hypothesis that the use of >0.5 eq. of the resolving agent is detrimental to the enantiomeric ratio of the final diamine.

The standout result from this initial small screen of conditions was the formation of a diastereomeric salt between **26** and (–)-**369** with the salt being isolated in 12% yield (entry 2). After release of the diamine using aqueous base, (–)-**26** was obtained in 98:2 er. Although the yield was low, the er of (–)-**26** was excellent (98:2 er). Encouraged by this result, and the fact that isolatable solids were formed in three of the four cases with (–)-**369**, a wide solvent screen using (–)-**369** as the resolving agent was initiated with a view to improving the yield, whilst maintaining the high er. The results are shown in Table 5.3, with the yields of the diastereomeric salts given along with the enantiomeric ratio, determined by CSP-GC of the reformed (–)-sparteine surrogate (–)-**26**.



26
0.1 mmol

(–)-**26**

Entry	Solvent	Yield (%)[a]	Er[b]
1	MeOAc	33	77:23
2	EtOAc	40	80:20
3	^{n}PrOAc	35	77:23
4	^{i}PrOAc	33	69:31
5	BuOAc	38	66:34
6	MEK	–	–
7	MIBK	–	–
8	Et_2O	25	63:27
9	THF	31	81:19
10	2-Me THF	25	67:33
11	CPME	28	74:26
12	Toluene	40	57:43
13	Cyclohexane	–	–
14	BuCN	–	–
15	PhCN	–	–
16	19:1 MeCN:H_2O	–	–
17	9:1 MeCN:H_2O	–	–
18	4:1 MeCN:H_2O	–	–
19	4:1 MeCN:acetone	23	97:3
20	1:1 MeCN:acetone	23	90:10

[a] Yield of the diastereomeric salts. [b] Er of the free base determined by CSP-GC [(–)-**26**:(+)-**26**].

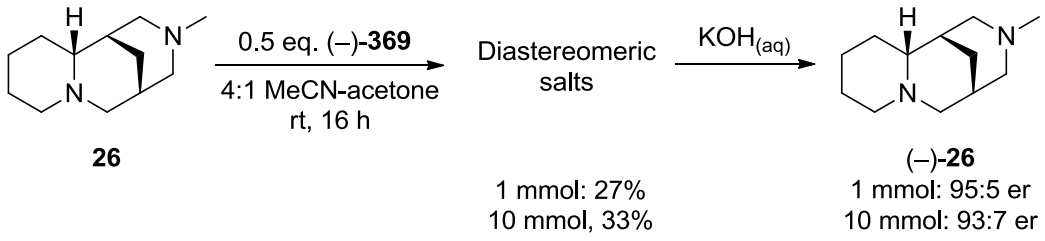
Table 5.3 Solvent screen for the resolution of **26** with (–)-**369**

Fifteen solvents were initially assessed for their ability to facilitate the resolution of **26** with (–)-**369** (Table 5.3, entries 1-15). The solvents chosen principally composed of esters (entries 1-5), ketones (entries 6 and 7), ethers (entries 8-11) and nitriles (entries 14 and 15). Of the 15 solvents tested, diastereomeric salts were isolated in ten cases, with yields ranging from 25% (entry 10) to 40% (entries 2 and 12). Disappointingly, the enantiomeric ratios of (–)-**26** were only modest, ranging from 57:43 er (entry 12) to

80:20 er (entry 2). Although yields were improved over the resolution in MeCN (12%, see Table 5.2, entry 2) the enantiomeric ratios were greatly reduced, being of no practical benefit for the synthesis of (–)-**26** for use in asymmetric lithiation chemistries.

Attention was then focussed on improving the yield by using a co-solvent with MeCN (entries 16-20). The addition of water resulted in failure to form crystals (entries 16-18). More promisingly, the use of a 4:1 mixture of MeCN-acetone (entry 19) gave the diastereomeric salts in an improved 23% yield and the (–)-sparteine surrogate (–)-**26** in 97:3 er, a comparable level of enantioenrichment as seen with neat MeCN. Increasing the amount of co-solvent to a 1:1 mixture of MeCN-acetone also resulted in the diastereomeric salts being obtained in 23% yield, although the enantiomeric ratio of (–)-**26** dropped to 90:10 er (entry 20).

The use of a small amount of acetone as a co-solvent resulted in an increase in yield, without significant loss of enantioenrichment. It was felt that this system could be used to access significant quantities of (–)-**26** in high er. To demonstrate the suitability of (–)-acid (–)-**369** for the resolution of **26** in 4:1 MeCN-acetone, scale-up of the procedure was undertaken (Scheme 5.26). When the resolution was performed using 1.0 mmol of **26** (the volume of solvent was scaled equally), the diastereomeric salts were isolated in 27% yield, and free diamine (–)-**26** in 95:5 er. On a 10 mmol scale, resolution gave the salts in 33% yield and free diamine (–)-**26** in 93:7 er. Unfortunately, scale-up of this procedure led to less selective resolution, with an increase in yield of the isolated salt and a related drop in enantioenrichment.



Scheme 5.26 Resolution of **26** with (–)-**369** in 4:1 MeCN-acetone

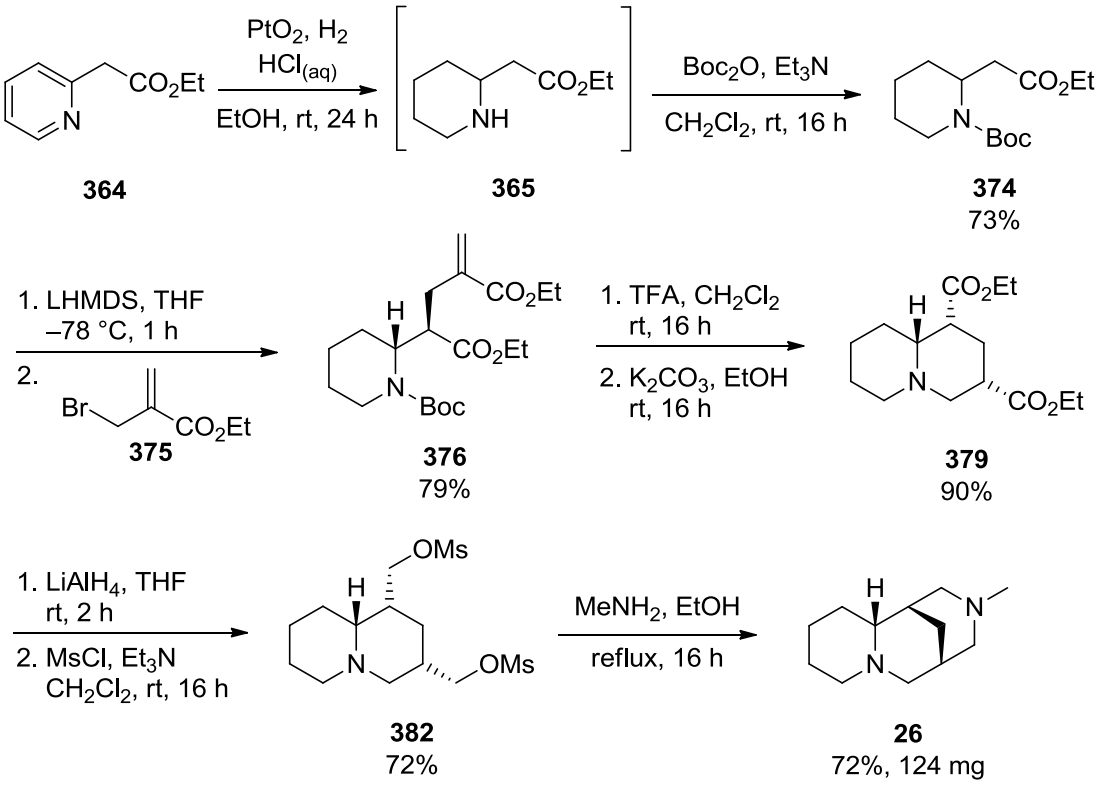
In summary, the resolution of racemic sparteine surrogate **26** was revisited with a moderate level of success. After a small screen of resolving agents (**367**-**370**) and a wide solvent screen, it was found that, on a small scale (0.1 mmol), **26** could be

resolved using (–)-*O,O*'-di-*p*-toluoyl-L-tartaric acid (–)-**369** in 4:1 MeCN-acetone, producing enantioenriched (–)-**26** in 97:3 er (23% yield of the diastereomeric salt).

The reduction in enantiomeric ratio with increasing scale was disappointing. Nevertheless, this procedure serves as a good preliminary result, and future work may be able to improve the resolution process.

5.3 Development of a Scalable Synthesis of Enantiopure (–)-Sparteine Surrogate

The route to racemic sparteine surrogate **26** recently developed by Canipa and O'Brien[220] was thought to be a promising starting point for the synthesis of enantiopure (–)-sparteine surrogate (–)-**26**. The synthetic route is summarised in Scheme 5.27.



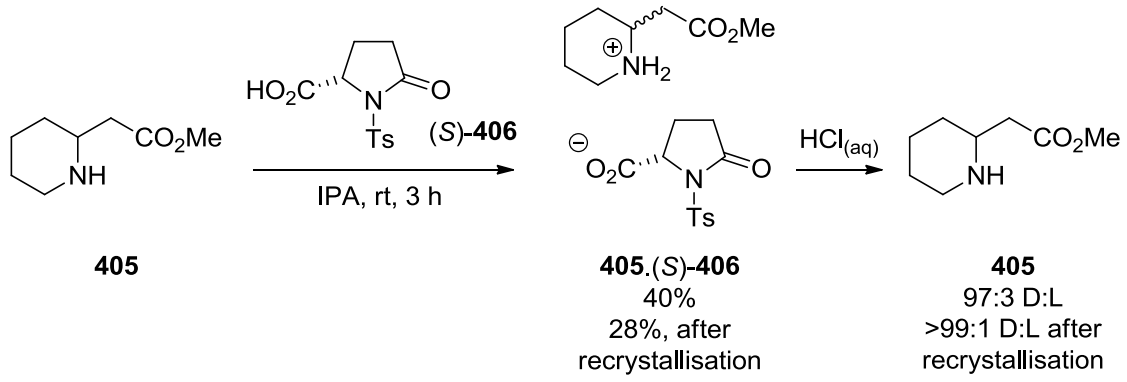
Scheme 5.27 O'Brien and Canipa's synthesis of racemic sparteine surrogate **26**

Due to several promising factors, this route was chosen for further investigation with a view to developing a high yielding, scalable and operationally simple synthesis of (–)-**26**. The major advantage of this route was that the two key steps, the alkylation of **374** with LHMDS and bromoacrylate **375** to give di-ester **376**, and the subsequent intramolecular conjugate addition to **379**, proceeded with full diastereoselectivity. Additionally, all steps are operationally straightforward and generally high yielding, with racemic sparteine surrogate **26** being isolated in 27% overall yield. The main drawback of this route is that it involved many purification steps, with compounds **374**, **376**, **379** and **382** isolated by flash column chromatography, and the sparteine surrogate **26** isolated by vacuum distillation. It was envisaged that this synthesis could be streamlined by removing some of the purification steps.

5.3.1. Synthesis of an Enantiopure *β*-Amino Ester Intermediate by Resolution

The first challenge in the synthesis enantiopure sparteine surrogate (–)-**26** was the generation of an enantiopure *β*-amino ester such as **365** or the *N*-Boc protected *β*-amino ester **374**. The preparation of such enantioenriched homopipecolinic acid derivatives has been reported through the homologation of pipecolic esters,[238,239] the conjugate addition of chiral amine derivatives to *α*,*β*-unsaturated esters and subsequent cyclisation,[240-243] S_N2 displacement–cyclisation of *α*,*β*-unsaturated esters using a chiral amine,[45,225,244] hydrogenation of enamide esters using a chiral auxiliary[245,246] and the diastereoselective allylation of a chiral iminium ion.[226] Additionally, classical resolution of a piperidinyl ethanol derivative and subsequent oxidation has been described.[223,247]

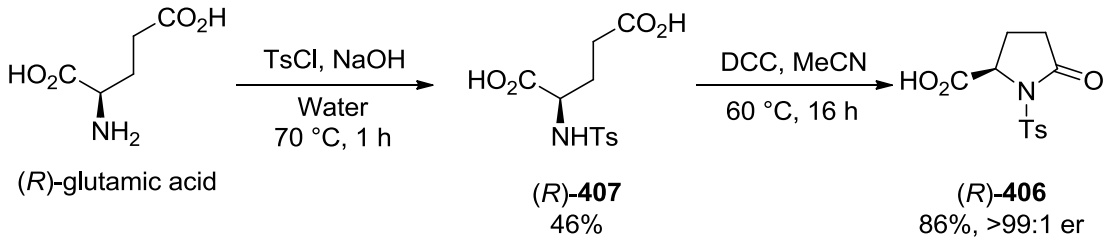
Although preliminary work into the resolution of *β*-amino ester **365** was undertaken within the O'Brien group[220] (see Scheme 5.13), a procedure that gave greater levels of er was desired. In 2009, workers at Solvay reported the resolution of cyclic *β*-amino methyl ester **405** using carboxylic acid (*S*)-**406** in IPA (Scheme 5.28).[248] Diastereomeric salt **405**.(*S*)-**406** was isolated in 40% yield and release of the amine with $HCl_{(aq)}$ gave **405** in a 97:3 ratio of D:L isomers. Recrystallisation of the salt from IPA gave **405**.(*S*)-**406** in 28% overall yield and subsequently gave **405** in >99:1 D:L.



Scheme 5.28

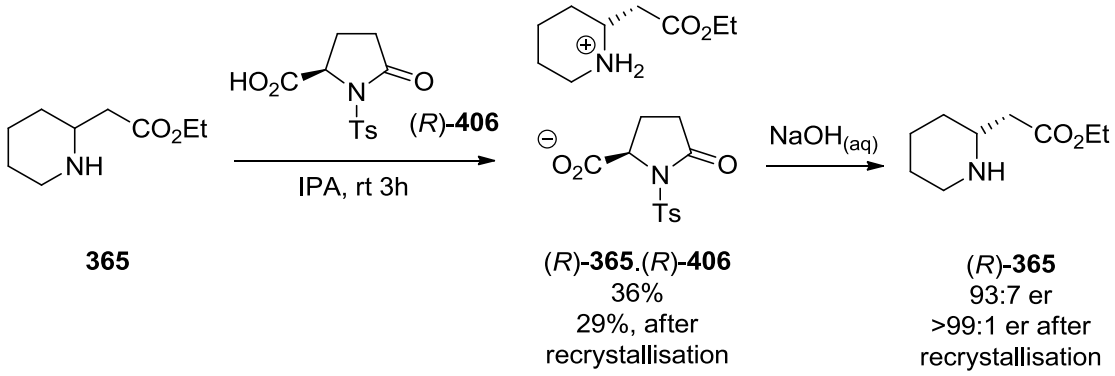
Using this work by researchers at Solvay, the resolution of ethyl ester analogue **365** was attempted. First, the synthesis of chiral acid (*R*)-**406** was accomplished in two steps from unnatural (*R*)-glutamic acid (Scheme 5.29). Tosylation of (*R*)-glutamic acid proceeded in 46% yield to give (*R*)-**407**,[249] followed by DCC facilitated intramolecular amidation to give tosyl pyroglutamic acid (*R*)-**406** in 86% yield and 40% yield over two

steps. Resolving agent (*R*)-**406** was shown to be enantiopure by CSP-HPLC by comparison of the methyl ester derivative with a racemic sample.



Scheme 5.29

Next, the resolution of *β*-amino ester **365** was performed (Scheme 5.30). Diastereomeric salt formation between **365** and chiral acid (*R*)-**406** at 5 °C was successful, with the salt (*R*)-**365**.(*R*)-**406** being isolated in 36% yield. After derivatisation, (*R*)-**365** was found to have 93:7 er. Recrystallisation of the salt from IPA resulted in (*R*)-**365**.(*R*)-**406** being isolated in an overall 29% yield; after derivatisation (*R*)-**365** was shown to have 99:1 er.



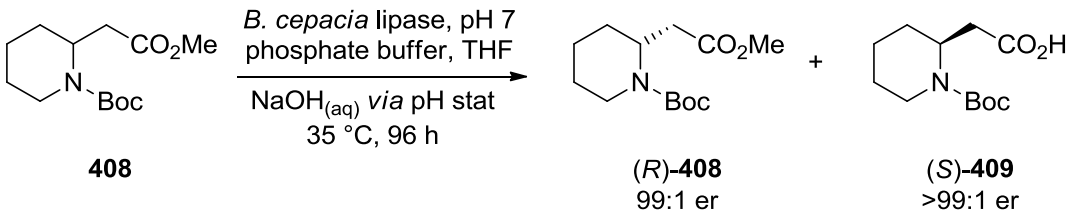
Scheme 5.30

The enantiomeric ratio was determined using a laborious process. A small portion of the salt (*R*)-**365**.(*R*)-**406** was treated with $NaOH_{(aq)}$ to release (*R*)-**365**. Then, Boc protection under standard conditions gave (*R*)-**374** which was analysed by CSP-HPLC. The absolute configuration of (*R*)-**374** was determined by comparison of the optical rotation ($[\alpha]_D$ +7.5 (*c* 1.0 in $CHCl_3$)) with a known sample ($[\alpha]_D$ +7.4 (*c* 1.0 in $CHCl_3$)).[225]

The resolution process of **365** was comparable with that reported for the methyl ester analogue **405**, giving enantiopure ester (*R*)-**365** in 29% yield after one recrystallisation from IPA. Although this material was of sufficient quality for the synthesis of enantiopure sparteine surrogate (–)-**26** there were several prohibitive drawbacks. The

yield of (*R*)-**365**.(*R*)-**406** was relatively low (29%) and the procedure was laborious, requiring the synthesis of the resolving agent (*R*)-**406** (from the relatively expensive unnatural (*R*)-glutamic acid). Additionally, recrystallisation of the diastereomeric salt and a lengthy procedure to determine the enantiomeric excess of the resolved cyclic *β*-amino ester (*R*)-**365** were required. An alternative, simpler resolution procedure for acquiring an enantiopure cyclic *β*-amino ester was desired and attention was turned to enzymatic methods.

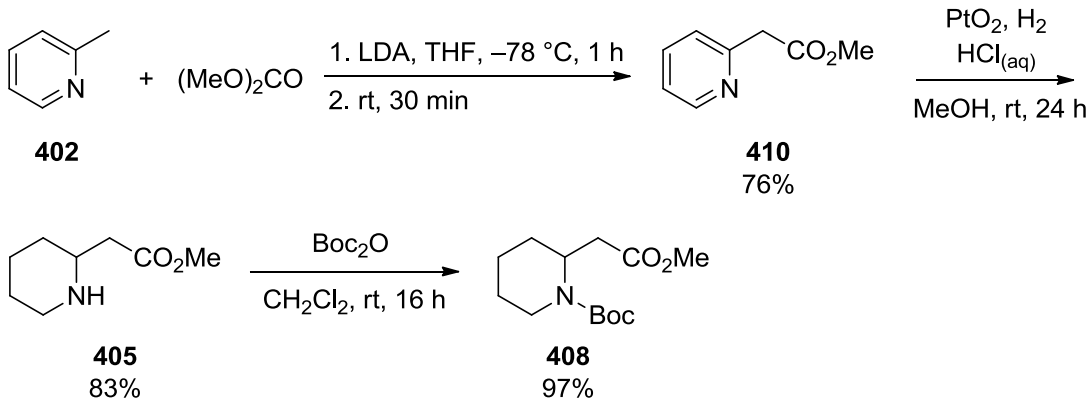
Enzymatic kinetic resolution of homopipecolinic esters through selective hydrolysis of the ester functionality using pig liver esterase has been reported. However, the er of both the ester and acid products was low.[250,251] Recently, a highly enantioselective lipase-catalysed transesterification procedure was reported, although flash column chromatography was required to separate the resulting esters.[252] Lipases are commonly used in the kinetic resolution of racemates[253] and, in 2004, Pousset and co-workers reported the enzymatic kinetic resolution of *N*-Boc protected methyl ester **408** using a lipase from *Burkholderia cepacia*.[254] Selective hydrolysis of (*S*)-**408** in phosphate buffer (pH 7.0) and THF was performed at 35 °C for 96 h, with the pH maintained through addition of $NaOH_{(aq)}$ using a pH stat (Scheme 5.31). Residual *β*-amino ester (*R*)-**408** was recovered with 99:1 er and acid (*S*)-**409** was formed in >99:1 er. Although no yields were given, the high levels of er in this reaction were manifested by a high conversion. In fact, the E factor (a measure of the selectivity of the enzyme)[253,255,256] was >100 for this reaction. The products were isolated simply by removal of the enzyme by filtration through Celite® followed by a simple acid/base workup gave ester (*R*)-**408** and acid (*S*)-**409**.



Scheme 5.31

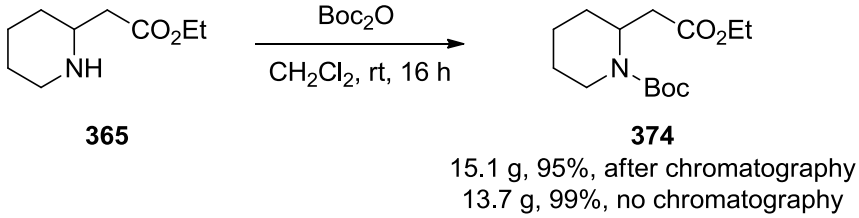
It was envisaged that this enzymatic resolution procedure could be used to access significant quantities of a highly enantioenriched *β*-amino methyl ester or ethyl ester (*R*)-**408** or (*R*)-**374**. Synthesis of requisite the *N*-Boc methyl ester **408** was

accomplished on a multi-gram scale from 2-picoline **402** (Scheme 5.32). In an analogous fashion to the reaction already detailed (see Scheme 5.18), methyl 2-piperidyl acetate **410** was synthesised in 76% yield by deprotonation of **402** and trapping with dimethyl carbonate. Subsequent hydrogenation in the presence of platinum(IV) oxide in MeOH gave piperidine **405** in 83% yield. Finally *N*-Boc protection was accomplished using Boc_2O giving **408** in 97% after chromatography.



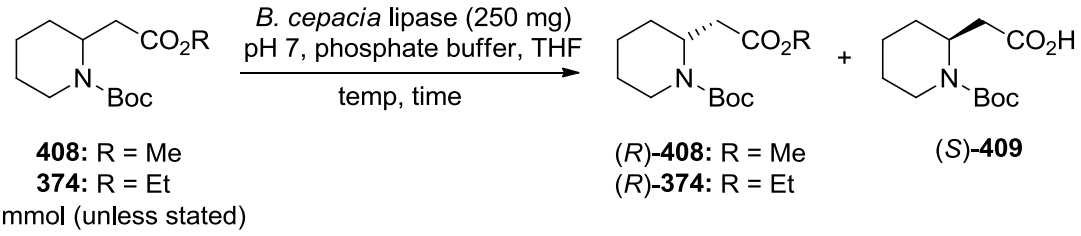
Scheme 5.32

Similarly, *N*-Boc ethyl ester **374** was synthesised by Boc protection of piperidine **365** (synthesis detailed in Scheme 5.19) giving *N*-Boc ester **374** in 95% yield after chromatography (Scheme 5.33). It was found that the need for chromatography could be eliminated by using 1.0 eq. of Boc_2O, with **374** being obtained in 99% yield on >10 g scale.



Scheme 5.33

With significant amounts of starting material in hand, a study into the enzymatic resolution of racemic cyclic *N*-Boc esters **408** and **374** was undertaken with a view to generating enantiopure cyclic *N*-Boc esters. The results are presented in Table 5.4. Due to the unavailability of a pH stat, the investigation was conducted without the use of such an instrument.



408: R = Me
374: R = Et
1 mmol (unless stated)

(*R*)-**408:** R = Me
(*R*)-**374:** R = Et

(*S*)-**409**

Entry	Substrate	Temp / °C	Time / h	(*R*)-408 / (*R*)-374		(*S*)-409		E[c]
				Yield (%)	er[a]	Yield (%)	er[b]	
1	**408**	rt	48	41	88:12	42	87:13	16
2	**408**	35	48	47	97:3	40	>99:1	>100
3	**408**	50	28	45	90:10	39	96:4	29
4	**374**	rt	24	47	97:3	44	98:2	>100
5	**374**	rt	48	42	>99:1	46	92:8	>100
6	**374**	35	24	42	>99:1	42	96:4	>100
7	**374**	35	72[d]	42	>99:1	44	95:5	>100
8	**374**	35	48[e]	45	>99:1	48	96:4	>100
9	**374**	35	64[f]	46	>99:1	44	96:4	>100

[a] Er determined by CSP-HPLC (*R*)-**408**/**374**:(*S*)-**408**/**374**. [b] Er determined by CSP-HPLC of methyl ester derivative (*S*)-**408**, (*S*)-**408**:(*R*)-**408**. [c] $E = \ln[ee_s(1- ee_p)]/(ee_s + ee_p)/\ln[ee_s(1 + ee_s)]/(ee_p + ee_s)$.[254,255] [d] Half the amount of lipase (125 mg). [e] 10 mmol scale, 2.5 g lipase. [f] 50 mmol scale, 12.5 g lipase.

Table 5.4 Enzymatic resolution of cyclic *N*-Boc esters **408** and **374**

When enzymatic resolution of 1.0 mmol of methyl ester **408** was performed at room temperature in 8:1 buffered water-THF, using 250 mg of lipase for 48 h, residual ester (*R*)-**408** was isolated in 41% yield and 88:12 er and the acid (*S*)-**409** was isolated in 42% yield and 87:13 er (Table 5.4, entry 1). The E factor[254,255] for this reaction, a measure of the selectivity of the enzyme under specific conditions, was only 16. The er of ester (*R*)-**408** was measured directly by CSP-HPLC, whereas acid (*S*)-**409** had to be converted into the corresponding methyl ester (*S*)-**408** using trimethylsilyldiazomethane before CSP-HPLC analysis could be performed.

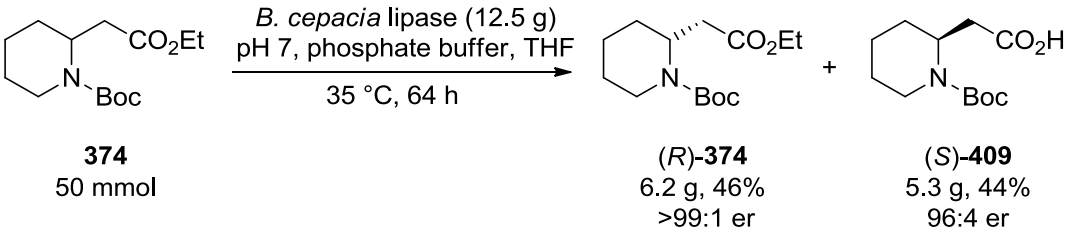
Next, the resolution was repeated at 35 °C and 50 °C (entries 2 and 3) to assess the effect of temperature on the selectivity of the resolution. When performed at 35 °C (the temperature at which Pousset and co-workers ran resolutions[248]) for 48 h, residual ester (*R*)-**408** was isolated in 47% yield and 97:3 er and acid (*S*)-**409** was isolated in 40% yield and >99:1 er, with the E factor being >100. Resolution of methyl ester **408** was

much more selective at 35 °C than at room temperature (entries 1 and 2). The results obtained when the resolution was run at 35 °C for 48 h indicate that the resolution was not left for sufficient time to generate enantiopure ester (*R*)-**408** (Pousset left a similar reaction for 96 h to reach completion). Although the use of a pH stat was not essential for the resolution, it would have the advantage of allowing the user to know when the resolution reached completion (by monitoring the amount of NaOH that has been added to the mixture). At 50 °C (entry 3), resolution of **408** was much less selective (E = 29).

Then, enzymatic resolution of the preferred substrate, ethyl ester **374** was investigated. Resolution at room temperature, for 24 h (entry 4), was highly selective (E >100) resulting in residual ethyl ester (*R*)-**374** being isolated in 47% yield and 97:3 er. The acid (*S*)-**409** was isolated in 44% yield and 98:2 er. Extending the reaction time to 48 h at room temperature (entry 5) led to enantiopure (*R*)-**374** being isolated in 42% yield (>99:1 er). Fortuitously, kinetic resolution of ethyl ester **374** was much more selective than with methyl ester **408** (entries 1 and 5), and optimisation of this result was pursued to generate an efficient process. Elevation of the temperature to 35 °C (entry 6) led to isolation of enantiopure (*R*)-**374**, in 42% yield in 24 h. The resolution of ethyl ester **374** was not only more selective than the resolution of methyl ester **408** but also faster (entries 2 and 6). The time required for complete hydrolysis of (*S*)-**374** was determined by CSP-HPLC of aliquots of the reaction mixture after filtration and work-up.

In order to increase the efficiency of the process, an attempt was made to lower the amount of lipase required. Reducing the amount of lipase by half (entry 7) increased the time to reach completion to 72 h. This time was prohibitively long. As the enzyme was relatively cheap the high enzyme loading was not an issue.

With a high yielding method for the resolution of ethyl ester **374** on a small scale established, the process was scaled up to 10 mmol (entry 8). The resolution took longer to reach completion (48 h), but nevertheless 1.2 g of enantiopure *N*-Boc ester (*R*)-**374** (>99:1 er) was isolated in 45% yield (entry 8). Scaling the process to 50 mmol, using 12.5 g of lipase resulted in 6.2 g of (*R*)-**374** being isolated in 46% yield and >99:1 er after 64 h (entry 9 and Scheme 5.34). Acid (*S*)-**409** was obtained in 44% yield, and 96:4 er. The increase in the time required for complete hydrolysis of (*S*)-**374** on increasing scale may be due to the increasing concentration of the reaction, which was changed due to the large volumes of solvent required on scale.



374
50 mmol

(*R*)-**374**
6.2 g, 46%
>99:1 er

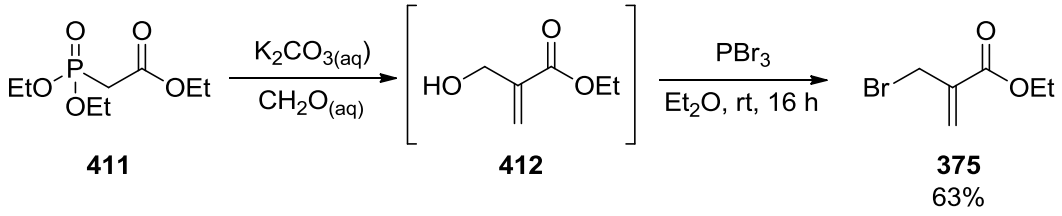
(*S*)-**409**
5.3 g, 44%
96:4 er

Scheme 5.34

In summary, the enzymatic resolution of cyclic *N*-Boc ethyl ester **374** using lipase from *Burkholderia cepacia* at 35 °C is highly selective (E >100) and high yielding. Importantly, the process is cheap, operationally simple, scalable and requires no purification of the enantioenriched ester (*R*)-**374**. The optimised method is highly suitable for the generation of significant quantities of enantiopure *N*-Boc ester (*R*)-**374** for the synthesis of the (–)-sparteine surrogate (–)-**26**. It is envisaged that if the opposite enantiomer of *N*-Boc ester (*S*)-**374** was required for the synthesis of (+)-**26**, it could be obtained by running the resolution for a shorter amount of time to generate enantiopure acid (*S*)-**409**. Subsequent esterification could then form ethyl ester (*S*)-**374**.

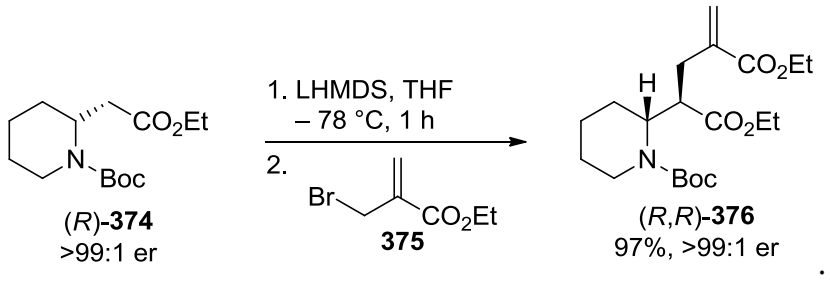
5.3.2 Synthesis of Enantiopure (–)-Sparteine Surrogate

Synthesis of enantiopure cyclic *N*-Boc ester (*R*)-**374** was achieved in three steps from ethyl-2-pyridyl acetate **364**, without the need for chromatography, in 41% overall yield. Focus was turned to improving the synthesis of (–)-sparteine surrogate (–)-**26** by further reducing the number of isolation operations needed.[220] First, synthesis of ethyl (*α*-bromomethyl)acrylate **375** was required as an electrophile for use in the diastereoselective alkylation of cyclic *N*-Boc ester (*R*)-**374**. This was accomplished using the reported procedure.[221] Treatment of triethyl phosphonoacetate **411** with aqueous K_2CO_3 and formaldehyde gave alcohol **412** which, without isolation, was treated with PBr_3 to give ethyl (*α*-bromomethyl)acrylate **375** in 63% after distillation (Scheme 5.35).



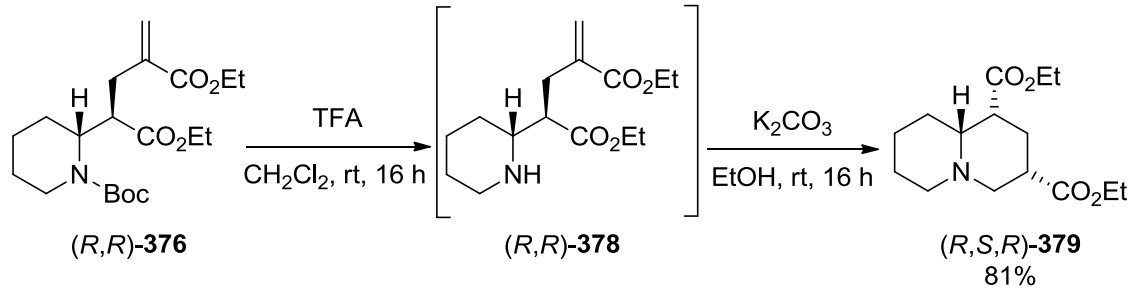
Scheme 5.35

With bromo acrylate **375** in hand, alkylation of (*R*)-**374** using O'Brien and Canipa's conditions of 1.4 eq. LHMDS in THF at –78 ° C for 1 h followed by 1.4 eq. of **375** resulted in di-ester (*R*,*R*)-**376** being formed as a single diastereomer (by ^{1}H NMR spectroscopy). Isolation by chromatography gave (*R*,*R*)-**376** in 97% yield (Scheme 5.36). The relative stereochemistry has previously been established by Canipa *via* conversion into the sparteine surrogate **26**, and explanation of the observed diastereoselectivity was shown in Scheme 5.8. Analysis of di-ester (*R*,*R*)-**376** by CSP-HPLC, in comparison with a racemic sample of **376** (prepared in an analogous fashion, full details in Chapter 6.6), showed that no epimerisation had occurred during this step.



Scheme 5.36

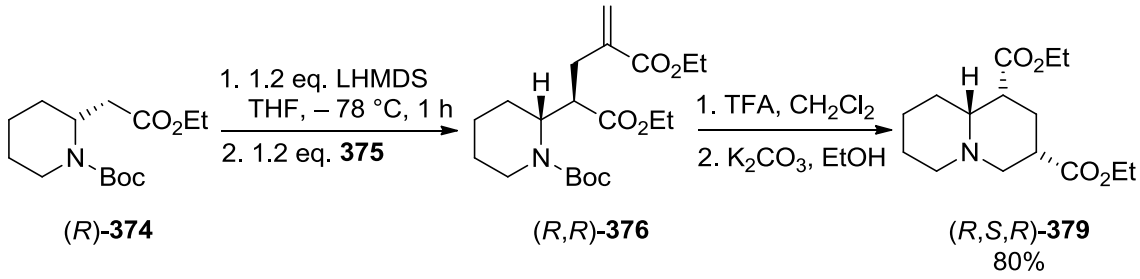
Next, annulation was performed as previously described, through *N*-Boc deprotection of di-ester (*R*,*R*)-**376** using TFA, followed by diastereoselective base-mediated intramolecular conjugate addition of the resulting secondary amine (*R*,*R*)-**378** onto the *α*,*β*-unsaturated ester. Bicyclic di-ester (*R*,*S*,*R*)-**379** was obtained in 81% yield as a single diastereomer (Scheme 5.37). The stereoselectivity was fully in line with that noted by Canipa and was rationalised using the model shown in Scheme 5.10.



(*R*,*R*)-**376** (*R*,*R*)-**378** (*R*,*S*,*R*)-**379** 81%

Scheme 5.37

It was found that the enolate alkylation, deprotection and annulation steps could be telescoped without any loss of overall yield. Alkylation of (*R*)-**374** was performed using a decreased amount (1.2 eq.) of both LHMDS and bromo acrylate **375**, followed by Boc deprotection and base-mediated intramolecular Michael addition to give di-ester (*R*,*S*,*R*)-**379** as a single diastereomer in 80% yield over the three steps (Scheme 5.38). From pyridine ester **364**, bicyclic diester (*R*,*S*,*R*)-**379** was synthesised in 33% yield and >99:1 er over six steps. Only one purification operation was required with bicyclic diester (*R*,*S*,*R*)-**379** being purified by flash column chromatography.



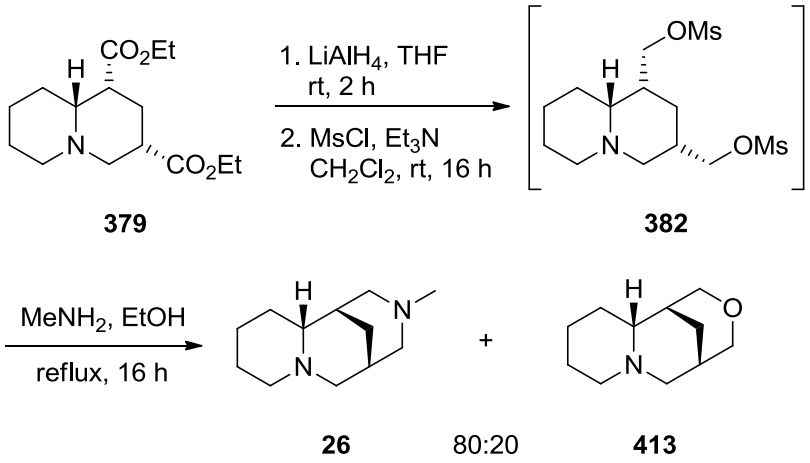
(*R*)-**374** (*R*,*R*)-**376** (*R*,*S*,*R*)-**379** 80%

Scheme 5.38

With the requisite stereocentres and functionality in place, attention was focussed on the end game. Canipa and O'Brien reduced di-ester **379** to diol **381** with $LiAlH_4$ and then formed bis mesylate **382** under standard conditions. Following isolation by flash column chromatography, double displacement of the di-mesylate **382** with methylamine in EtOH gave sparteine surrogate **26** (see Scheme 5.12). It was envisaged that it may be possible to streamline the process by telescoping the three steps, removing the need for purification of di-mesylate **382** by flash column chromatography.

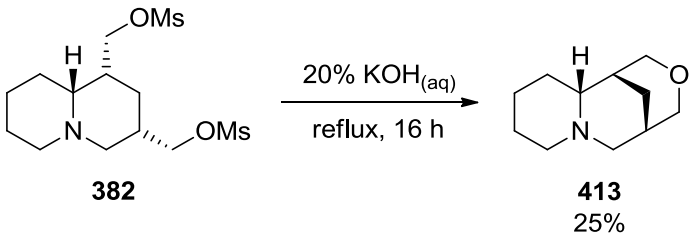
Optimisation studies were carried out on a racemic system. Reduction of di-ester **379** with $LiAlH_4$ and subsequent mesylation to di-mesylate **382** occurred without complication (Scheme 5.39). However, treatment of crude di-mesylate **382** with a

commercial solution of methylamine in EtOH (8 M) at reflux under an argon atmosphere led to an 80:20 mixture (by ^{1}H NMR spectroscopy of the crude product) of the desired sparteine surrogate **26** and tetrahydropyran **413**, whose structure was tentatively assigned by ^{1}H NMR spectroscopy and mass spectrometry.



Scheme 5.39

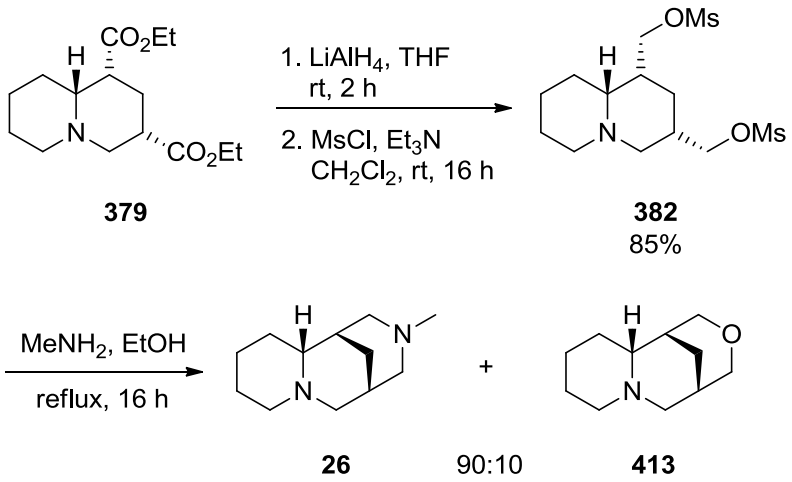
Confirmation of the structure of the by-product was accomplished by synthesising a pure sample of tetrahydropyran **413** using a related procedure (Scheme 5.40).[257] Refluxing di-mesylate **382** in 20% aqueous KOH, resulted in tetrahydropyran **413** being isolated in 25% yield, which gave an identical ^{1}H NMR spectrum to the impurity previously observed.



Scheme 5.40

It was hypothesised that tetrahydropyran **413** may have been formed during the mesylation step by initial formation of a monomesylate and intramolecular displacement. Careful analysis of the ^{1}H NMR spectrum of crude **382** indicated that this was not the case. Nevertheless, in an endeavour to eliminate the unwanted side reaction, di-mesylate **382** was purified by flash column chromatography before the double displacement was undertaken, with di-mesylate **382** being isolated cleanly in 85% yield

(Scheme 5.41). Disappointingly, treatment of pure **382** with ethanolic methylamine at reflux led to a 90:10 mixture of surrogate **26** and the tetrahydropyran by-product **413**.



Scheme 5.41

Attempts to separate the sparteine surrogate **26** from tetrahydropyran **413** by vacuum distillation or selective salt formation with (–)-*O*,*O*'-di-*p*-toluoyl-L-tartaric acid (–)-**369** were unsuccessful.

Figure 5.5 shows the ^{1}H NMR spectra of: (i) the 90:10 mixture of sparteine surrogate **26** and tetrahydropyran **413**, (ii) pure (+)-sparteine surrogate (+)-**26** derived from (–)-cytisine and (iii) pure tetrahydropyran **413**. Analysis of these three spectra showed that the sparteine surrogate **26** synthesised from di-ester **379** was contaminated with tetrahydropyran **413**. The characteristic signals of **413**, specifically the four signals for the OCH protons between 4.2-3.5 ppm are evident in Figure 5.5 (i).

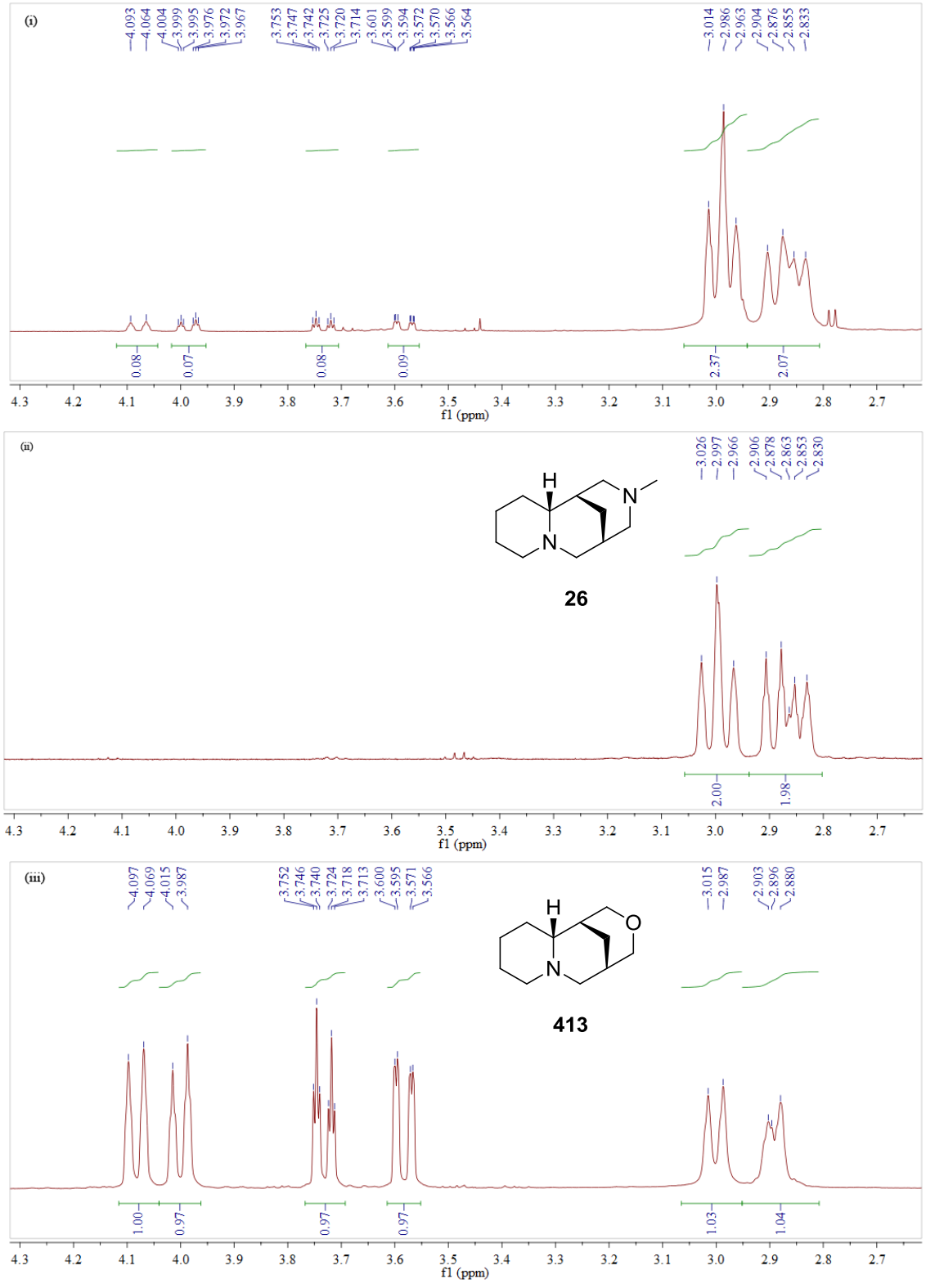
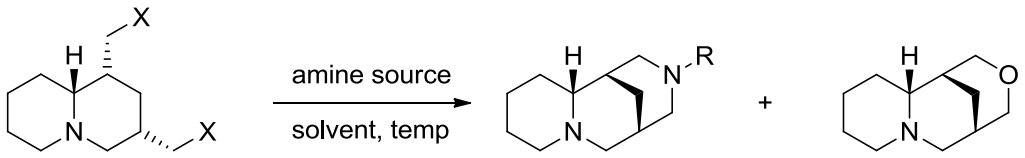


Figure 5.5 ^{1}H NMR spectra of i) 90:10 mixture of **26:413**, ii) sparteine surrogate **26** and iii) tetrahydropyran **413**

Canipa's previous work on the synthesis of the sparteine surrogate **26** by double displacement of di-mesylate **382** led to the formation of only a trace amount (2-3%) of

the tetrahydropyran by-product **413**.[220] However, in this investigation, a 90:10 to 80:20 inseparable mixture of sparteine surrogate **26** and tetrahydropyran **413** was routinely obtained when using commercial ethanolic methylamine. Previous work by Breuning on the synthesis of oxa-bispidines *via* double displacement of a di-mesylate with methylamine was also reported to proceed without issue.[228,229]

Significant effort was thus applied to the problem of tetrahydropyran formation, with efforts to change both the leaving group and amine source proving futile. The results of these investigations are briefly summarised in Table 5.5. Ratios of products were determined from analysis of the ^{1}H NMR spectra of crude reaction mixtures.



382: X = OMs
414: X = OTs
415: X = I

413

Entry	Substrate	Conditions	Outcome
1	**414**	$MeNH_2$ (8 M, EtOH), reflux, 16 h	65:35 **26**:**413**
2	**415**	$MeNH_2$ (8 M, EtOH), reflux, 16 h	95:5 **26**:**413**, unidentified by-products
3	**382**	$MeNH_2$ (8 M, EtOH), rt, 4 d	90:10 **26**:**413**
4	**382**	$MeNH_2$ (8 M, EtOH), 4Å MS, reflux, 16 h	80:20 **26**:**413**
5	**382**	$MeNH_2$ (2.0 M, THF), reflux, 16 h	No reaction
6	**382**	$MeNH_2$ (2.0 M, THF), 70 °C, pressure tube, 5 d	Decomposition
7	**382**	$MeNH_2$ (2.0 M, THF), 70 °C, EtOH, pressure tube, 16 h	No Reaction
8	**382**	$MeNH_2$ (2.0 M, MeOH), reflux, 16 h	90:10 **26**:**413**
9	**382**	$MeNH_2$.HCl (10 eq.), Et_3N (10 eq.), EtOH, reflux, 16 h	No reaction
10	**382**	NH_3 (0.5 M, dioxane), 70 °C, pressure tube, 5 d	No Reaction
11	**382**	NH_3 (7 M, MeOH), 70 °C, pressure tube, 3 d	No Reaction
12	**382**	Methoxyamine.HCl (5 eq.), Et_3N (7 eq.), THF, reflux, 16 h	No Reaction

Table 5.5 Attempts to prevent the formation of tetrahydropyran **413**

It was thought that the di-mesylate **382** may have been undergoing decomposition under the reaction conditions through deprotonation α to sulfur. Attempts at changing the leaving group to either a tosylate (Table 5.5, entry 1) or iodide (entry 2) did not improve the reaction outcome. Employing di-tosylate **414** under standard conditions (8 M methylamine in EtOH, reflux, 16 h) gave a 65:35 mixture of **26** and tetrahydropyran **413** (entry 1). Di-iodide **415** resulted in an improved 95:5 mixture of **26** and **413**

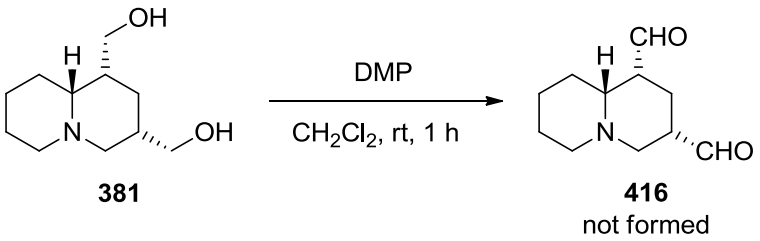
although other unidentified by-products were formed (entry 2). It was hypothesised that the methylamine may have been evaporating under the reaction conditions and subsequent thermal decomposition of the residual di-mesylate **382** may have been leading to the formation of tetrahydropyran **413**. To test this, pure di-mesylate **382** was stirred in 8 M ethanolic methylamine at room temperature in a sealed system for 4 d (entry 3). A 90:10 mixture of **26** and **413** was isolated, refuting this hypothesis.

It may have been possible that the commercial methylamine solution contained either water or methylammonium hydroxide. Therefore, the reagent was dried over 4Å molecular sieves prior to the addition of **382**. No improvement was seen with an 80:20 mixture of **26** and **413** formed (entry 4). Several other commercial solutions of methylamine were obtained and their use investigated (entries 5-8). 2.0 M methylamine in THF gave no product using the standard reaction conditions (16 h, reflux, entry 5). An analogous reaction at 70 °C for 5 d in a sealed pressure tube was performed to prevent the possible evaporation of methylamine. This led only to decomposition products (entry 6). A solution of **382** in a 1:1 mixture of 2.0 M THF solution of methylamine and EtOH was heated at 70 °C for 16 h in a sealed pressure tube, but no reaction was observed. Next, a solution of 2.0 M methylamine in MeOH was used. However, this only gave an 80:20 mixture of **26** and **413** (entry 8). An attempt to derive anhydrous methylamine *in situ* from methylamine hydrochloride (previously flame-dried under reduced pressure) and triethylamine in EtOH was undertaken. Subsequent heating of **382** to reflux for 16 h under these conditions gave no products (entry 9). Similarly, the use of anhydrous ammonia solutions (either 0.5 M in dioxane or 7 M in MeOH, entries 10 and 11 respectively) returned only unreacted starting material **382**. Finally, the use of methoxyamine hydrochloride and triethylamine in THF at reflux also resulted in no reaction of **382** (entry 12).

Although it should have been possible to perform a double displacement of di-mesylate **382** using a methylamine solution as reported previously,[220] the significant formation of the inseparable tetrahydropyran by-product **413** was insurmountable. An alternative strategy was thus sought.

It was envisaged that a double reductive amination on di-aldehyde **416** using methylamine would result in formation of only the desired sparteine surrogate **26**.[258-260]

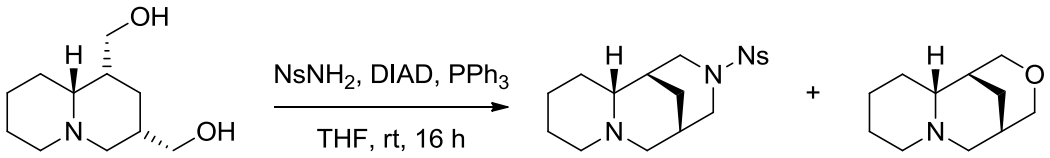
Disappointingly, attempted oxidation of diol **381** with DMP to form the requisite di-aldehyde **416** resulted in a complex mixture of products (Scheme 5.42).



381 **416** not formed

Scheme 5.42

Other approaches for ring-closure were considered. In 2004 Fukuyama reported the formation of a nine-membered cyclic amine in the synthesis of strychnine *via* a double Mitsunobu reaction between a diol and nosyl amine.[261] Inspired by this, an analogous reaction using diol **381** was undertaken (Scheme 5.43). Treatment of diol **381** with DIAD, PPh_3 and nosyl amine in THF resulted in the formation of the desired bispidine **417**, isolated in 10% yield. Disappointingly, tetrahydropyran **413** was isolated in 63% yield. In this case the two products were easily separated, but the low yield of bispidine **417** precluded this method being used for the synthesis of the sparteine surrogate **26**.



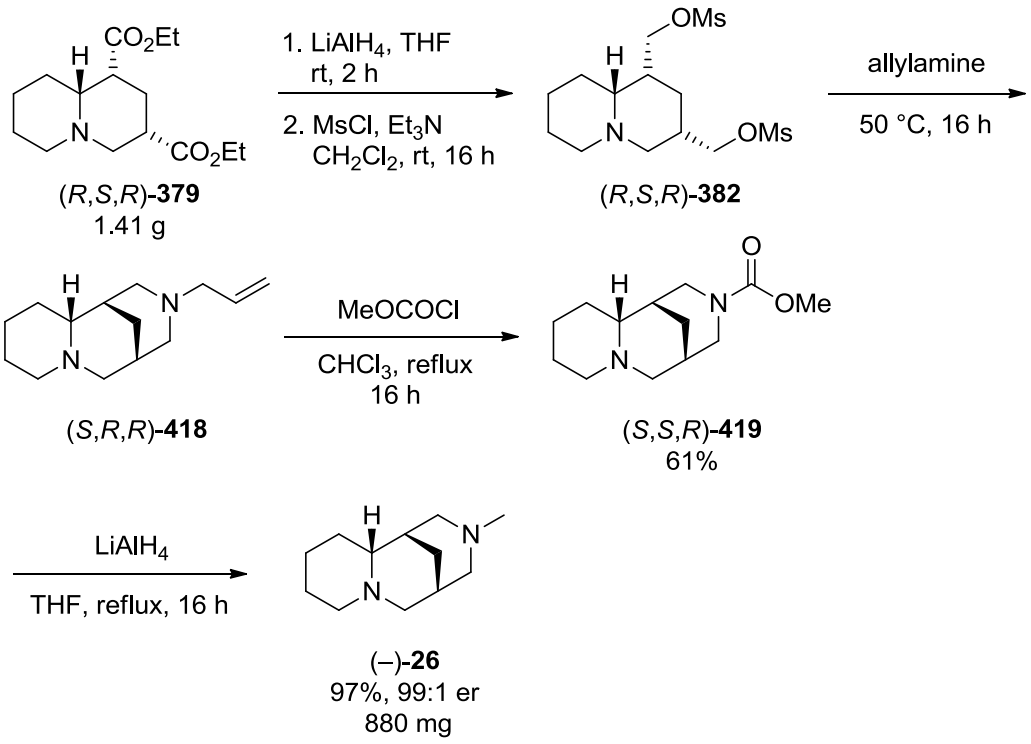
381 **417** 10% **413** 63%

Scheme 5.43

With the failure of both the reductive amination and Mitsunobu end-games, and the double displacement of di-mesylate **382** with methylamine proving problematic, an alternative amine source for the double displacement of **382** was investigated.

It was found that displacement of enantiopure di-mesylate (*R*,*S*,*R*)-**382**, formed from di-ester (*R*,*S*,*R*)-**379**, could be accomplished cleanly using neat allylamine (dried by distillation over CaH_2) at 50 °C under an argon atmosphere to give crude bispidine (*S*,*R*,*R*)-**418** (Scheme 5.44). Excess allylamine was easily removed under reduced pressure. There was no evidence of any tetrahydropyran **413** in the ^{1}H NMR spectrum

of the crude product. Allyl bispidine (*S*,*R*,*R*)-**418** was not purified. Instead, the allyl group was displaced using methyl chloroformate in $CHCl_3$ at reflux to give methyl carbamate (*S*,*S*,*R*)-**419** which, after purification by flash column chromatography, was isolated in 61% yield over four steps from di-ester (*R*,*S*,*R*)-**379**. Finally, reduction of methyl carbamate (*S*,*S*,*R*)-**419** was accomplished using $LiAlH_4$ in THF at reflux to give (–)-sparteine surrogate (–)-**26** in 97% yield. Final distillation of (–)-**26** was not necessary as it was pure by ^{1}H NMR spectroscopy. 880 mg of (–)-**26** was synthesised using this method and analysis by CSP-GC showed that (–)-**26** had 99:1 er. The absolute stereochemistry of (–)-**26** was determined unambiguously by CSP-GC and by comparison of the optical rotation of synthetic (–)-**26** ($[\alpha]_D$ –28.4 (*c* 1.0 in EtOH)) with a sample of (+)-**26** derived from (–)-cytisine ($[\alpha]_D$ +26.5 (*c* 1.0 in EtOH)).[213]



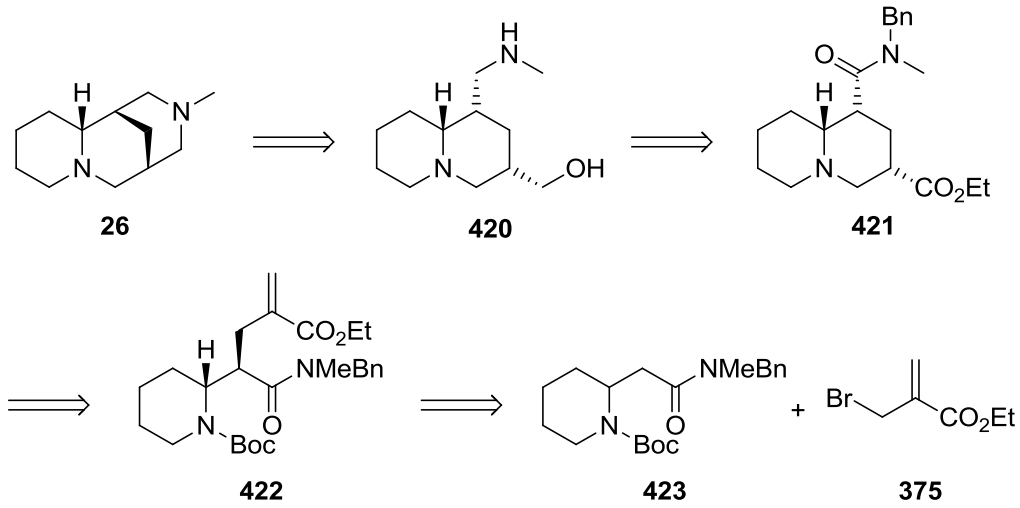
Scheme 5.44 Synthesis of (–)-sparteine surrogate (–)-**26** from (*R*,*S*,*R*)-**379**

Although this end-game from di-ester (*R*,*S*,*R*)-**379** was lengthy, it allowed the preparation of enantiopure (–)-**26** uncontaminated with tetrahydropyran by-product **413**. The synthesis was accomplished in nine steps with a 19% overall yield from commercially available ethyl 2-pyridyl acetate **364**. Importantly, many of the steps were telescoped and only two purification steps required, with bicyclic ester (*R*,*S*,*R*)-**379** and methyl carbamate (*S*,*S*,*R*)-**419** being purified by flash column chromatography. This,

along with the fully diastereoselective nature of the two key steps (see Scheme 5.27), allowed the synthesis to be performed on scale, with 880 mg (99:1 er) of the (–)-sparteine surrogate (–)-**26** synthesised.

5.3.3 Early Incorporation of Amine Functionality

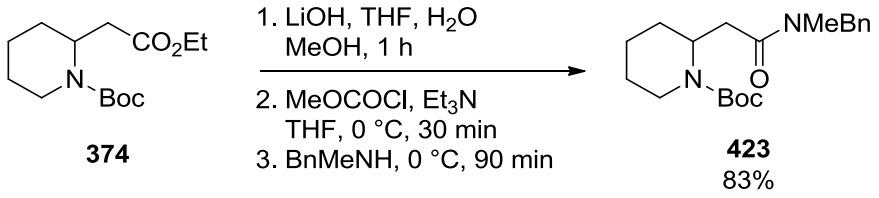
With the failure to effect the double displacement of di-mesylate **382** with a source of methylamine, and the resultant stepwise conversion of di-mesylate (*R*,*S*,*R*)-**382** into sparteine surrogate (–)-**26**, alternative routes that allowed introduction of amine functionality earlier in the synthesis were investigated. It was envisaged that this tactic would allow a streamlined synthesis of the (–)-sparteine surrogate (–)-**26**. Scheme 5.45 details the retrosynthesis of such a route. It was proposed that the bispidine framework of **26** could be constructed from amino alcohol **420** by selectively activating the primary alcohol, which itself could be prepared from **421** by reduction of both ester and amide groups followed by *N*-debenzylation. The bicyclic amide **421** could be accessed using *N*-Boc deprotection/intramolecular conjugate addition chemistry from compound **422**, which in turn could be made by performing a diastereoselective alkylation on amide **423** with LHMDS and bromoacrylate **375**.



Scheme 5.45 Retrosynthesis of sparteine surrogate **26** from amide **423**

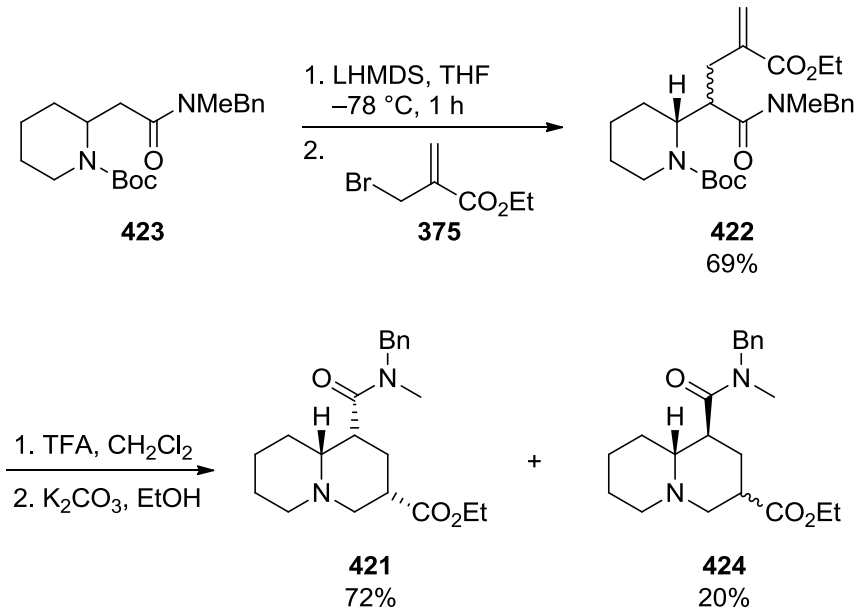
A racemic synthesis was investigated. To start with amide **423** was synthesised from *N*-Boc ester **374** (Scheme 5.46). Saponification of ester **374** was achieved under standard conditions using lithium hydroxide. Activation of the resulting carboxylic acid with

methyl chloroformate in the presence of triethylamine followed by addition of *N*-benzyl methylamine gave amide **423** in 83% yield over the three steps



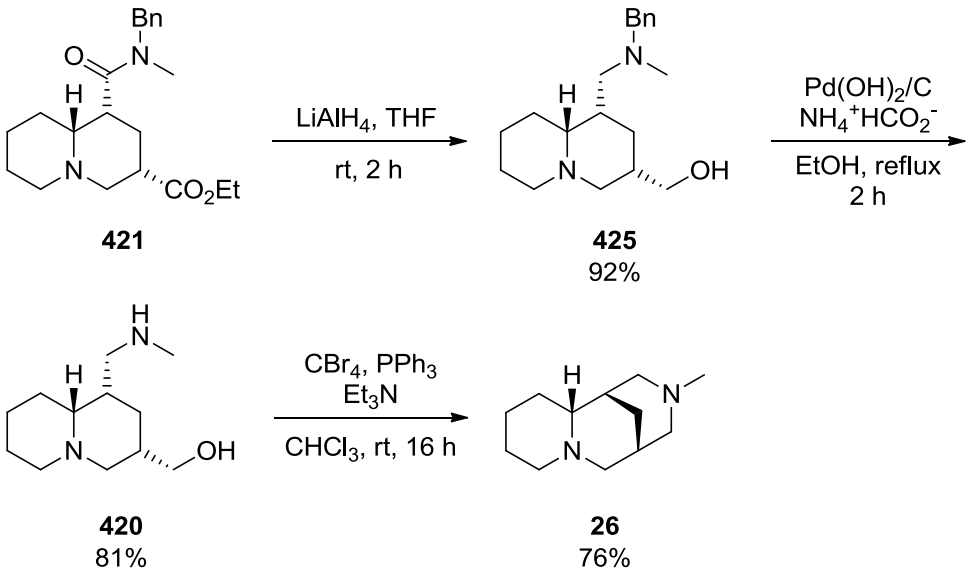
Scheme 5.46

Alkylation of amide **423** with LHMDS and acrylate **375** at –78 °C in THF gave alkylation product **422** as an unconfirmed mixture of diastereomers in 69% yield (Scheme 5.47). The diastereomeric ratio was undeterminable due to the complexity of the ^{1}H NMR spectrum of **422**, caused by two sets of rotamers. An attempt to simplify the spectrum using high temperature NMR studies in DMSO-d_6, forcing rotamers to interconvert on a NMR time scale, did not simplify the spectrum sufficiently. Nevertheless, the mixture of diastereomeric esters **422** was converted into bicyclic amides **421** and **424** by subjecting the mixture to TFA, to facilitate *N*-Boc deprotection, followed by base-mediated intramolecular conjugate addition. An 80:20 mixture of diastereomeric amides **421** and **424** was formed (by analysis of a ^{1}H NMR spectrum of the crude product) and the amides isolated in 72% and 20% yield respectively. The relative stereochemistry of the major diastereomer was assigned by analogy with that observed in the intramolecular conjugate addition of di-ester **376** (see Scheme 5.9), and was confirmed by completion of the synthesis of sparteine surrogate **26** (see Scheme 5.48). The relative stereochemistry of the minor diastereomer **424** is unknown. It is possible, but unlikely, that the enolate alkylation to **422** proceeds with complete stereoselectivity and the following Boc deprotection/intramolecular conjugate addition occurs with poor diastereoselectivity.



Scheme 5.47

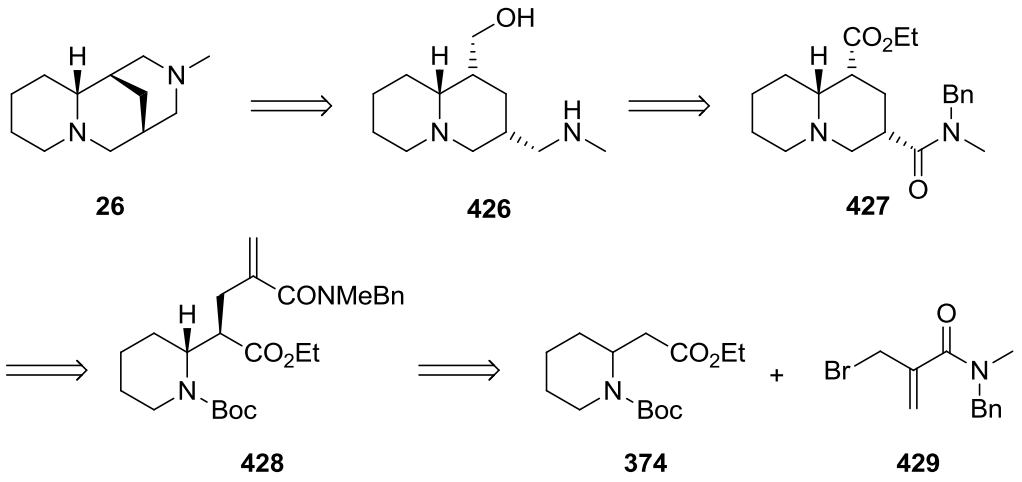
Synthesis of the sparteine surrogate **26** was completed from amido ester **421** as shown in Scheme 5.48. Reduction of both the ester and amide functionalities of **421** with $LiAlH_4$ in THF at room temperature gave amino alcohol **425** in 92% yield. *N*-Benzyl deprotection of **425** was accomplished using transfer hydrogenation conditions ($Pd(OH)_2/C$ and ammonium formate in EtOH at reflux) to give secondary amino alcohol **420** in 81% yield. The synthesis was completed following activation of the primary alcohol of **420** using Appel conditions (CBr_4, PPh_3) and concurrent cyclisation in the presence of triethylamine. Racemic sparteine surrogate **26** was isolated in 76% after vacuum distillation. The completion of the synthesis proved the relative stereochemistry of **421**.



Scheme 5.48

Although this route was not fully diastereoselective, separation of diastereomers **421** and **424** by flash column chromatography after the intramolecular conjugate addition was simple. Hence, it was thought that this route may be viable for the synthesis of significant quantities of pure sparteine surrogate (–)-**26**. When scale-up was undertaken, alkylation of amide **423** with LHMDS and bromo acrylate **375** on a 2 g scale returned the desired alkylation product **422** in only 23% yield with a number of unidentifiable by-products. All attempts to understand and control this reaction and develop a robust, reproducible procedure failed and the alkylation of **423** remained unpredictable. For this reason, and the fact that the route involved the formation and separation of diastereomers **421** and **424**, attention was turned to an alternative synthesis of the sparteine surrogate (–)-**26**.

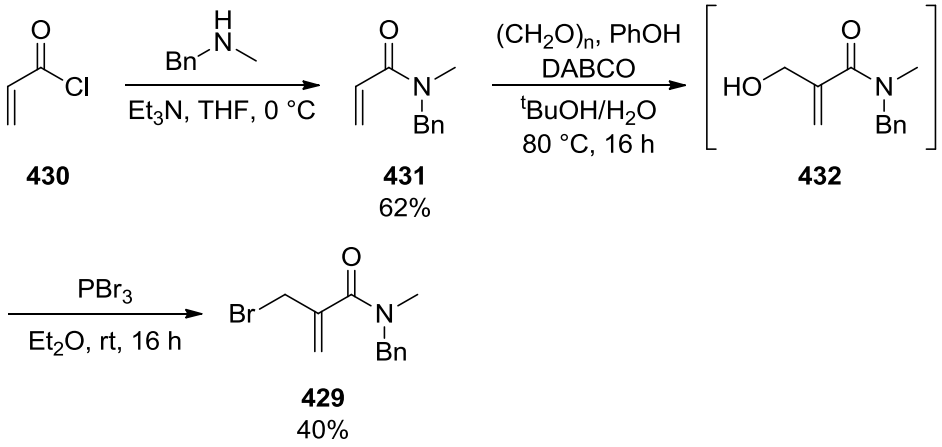
It was envisaged that the amine functionality could be introduced earlier in the synthetic route by employing the use of a substituted acrylamide or acrylonitrile partner in the alkylation step. Literature precedent and the result obtained from the alkylation of **423** (see Scheme 5.47) suggested that the presence of an ethyl ester group on the cyclic *β*-amino ester partner **374** might be essential for complete diastereoselectivity within these alkylation reactions.[222,223] Introducing the masked amine in the electrophile might result in high diastereoselectivity as an ester enolate could be used. The retrosynthesis of such a route is shown in Scheme 5.49.



Scheme 5.49 Retrosynthesis of sparteine surrogate **26** from amide **429**

It was proposed that the end-game to complete the synthesis of **26** would be analogous to that already described in Scheme 5.48. This involved activation of the alcohol functionality in amino alcohol **426**, after synthesis from amide **427** by reduction of both ester and amide groups followed by *N*-debenzylation. The bicyclic amide **427** could be accessed using the *N*-Boc deprotection/intramolecular conjugate addition from **428**, which in turn could be made by performing a possibly diastereoselective alkylation of cyclic *β*-amino ester **374** with LHMDS and acrylamide **429**.

The synthesis began with preparation of *α*-bromomethyl acrylamide **429** in three steps (Scheme 5.50). Treatment of acryloyl chloride **430** with *N*-methylbenzylamine in the presence of triethylamine gave acrylamide **431** in 62% yield. Subsequent alcohol catalysed Baylis-Hillman reaction (as investigated by Aggarwal and Lloyd-Jones[262]) with paraformaldehyde[263] formed crude primary alcohol **432**, which was converted into *α*-bromomethyl acrylamide **429** in 40% yield using PBr_3.

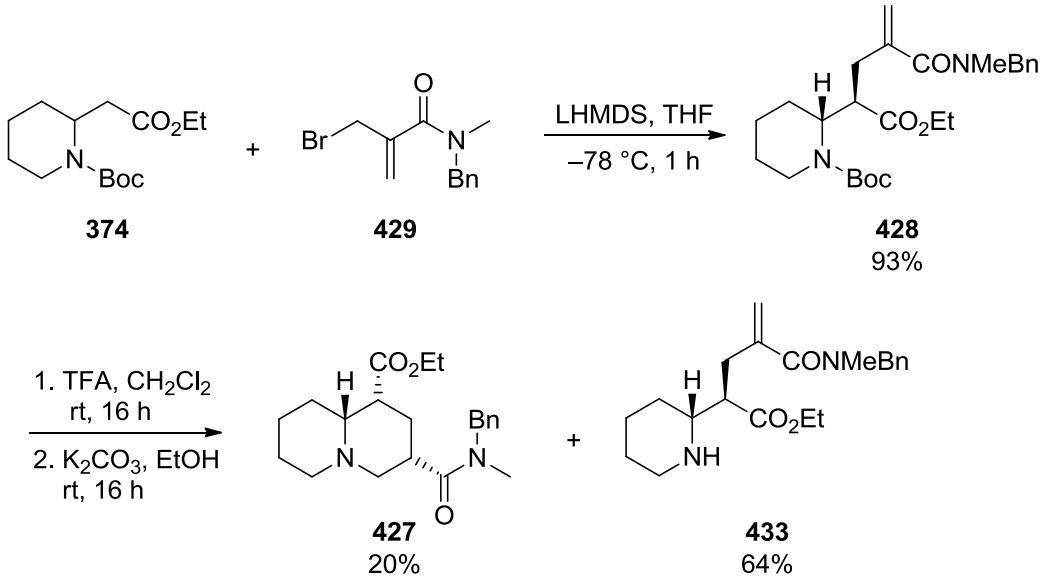


430 **431** 62% **432**

429 40%

Scheme 5.50

With acrylamide **429** in hand, the key alkylation of cyclic *β*-amino ester **374** was investigated (Scheme 5.51). Gratifyingly, alkylation of **374** with 1.2 eq. LHMDS in THF at –78 °C, followed by addition of *α*-bromomethyl acrylamide **429** resulted in amido ester **428** being formed as a single diastereomer in 93% yield. Subsequent TFA-mediated Boc deprotection was performed, followed by attempted base-mediated diastereoselective intramolecular conjugate addition. However, stirring the reaction in a mixture of K_2CO_3 and EtOH for 16 h gave bicyclic compound **427** in only 20% yield, with secondary amine **433** being recovered in 64% yield. It is assumed that the relative stereochemistry of **428** and **427** is the same as other examples, but this has not been confirmed.



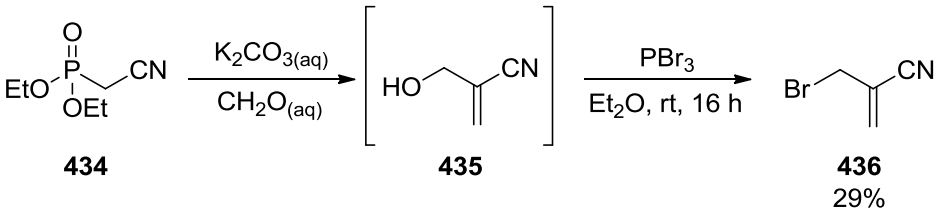
374 **429** **428** 93%

427 20% **433** 64%

Scheme 5.51

It is clear that intramolecular conjugate addition into the acrylamide moiety of **433** is significantly slower than the comparable reaction with amino acrylate **377** (see Scheme 5.37). Due to the low yield of the conjugate addition, this route was abandoned and alternative Michael acceptors were investigated. However, it is feasible that the intramolecular Michael addition of **433** could be optimised with future work. Initial studies showed heating **433** in a mixture of K_2CO_3 and EtOH at reflux resulted in epimerisation of at least one of the stereocentres.

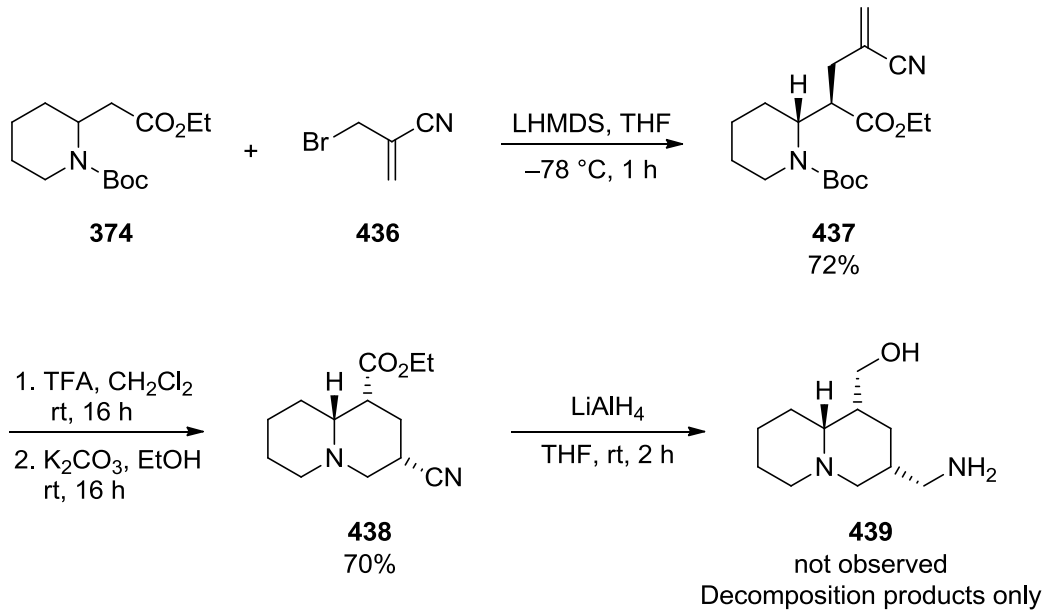
It was anticipated that use of *α*-bromomethyl acrylonitrile **436** would result in a more reactive Michael acceptor. Synthesis of **436** was accomplished according to a literature procedure[264] and in an similar manner to *α*-bromomethyl acrylate **437**. Treatment of diethyl cyanomethylphosphonate **434** with saturated aqueous K_2CO_3 and aqueous formaldehyde gave crude alcohol **435**. Subsequent bromination using PBr_3 formed *α*-bromomethyl acrylonitrile **436** in 29% yield (Scheme 5.52).



434 **435** **436**
29%

Scheme 5.52

Diastereoselective alkylation of *N*-Boc ester **374** with **436** proceeded without issue, giving compound **437** as a single diastereomer in 72% yield (Scheme 5.53). Subsequent tandem *N*-deprotection/Michael addition occurred with complete stereoselectivity, giving bicyclic nitrile **438** in 70% yield. The relative stereochemistry of **437** and **438** was assumed. As expected, the use of the more reactive Michael acceptor **437** resulted in the complete conversion into bicyclic compound **438**. Unfortunately, an attempt at simultaneous reduction of ester and nitrile functionalities using $LiAlH_4$ did not produce amino alcohol **439**, and instead resulted in a complex mixture of decomposition products.

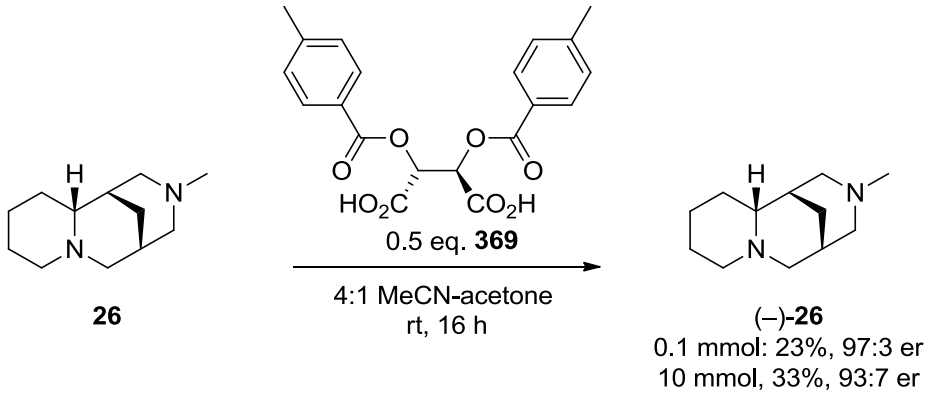


Scheme 5.53

Although introduction of amine functionality earlier in the route through the use of acrylamide **429** and acrylonitrile **436** have not yet led to a practical, scalable route to the sparteine surrogate **26**, it is possible with further experimentation that they might. More forcing conditions for the intramolecular Michael addition onto acrylamide **428** (see Scheme 5.51) or use of a suitable reducing agent for the reduction of nitrile **438** to amino alcohol **439** may allow development of a short, efficient synthesis of (–)-**26**.

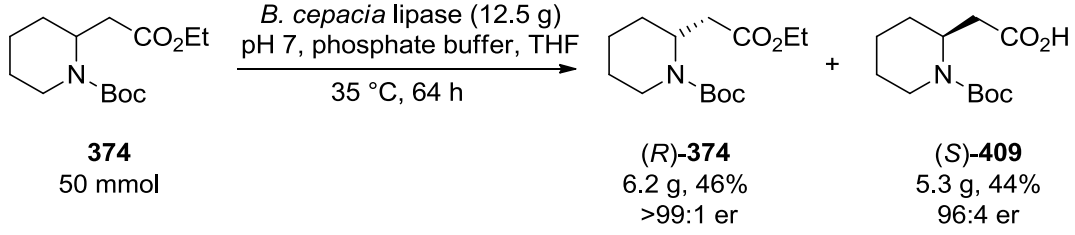
5.4 Conclusions and Future Work

A classical resolution of racemic sparteine surrogate **26** was successfully developed to give highly enantiomerically enriched (–)-**26**. After a wide screen of solvent systems, resolution of **26** was accomplished using (–)-**369** in 4:1 MeCN-acetone. The diastereomeric salt of (–)-**26** was isolated in 23% yield and (–)-**26** in 97:3 er (Scheme 5.54). Scale-up to 10 mmol resulted in a small drop in enantioenrichment, with the salt of (–)-**26** isolated in 33% yield and (–)-**26** in 93:7 er. Further optimisation studies may find an alternative solvent system that would allow (–)-**26** to be isolated in greater yield and with a higher degree of enantioenrichment.



Scheme 5.54

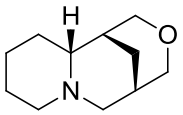
Secondly, a synthesis of enantiopure (–)-sparteine surrogate (–)-**26** has been accomplished using a modified procedure developed within the O'Brien group.[220] A key intermediate, *β*-amino ester (*R*)-**374** was obtained as a single enantiomer through both classical resolution and enzymatic resolution methods, with the latter procedure being the most useful. Ester (*R*)-**374** was generated on a multi-gram scale using a lipase from *Burkholderia cepacia*, employing a modification of Pousset's published method (Scheme 5.55).[254]



Scheme 5.55

Although significant issues with formation of by-product tetrahydropyran **413** were encountered in the final step of the synthesis of (–)-**26**, this was overcome by modifying the route. The synthesis of (–)-**26** was accomplished in 9 steps and 19% overall yield. Importantly, the synthetic steps are easy to perform, high yielding and scalable. Optimisation resulted in only two purification operations being required throughout the synthesis allowing the rapid synthesis of 880 mg (99:1 er) of the (–)-sparteine surrogate (–)-**26**. To date, this is the most practical synthesis of (–)-**26** reported and could possibly be commercialised in the future.

The main limitation of the method developed is that the end-game required for completion of the synthesis is lengthy. Future work may result in identification of reliable conditions for the double displacement of di-mesylate **382** with methylamine, without the formation of the tetrahydropyran by-product **413** (Figure 5.6). Alternatively, future work may be able to build upon the initial investigation into the incorporation of masked amine functionality earlier in the synthesis, resulting in a higher yielding, streamlined synthesis of (–)-**26**.



413

Figure 5.6

A purposeful, improved synthesis of tetrahydropyran **413** and other heteroatom derivatives from an enantiopure intermediate could be undertaken. The investigation of the use of these ligands as chiral ligands for metal-catalysed asymmetric reactions could be an interesting avenue of research.

Chapter Six: Experimental

6.1 General Methods

All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Et_2O and THF were freshly distilled from sodium and benzophenone. MTBE and toluene were distilled over CaH_2. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[265] All diamines used in lithiation reactions were distilled over CaH_2 before use. 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 $CDCl_3$, 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. Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points given for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer or a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. Chiral stationary phase GC was performed on a Hewlett Packard 6980 series chromatograph. *In situ* ReactIR™ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer with a silicon-tipped (SiComp) probe. Baseline correction was performed at 1737-1750 cm^{-1}, with peak smoothing at 0-29.8cm^{-1}.

6.2 General Procedures

General Procedure A: Racemic lithiation/trapping using *s*-BuLi/THF

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) in THF (4-7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1-3 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) (and saturated $NaHCO_{3(aq)}$ (10 mL) or 20% $NaOH_{(aq)}$ (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product

General Procedure B: Racemic lithiation/trapping using *s*-BuLi/TMEDA

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and TMEDA (1.3 eq.) in solvent (4-7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min – 1 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) (and saturated $NaHCO_{3(aq)}$ (10 mL) or 20% $NaOH_{(aq)}$ (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product

General Procedure C: Asymmetric lithiation/trapping using *s*-BuLi/diamine with pre-mixing of diamine and s-BuLi

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of diamine (1.3 eq.) in Et_2O (4-6 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc piperazine (1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 10 min – 6 h.

Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) (and saturated $NaHCO_{3(aq)}$ (10 mL) or 20% $NaOH_{(aq)}$ (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure D: Asymmetric Lithiation/trapping using *s*-BuLi/diamine without pre-mixing of diamine and s-BuLi

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and diamine (1.3 eq.) in solvent (4-7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min – 3 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) (and saturated $NaHCO_{3(aq)}$ (10 mL) or 20% $NaOH_{(aq)}$ (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product

General Procedure E: Racemic lithiation/trapping using *s*-BuLi/TMEDA *via* cuprate

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and TMEDA (1.3 eq.) in solvent (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then a solution of CuCN.2LiCl (0.5 eq.) in THF (1-2 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then, the electrophile (2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) (and saturated $NaHCO_{3(aq)}$ (10 mL) or 20% $NaOH_{(aq)}$ (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure F: Classical resolution of the sparteine surrogate 26

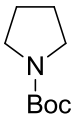
A solution of resolving agent (0.05 mmol, 0.5 eq.) in minimum amount of solvent was added to a stirred solution of **26** (19 mg, 0.10 mmol, 1.0 eq.) in solvent (20 µL) at rt. The resulting mixtures were stirred at rt for 16 h. Solvent (0.2 mL) was added, crystals (if formed) were filtered, washed with solvent (0.6 mL) and dried under reduced pressure. Then, the crystals were dissolved in 20% $KOH_{(aq)}$ (3 mL) and MTBE (2 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 2 mL). The combined organics were dried by passing through a PTFE membrane under gravity and evaporated under reduced pressure to give resolved surrogate **26**. The er of **26** was determined by CSP-GC using cyclodex-B column (110-140 °C, 1 °C/min), (+)-**26** 22.8 min, (–)-**26** 23.1 min

General Procedure G: Lipase catalysed enzymatic resolution of alkyl 2-(pyridin-2-yl)acetates

A solution of alkyl 2-(pyridin-2-yl)acetate (1-50 mmol, 1.0 eq.) in THF (2-50 mL) was added in one portion to a gently stirred 1:1 mixture of 0.1 M phosphate buffer (pH 7.0) and H_2O (16-400 mL). Lipase from *Burkholderia cepacia* (125 mg-12.5 g) was added in one portion and the reaction was stirred at the specified temperature (rt to 50 °C) for a specified time (24–120 h). Upon cooling to rt (if necessary) the mixture was filtered through Celite® and washed with H_2O (20-200 mL) and Et_2O (20-200 mL). 20% $NaOH_{(aq)}$ (20-200 mL) was added to the filtrate and the resulting mixture was extracted with Et_2O (3 × 10-100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the ester. The aqueous layer was acidified with 1M $HCl_{(aq)}$ and extracted with Et_2O (3 × 10-100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the acid.

6.3 Experimental for Chapter Two

tert-Butyl pyrrolidine-1-carboxylate 12

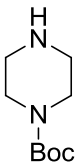


12

Pyrrolidine (4.27 g, 5.01 mL, 60 mmol, 1.2 eq.) was added dropwise to a stirred solution of di-*tert* butyl dicarbonate (10.91 g, 50 mmol, 1.0 eq.) in CH_2Cl_2 (200 mL) at 0 °C under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 2 h. Then, 1 M $HCl_{(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave *N*-Boc pyrrolidine **12** (8.38 g, 98%) as a colourless oil, bp 95-100 °C/2.7 mmHg (lit.,[266] bp 70-75 °C/0.05 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32-3.28 (m, 4H, NCH_2), 1.84-1.81 (m, 4H, CH_2), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.6 (C=O), 78.7 (CMe_3), 45.8 (NCH_2), 45.6 (NCH_2), 28.4 (CMe_3), 25.6 (CH_2), 24.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[266]

Lab Book Reference: JDF6_532

tert-Butyl piperazine-1-carboxylate 257



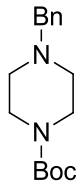
257

A solution of di-*tert*-butyl dicarbonate (20.0 g, 91.6 mmol, 1.0 eq.) in CH_2Cl_2 (200 mL) was added dropwise over 3 h to a stirred solution of piperazine **253** (15.8 g, 183.2 mmol, 2.0 eq.) in CH_2Cl_2 (500 mL) at rt. The resulting cloudy solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give a white solid.

Water (250 mL) was added and the insoluble solids were removed by filtration and washed with water (100 mL). The aqueous filtrate was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were evaporated under reduced pressure to give *N*-Boc piperazine **257** (14.1 g, 83%) as a white solid, mp 42-44 °C (lit.,[267] 42.5-45 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, *J* = 5.0 Hz, 4H, NCH_2), 2.79 (t, *J* = 5.0 Hz, 4H, NCH_2), 2.14 (s, 1H, NH), 1.41 (s, 9H, CMe_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.7 (C=O), 79.38 (*C*Me_3), 45.7 (NCH_2), 44.8 (NCH_2), 28.3 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[267]

Lab Book Reference: JDF2_126

tert-Butyl 4-benzylpiperazine-1-carboxylate 117

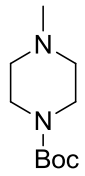


117

N-Boc piperazine **257** (7.30 g, 39.2 mmol, 1.0 eq.) and K_2CO_3 (10.85 g, 78.4 mmol, 2.0 eq.) were added portionwise to a stirred solution of benzyl chloride (4.96 g, 4.51 mL, 39.2 mmol 1.0 eq.) in EtOH (120 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 water (60 mL) and CH_2Cl_2 (60 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 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 petrol-EtOAc as eluent gave *N*-Boc-*N*′-benzyl piperazine **117** (9.18 g, 85%) as a white solid, mp 68-70 °C (lit.,[268] 72-75 °C); R_F (7:3 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 5H, Ph), 3.50 (s, 2H, CH_2Ph), 3.42 (t, *J* = 5.0 Hz, 4H, NCH_2), 2.38 (t, *J* = 5.0 Hz, 4H, NCH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.7 (C=O), 137.8 (*ipso*-Ph), 129.1 (Ph), 128.2 (Ph), 127.1 (Ph), 79.4 (*C*Me_3), 63.0 (CH_2Ph), 52.8 (NCH_2), 44.0 (NCH_2), 28.4 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[269]

Lab Book Reference: JDF1_14

tert-Butyl 4-methylpiperazine-1-carboxylate 151

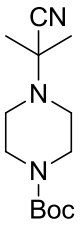


151

A solution of di-*tert*-butyl dicarbonate (21.6 g, 99.2 mmol, 1.1 eq.) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of *N*-methyl piperazine (9.0 g, 10 mL, 90.2 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for at rt for 16 h. Water (100 mL) and 20% $NaOH_{(aq)}$ (100 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers 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 **151** (16.54 g, 92%) as a colourless oil, bp 105-110 °C / 0.9 mmHg; R_F (9:1 CH_2Cl_2-MeOH) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (t, J = 5.0 Hz, 4H, NCH_2), 2.29 (t, J = 5.0 Hz, 4H, NCH_2), 2.24 (s, 3H, NMe), 1.41 (s, 9H, CMe_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 79.5 (*C*Me_3), 54.7 (NCH_2), 46.1 (NMe), 43.5 (NCH_2), 28.3 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[269]

Lab Book Reference: JDF1_85

***tert*-Butyl 4-(2-cyanopropan-2-yl)piperazine-1-carboxylate 258**

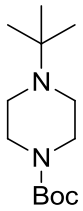


258

HCl (40.3 mL of a 2.0 M in Et_2O, 80.6 mmol, 1.5 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine **257** (12.6 g, 53.7 mmol, 1.0 eq.) in MeOH (60 mL) and CH_2Cl_2 (60 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in water (150 mL). NaCN (2.63 g, 53.7 mmol, 1.0 eq.) and then a solution of acetone (9.4 g, 11.8 mL, 161.2 mmol, 3.0 eq.) in water (20 mL) were added sequentially. The resulting mixture was stirred at rt under air for 48 h. Then, water (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *N*-Boc piperazine **258** (11.0 g, 81%) as a white solid which was sufficiently pure by ^{1}H NMR spectroscopy, mp 108-110 °C; IR ($CHCl_3$) 3018, 1686 (C=O), 1455, 1429, 1391, 1367, 1307, 1290, 1266, 1242, 1215, 1172, 1130, 750, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (t, J = 5.0 Hz, 4H, NCH_2), 2.59 (t, J = 5.0 Hz, 4H, NCH_2), 1.51 (s, 6H, CMe_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.4 (C=O), 119.8 (CN), 79.9 (*C*Me_3), 55.8 (*C*Me_2), 47.3 (NCH_2), 44.0 (NCH_2), 28.4 (C*Me*$_3$), 26.1 (C*Me*$_2$); MS (ESI) *m/z* 276 [$(M + Na)^+$, 40], 254 [$(M + H)^+$, 100], 198 [$(M – CMe_3)^+$, 50]; HRMS *m/z* calcd for $C_{13}H_{23}N_3O_2$ $(M + H)^+$ 254.1863, found 254.1864 (–0.2 ppm error).

Lab Book Reference: JDF5_447

***tert*-Butyl 4-*tert*-butylpiperazine-1-carboxylate 252**

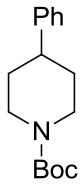


252

Methyl magnesium bromide (31.3 mL of a 3.0 M in Et_2O, 94.0 mmol, 3.0 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine **258** (7.9 g, 31.3 mmol, 1.0 eq.) in THF (150 mL) at 0 °C under Ar. After being allowed to warm to rt the reaction was allowed to stir at rt for 16 h. Then, the mixture was cooled to 0 °C and water (20 mL) was added dropwise. The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-94:6 CH_2Cl_2-MeOH as eluent gave *N*-Boc-*N'*-*tert*-butyl piperazine **252** (6.0 g, 79%) as a white solid, mp 49-51 °C; R_F (19:1 CH_2Cl_2-MeOH) 0.3; IR ($CHCl_3$) 2977, 1682 (C=O), 1429, 1366, 1288, 1267, 1247, 1169, 1128, 953, 864, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (t, J = 5.0 Hz, 4H, NCH_2), 2.50 (t, J = 5.0 Hz, 4H, NCH_2), 1.46 (s, 9H, $OCMe_3$), 1.06 (s, 9H, $NCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 79.2 ($OCMe_3$), 53.7 ($NCMe_3$), 45.8 (NCH_2), 44.6 (NCH_2), 28.3 (CMe_3), 25.7 (CMe_3); MS (ESI) *m/z* 243 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{26}N_2O_2$ $(M + H)^+$ 243.2067, found 243.2073 (–1.9 ppm error).

Lab Book Reference: JDF2_183

***tert*-Butyl 4-phenylpiperidine-1-carboxylate 66**

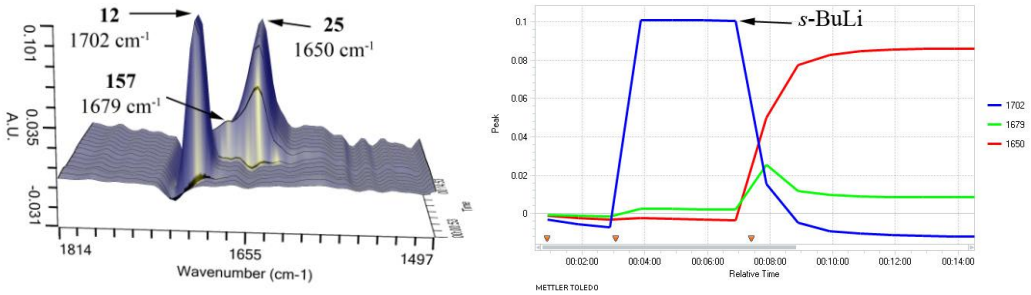


66

A solution of di-*tert*-butyl dicarbonate (3.0 g, 13.6 mmol, 1.1 eq.) in CH_2Cl_2 (20 mL) was added dropwise a stirred solution of 4-phenyl piperidine (2.0 g, 12.4 mmol, 1.0 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 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 19:1-4:1 petrol-EtOAc as eluent gave *N*-Boc piperidine **66** (3.2 g, 99%) as a pale yellow oil, R_F (9:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H, Ph), 7.23-7.19 (m, 3H, Ph), 4.29-4.20 (m, 2H, NCH), 2.80 (td, *J* = 13.0, 2.5 Hz, 2H, NCH), 2.64 (tt, *J* = 12.0, 3.5 Hz, 1H, C*H*Ph), 1.88-1.77 (m, 2H, CH), 1.64 (td, *J* = 12.5, 4.0 Hz, 2H, CH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.9 (C=O), 145.8 (*ipso*-Ph), 128.5 (Ph), 126.8 (Ph), 126.3 (Ph), 79.4 (*C*Me_3), 44.5 (NCH_2), 42.8 (*C*HPh), 33.3 (NCH_2CH_2), 28.6 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[270]

Lab Book Reference: JDF6_534

ReactIR™ monitoring of the lithiation of *N*-Boc-pyrolidine 12 (TMEDA)

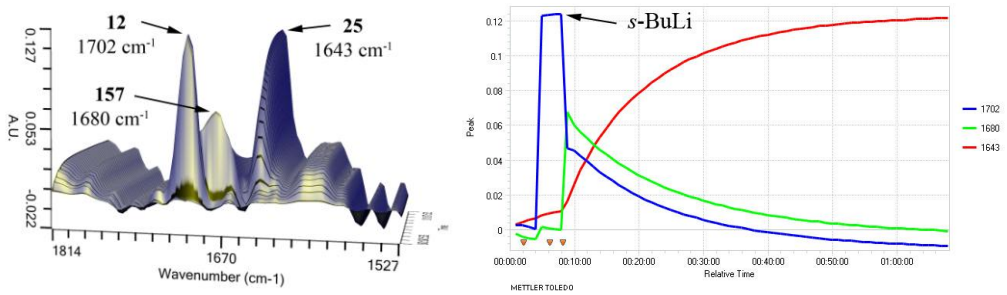


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 9 min.

For *N*-Boc-pyrrolidine **12**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **157**. A new peak at 1650 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **25**. After a lithiation time of 5 min, complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **25** was observed.

Lab Book Reference: JDF6_545

ReactIR™ monitoring of the lithiation of *N*-Boc-pyrolidine 12 ((–)-sparteine)



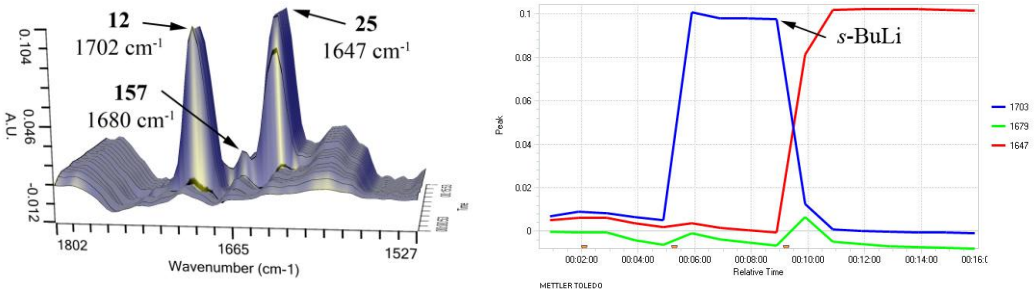
Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The

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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 60 min.

For *N*-Boc-pyrrolidine **12**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **157**. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **25**. After a lithiation time of 60 min, complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **25** was observed.

Lab Book Reference: JDF3_239

ReactIR™ monitoring of the lithiation of *N*-Boc-pyrolidine 12 ((+)-sparteine surrogate (+)-26)

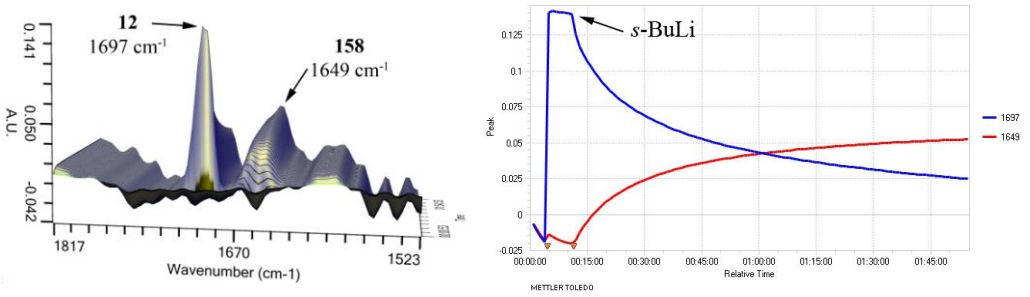


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 10 min.

For *N*-Boc-pyrrolidine **12**, a peak at 1704 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **157**. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **25**. After a lithiation time of 2 min, complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **25** was observed.

Lab Book Reference: JDF3_243

ReactIR™ monitoring of the lithiation of *N*-Boc-pyrolidine 12 (THF)

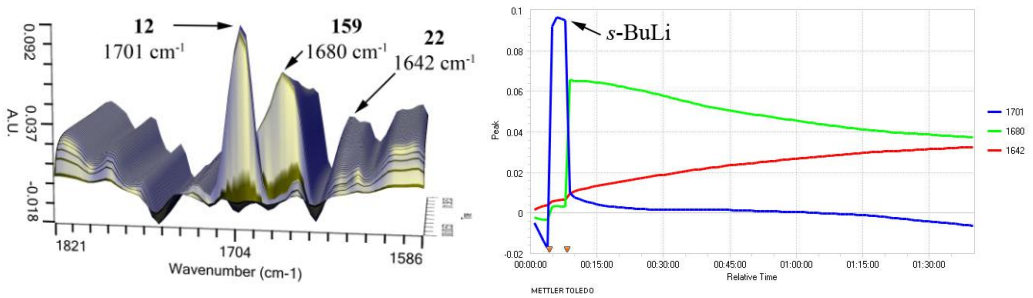


THF (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 100 min.

For *N*-Boc-pyrrolidine **12**, a peak at 1697 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1649 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **158**. After a lithiation time of 90 min, complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **158** was observed.

Lab Book Reference: JDF3_259

ReactIR™ monitoring of the lithiation of *N*-Boc-pyrolidine 12 (Et_2O)



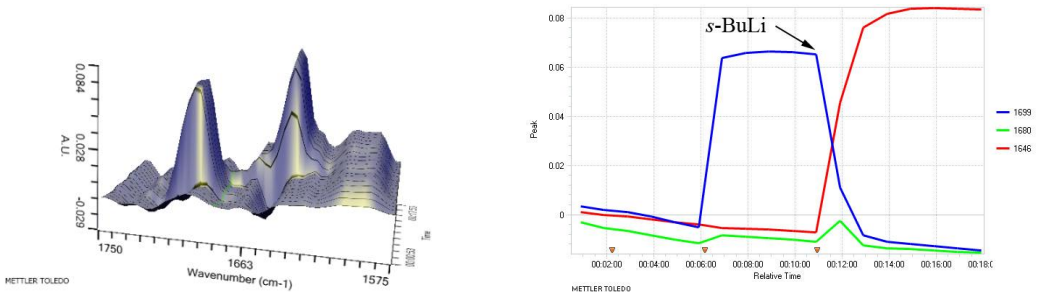
Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.) was added. The solution was stirred for 5 min (to verify the stability of readout

on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 90 min.

For *N*-Boc-pyrrolidine **12**, a peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **159**. A new peak at 1642 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **22**. After a lithiation time of 90 min, incomplete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **22** and *N*-Boc-pyrrolidine **12** was observed.

Lab Book Reference: JDF3_258

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-benzyl piperazine 117 (TMEDA)

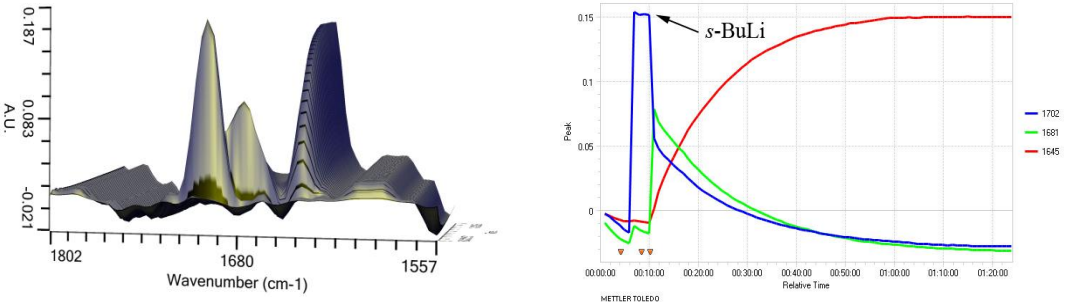


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 7 min.

For *N*-Boc-*N′*-benzyl piperazine **117**, a peak at 1699 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **160**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **161**. After a lithiation time of 5 min, complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate **161** was observed.

Lab Book Reference: JDF3_220

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-benzyl piperazine 117 ((–)-sparteine)

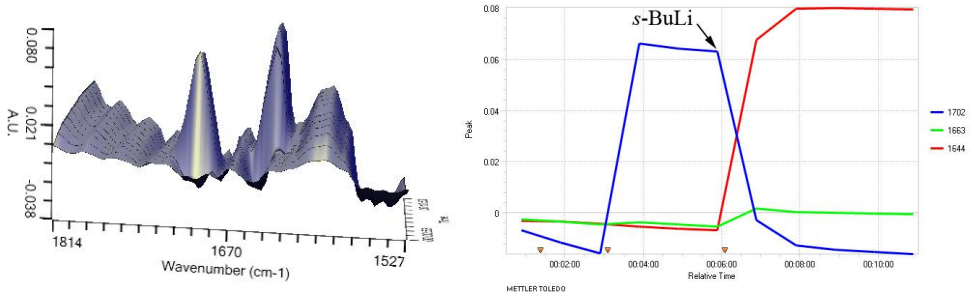


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 75 min.

For *N*-Boc-*N′*-benzyl piperazine **117**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **160**. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **161**. After a lithiation time of 1 h, complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate **161** was observed.

Lab Book Reference: JDF3_238

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-benzyl piperazine 117 ((+)-sparteine surrogate (+)-26)

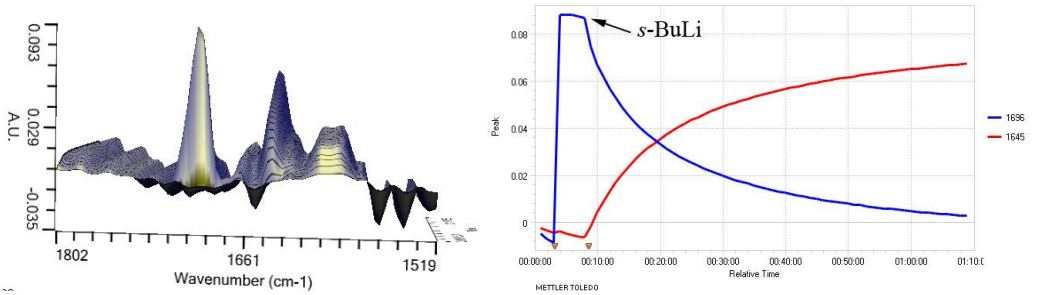


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 5 min.

For *N*-Boc-*N′*-benzyl piperazine **117**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1663 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **160**. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **161**. After a lithiation time of 2 min, complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate **161** was observed.

Lab Book Reference: JDF5_428

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-benzyl piperazine 117 (THF)

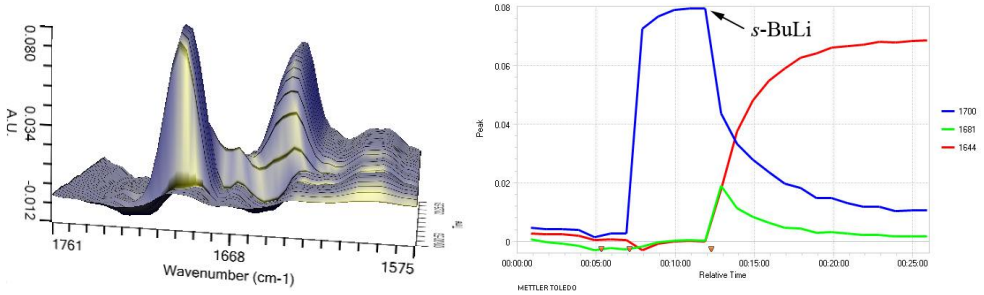


THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 1 h.

For *N*-Boc-*N′*-benzyl piperazine **117**, a peak at 1696 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 $\nu_{C=O}$ in the lithiated intermediate **162**. After a lithiation time of 1 h, almost complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate **162** was observed.

Lab Book Reference: JDF4_375

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine 152 (TMEDA)



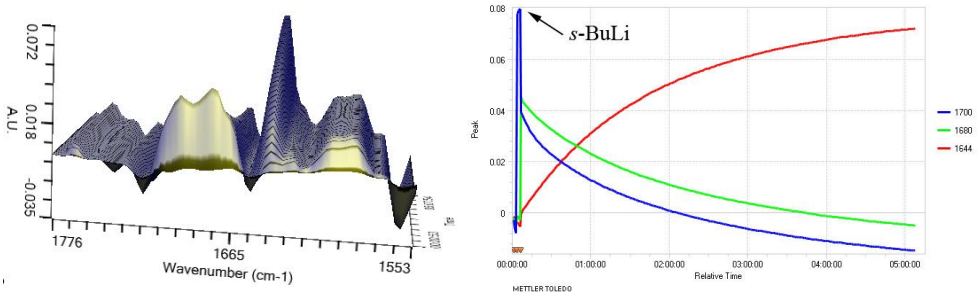
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol,

1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 15 min.

For *N*-Boc-*N′*-*tert*-butyl piperazine **152**, a peak at 1700 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **163**. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **164**. After a lithiation time of 15 min, complete lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine **152** to give the lithiated intermediate **164** was observed.

Lab Book Reference: JDF3_228

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine 152 ((–)-sparteine)

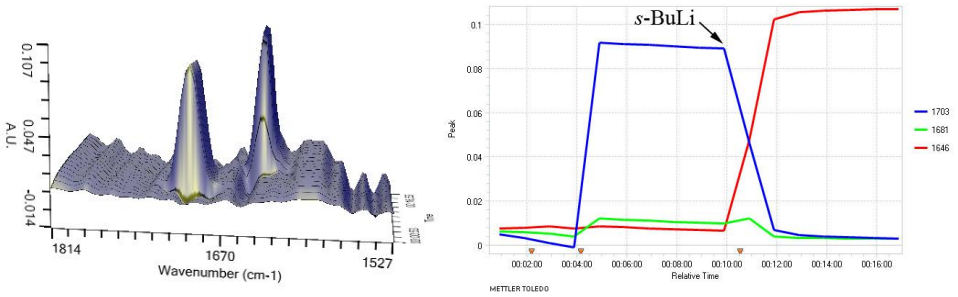


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 5 h.

For *N*-Boc-*N′*-*tert*-butyl piperazine **152**, a peak at 1700 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **163**. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **164**. After a lithiation time of 5 h, almost complete lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine **152** to give the lithiated intermediate **164** and *N*-Boc-*N′*-*tert*-butyl piperazine **152** was observed.

Lab Book Reference: JDF6_564

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine 152 ((+)-sparteine surrogate (+)-26)

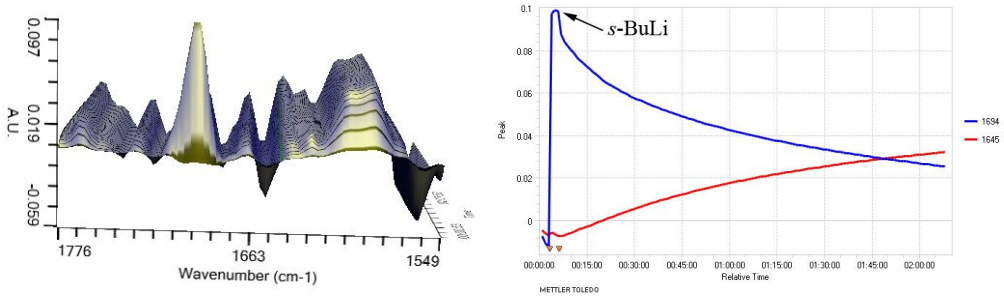


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution *N*-Boc-*N'*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 7 min.

For *N*-Boc-*N'*-*tert*-butyl piperazine **152**, a peak at 1703 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **163**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **164**. After a lithiation time of 6 min, complete lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine **152** to give the lithiated intermediate **164** was observed.

Lab Book Reference: JDF5_427

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine 152 (THF)

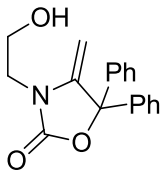


THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 2 h.

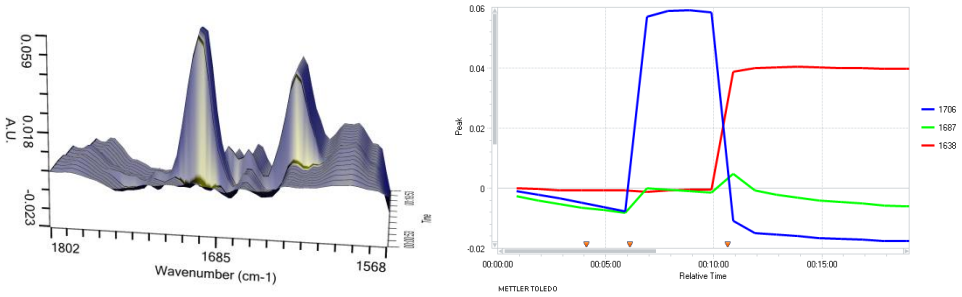
For *N*-Boc-*N′*-*tert*-butyl piperazine **152**, a peak at 1694 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **165**. After a lithiation time of 2 h, incomplete lithiation of *N*-Boc-*N′*-*tert*-butyl piperazine **152** to the give the lithiated intermediate **165** and *N*-Boc-*N′*-*tert*-butyl piperazine **152** was observed.

Lab Book Reference: JDF4_372

3-(2-Hydroxyethyl)-4-methylene-5,5-diphenyloxazolidin-2-one 169



169

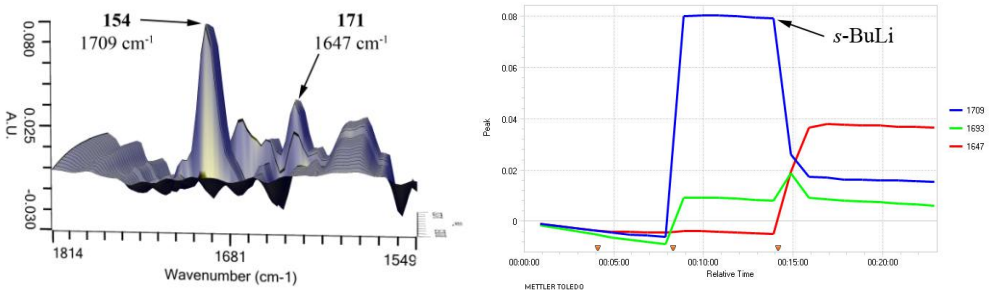


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc morpholine **155** (187 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1706 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc morpholine **155**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1687 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1638 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **166**. The solution was stirred at –78 °C for 10 min. Complete lithiation of *N*-Boc morpholine **155** to give the lithiated intermediate **166** had occurred within 1 min. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 30 min. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 1:1 petrol-EtOAc as eluent gave oxazolidinone **169** (119 mg, 40%) as a white solid, mp 88-91 °C; R_F (1:1 petrol-EtOAc) 0.5; IR ($CHCl_3$) 3624 (OH), 1761 (C=O), 1683 (C=C), 1448, 1400, 1336, 1231, 1022, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 10H, Ph), 4.64 (d, J = 3.0 Hz, 1H, C=C$H_A$$H_B$), 4.21 (d, J = 3.0 Hz, 1H, C=C$H_A$$H_B$), 3.88 (q, J = 5.5 Hz, 2H, OCH_2), 3.72 (t, J = 5.5 Hz, 2H, NCH_2), 2.01 (br s, 1H, OH); ^{13}C

NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 147.2 (*C*=CH_2), 140.3 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 127.1 (Ph), 89.3 (Ph_2CO), 86.7 (C=CH_2), 59.3 (NCH_2), 44.3 (OCH_2); MS (ESI) *m/z* 318 $[(M + Na)^+$, 100], 296 $[(M + H)^+$, 80], 252 $[(M - CH_2CH_2OH)^+$, 70]; HRMS *m/z* calcd for $C_{18}H_{17}NO_3$ $(M + H)^+$ 296.1281, found 296.1285 (–1.0 ppm error).

Lab Book Reference: JDF3_241

ReactIR™ monitoring of the lithiation of tert-butyl 3-isopropylimidazolidine-1-carboxylate 154 ((–)-sparteine)

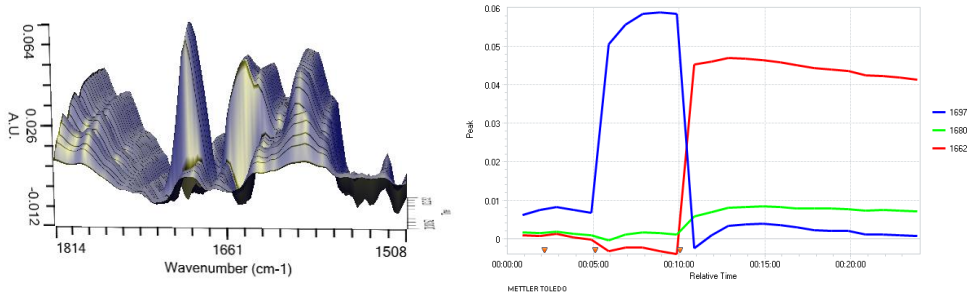


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution 3-isopropylimidazolidine-1-carboxylate **154** (214 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 10 min.

For 3-isopropylimidazolidine-1-carboxylate **154**, a peak at 1709 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1693 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **171**. After a lithiation time of 2 min, complete partial lithiation of 3-isopropylimidazolidine-1-carboxylate **154** to give the lithiated intermediate **171** and 3-isopropylimidazolidine-1-carboxylate **154** was observed.

Lab Book Reference: JDF3_240

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-(((2,4,6-triisopropylphenyl)sulfonyl)oxy)piperidine-1-carboxylate 156 (TMEDA)

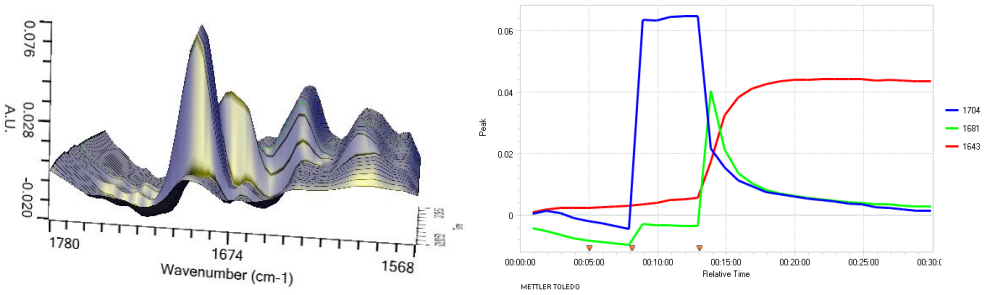


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (302 mg, 390 µL, 2.6 mmol, 1.3 eq.) was added followed by a solution of 4-trisyl-*N*-Boc piperidine **156** (467 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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 dropwise. The solution was stirred at –78 °C for 16 min.

For 4-trisyl-*N*-Boc piperidine **156**, a peak at 1697 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1662 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 1 min, complete lithiation of 4-trisyl-*N*-Boc piperidine **156** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_224

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-(((2,4,6-triisopropylphenyl)sulfonyl)oxy)piperidine-1-carboxylate 156 ((–)-sparteine)

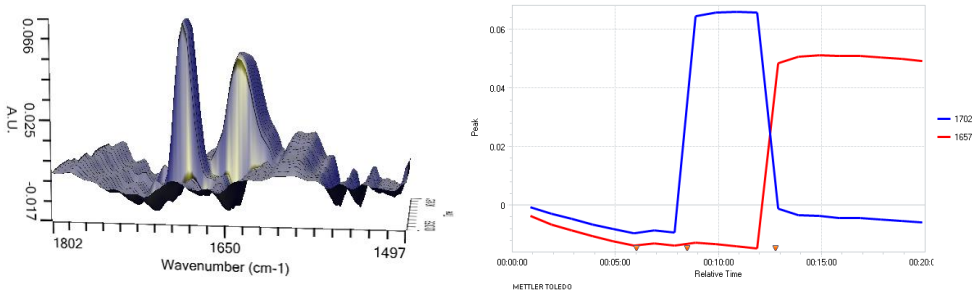


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (610 mg, 598 µL, 2.6 mmol, 1.3 eq.) was added followed by a solution of 4-trisyl-*N*-Boc piperidine **156** (467 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution 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 dropwise. The solution was stirred at –78 °C for 17 min.

For 4-trisyl-*N*-Boc piperidine **156**, a peak at 1704 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 10 min, complete lithiation of 4-trisyl-*N*-Boc piperidine **156** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_225

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-chloropiperidine-1-carboxylate 49 (TMEDA)

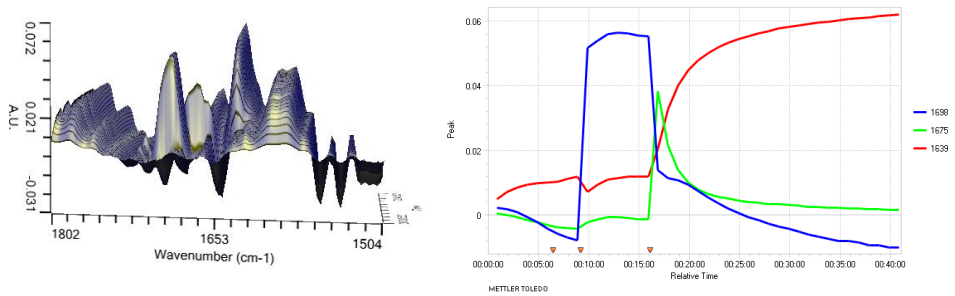


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (302 mg, 390 µL, 2.6 mmol, 1.3 eq.) was added followed by a solution of 4-chloro-*N*-Boc piperidine **49** (220 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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 dropwise. The solution was stirred at –78 °C for 8 min.

For 4-chloro-*N*-Boc piperidine **49**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1657 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 2 min, complete lithiation of 4-trisyl-*N*-Boc piperidine **49** to give the lithiated intermediate was observed. The pre-lithiation complex was not observed.

Lab Book Reference: JDF3_229

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-chloropiperidine-1-carboxylate 49 ((–)-sparteine)



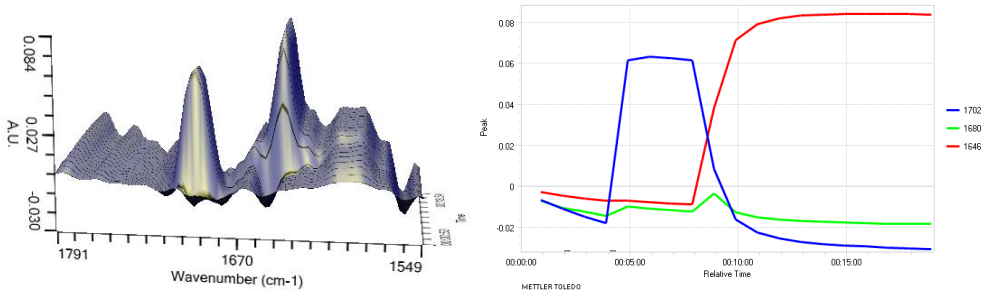
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (610 mg, 598 µL, 2.6 mmol, 1.3 eq.)

was added followed by a solution of 4-chloro-*N*-Boc piperidine **49** (220 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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 dropwise. The solution was stirred at –78 °C for 25 min.

For 4-trisyl-*N*-Boc piperidine **49**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1675 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1639 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 25 min, almost complete lithiation of 4-trisyl-*N*-Boc piperidine **49** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_227

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-methyl piperazine 151 (TMEDA)



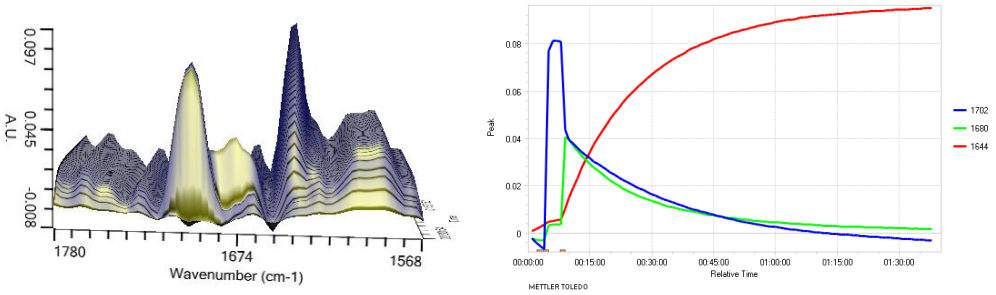
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 12 min.

For *N*-Boc-*N′*-methyl piperazine **151**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 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 *N*-Boc-*N′*-methyl piperazine **151** to give the lithiated intermediate was observed.

Lab Book Reference: JDF4_362

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-methyl piperazine 151 ((–)-sparteine)

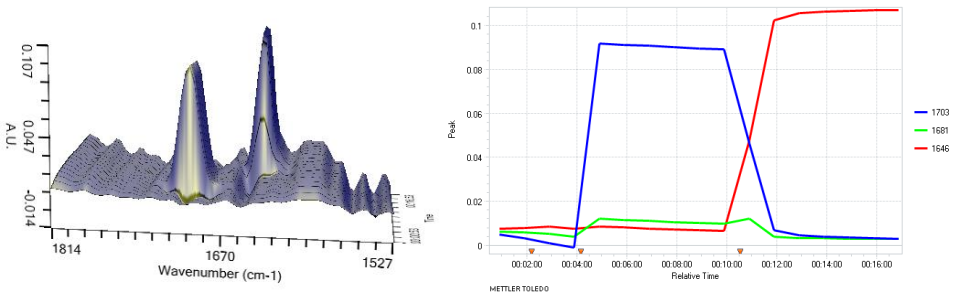


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 90 min.

For *N*-Boc-*N′*-methyl piperazine **151**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. 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 90 min, complete lithiation of *N*-Boc-*N′*-methyl piperazine **151** to give the lithiated intermediate was observed.

Lab Book Reference: JDF4_364

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-methyl piperazine 151 ((+)-sparteine surrogate (+)-26)

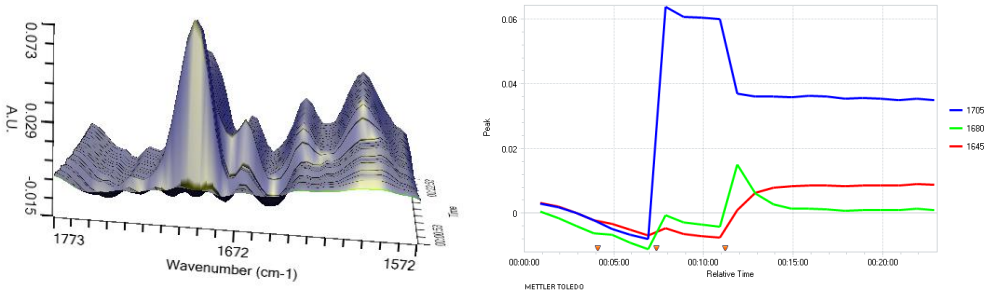


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 7 min.

For *N*-Boc-*N′*-methyl piperazine **151**, a peak at 1703 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 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-*N′*-methyl piperazine **151** to give the lithiated intermediate was observed.

Lab Book Reference: JDF5_427

ReactIR™ monitoring of the lithiation of *tert*-butyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate 68 ((+)-sparteine surrogate (+)-26)

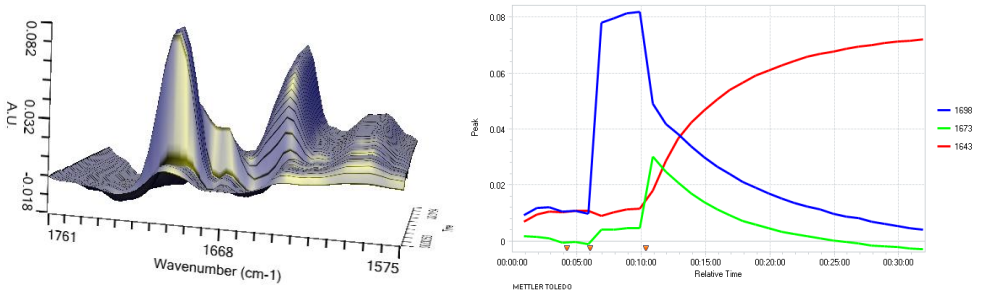


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of acetal **68** (243 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 12 min.

For acetal **68**, a peak at 1705 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 4 min, complete partial lithiation of acetal **68** to give the lithiated intermediate and acetal **68** was observed.

Lab Book Reference: JDF3_245

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate 98 (TMEDA)

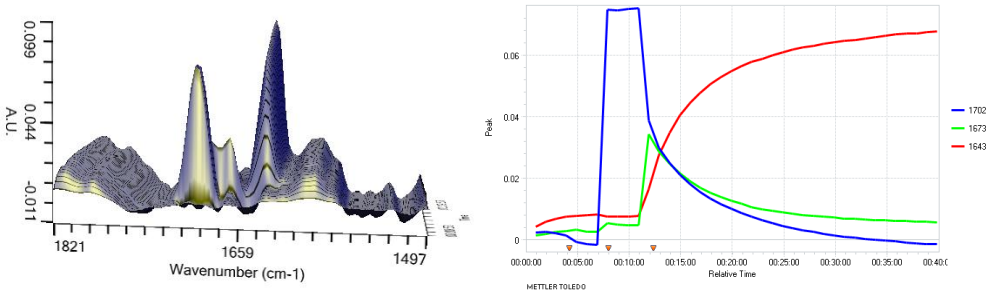


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of 4-OTIPS-*N*-Boc piperidine **98** (358 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 25 min.

For 4-OTIPS-*N*-Boc piperidine **98**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1673 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 25 min, almost complete lithiation of 4-OTIPS-*N*-Boc piperidine **98** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_230

ReactIR™ monitoring of the lithiation of *tert*-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate 98 ((+)-sparteine surrogate (+)-26)

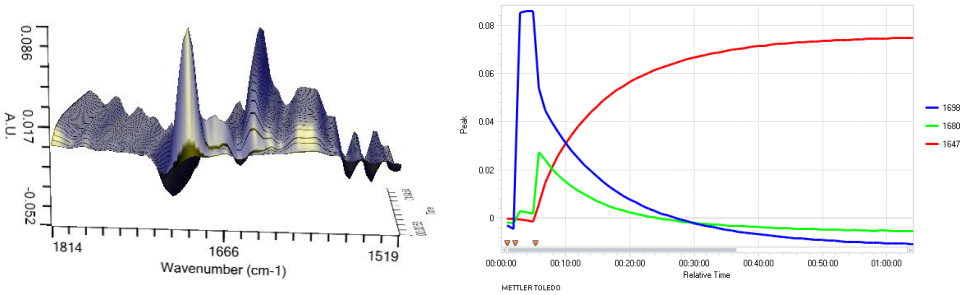


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of 4-OTIPS-*N*-Boc piperidine **98** (358 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 30 min.

For 4-OTIPS-*N*-Boc piperidine **98**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1673 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 30 min, complete lithiation of 4-OTIPS-*N*-Boc piperidine **98** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_244

ReactIR™ monitoring of the lithiation of 4-phenyl-*N*-Boc piperidine 66 (TMEDA)

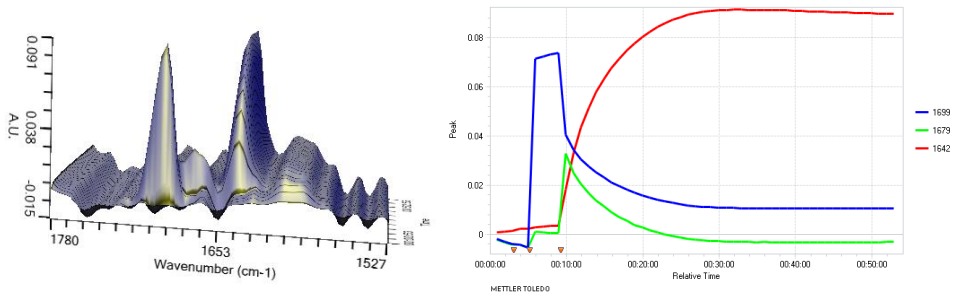


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of 4-phenyl-*N*-Boc piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 60 min.

For 4-phenyl-*N*-Boc piperidine **66**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 60 min, complete lithiation of 4-phenyl-*N*-Boc piperidine **66** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_221

ReactIR™ monitoring of the lithiation of 4-phenyl-*N*-Boc piperidine 66 ((+)-sparteine surrogate (+)-26)



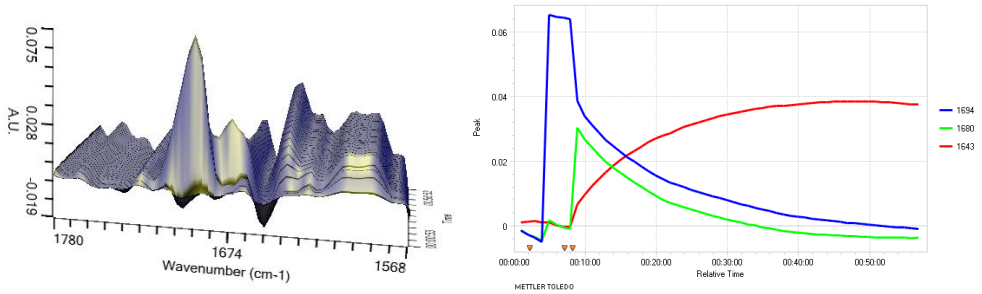
Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol,

1.3 eq.) in Et_2O (2 mL) was added followed by a solution of 4-phenyl-*N*-Boc piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 45 min.

For 4-phenyl-*N*-Boc piperidine **66**, a peak at 1699 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1642 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 20 min, complete lithiation of 4-phenyl-*N*-Boc piperidine **66** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_265

ReactIR™ monitoring of the lithiation of 4-methyl-*N*-Boc piperidine 97 (TMEDA)

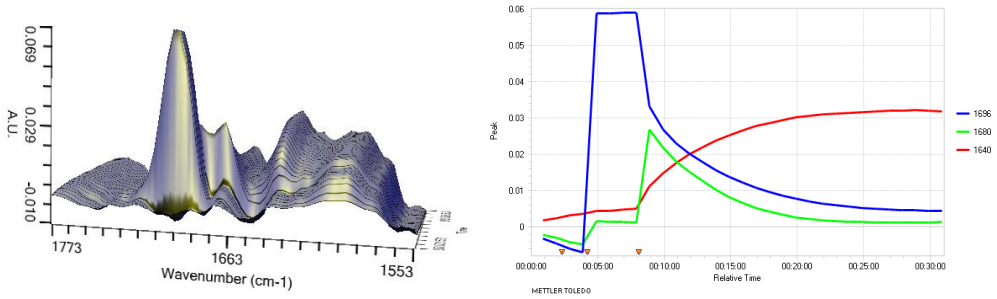


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –60 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of 4-methyl-*N*-Boc piperidine **97** (199 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –60 °C for 50 min.

For 4-methyl-*N*-Boc piperidine **97**, a peak at 1694 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 45

min, complete lithiation of 4-methyl-*N*-Boc piperidine **97** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_261

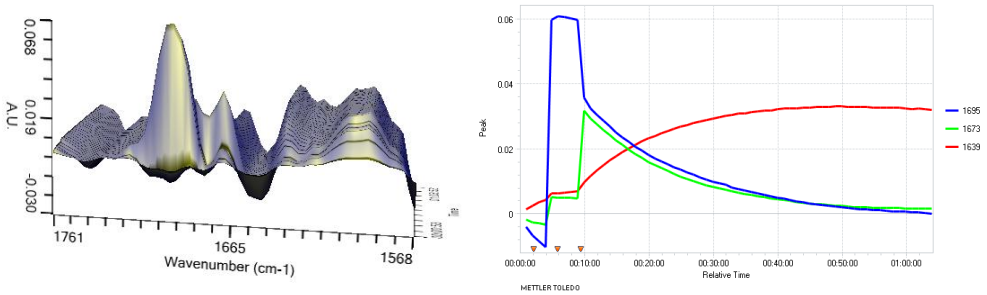


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –50 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of 4-methyl-*N*-Boc piperidine **97** (199 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –50 °C for 25 min.

For 4-methyl-*N*-Boc piperidine **97**, a peak at 1694 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 25 min, complete lithiation of 4-methyl-*N*-Boc piperidine **97** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_269

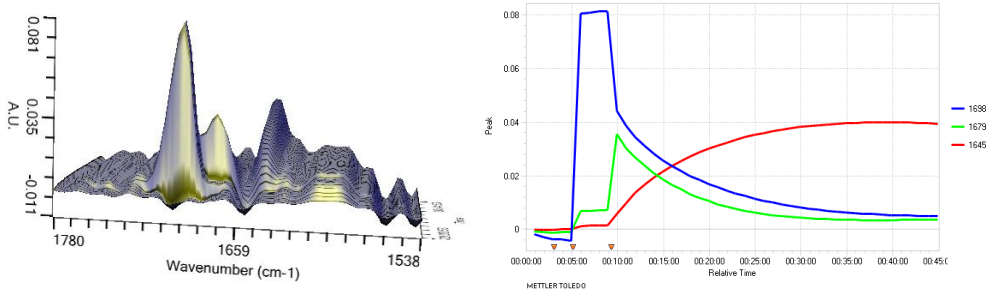
ReactIR™ monitoring of the lithiation of *N*-Boc piperidine 10 (TMEDA)



Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –60 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc piperidine **10** (185 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –60 °C for 55 min.

For *N*-Boc piperidine **10**, a peak at 1695 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1673 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1639 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 50 min, complete lithiation of *N*-Boc piperidine **10** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_260



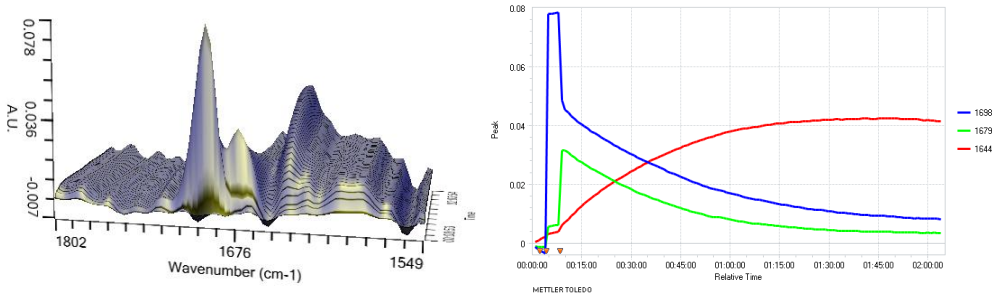
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –50 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc piperidine **10** (185 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on

ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –50 °C for 35 min.

For *N*-Boc piperidine **10**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 35 min, complete lithiation of *N*-Boc piperidine **10** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_266

ReactIR™ monitoring of the lithiation of *N*-Boc azepine 153 (TMEDA)

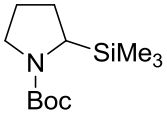


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –50 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc azepine **153** (199 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –50 °C for 2 h.

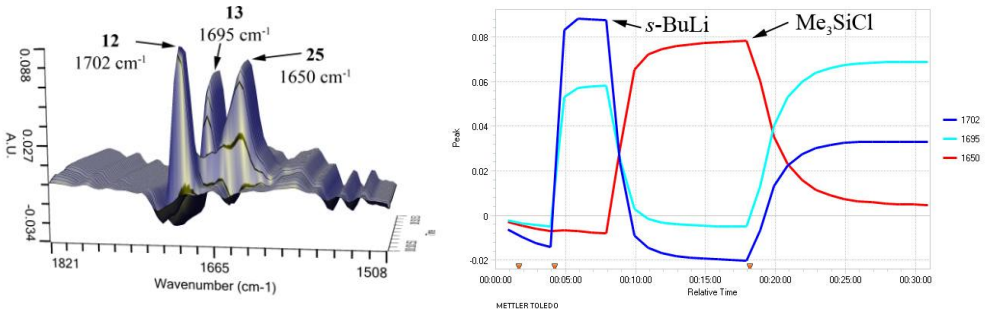
For *N*-Boc piperidine **1530**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 2 h, complete lithiation of *N*-Boc piperidine **153** to give the lithiated intermediate was observed.

Lab Book Reference: JDF3_268

tert-Butyl 2-(trimethylsilyl)pyrrolidine-1-carboxylate 13



13

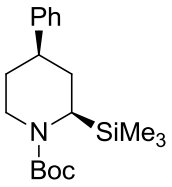


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1676 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1650 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **25**. The solution was stirred at –78 °C for 10 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate **25** had occurred. Then, Me_3SiCl (217 mg, 254 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **13**. The solution was stirred at –78 °C for 15 min. Complete trapping of lithiated intermediate **25** to give substituted *N*-Boc pyrrolidine **13** was observed after 15 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-Et_2O as eluent gave *N*-Boc pyrrolidine **13** (189 mg, 81%) as a pale yellow oil, R_F (9:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55–3.43 (m, 1H, NCH), 3.30–3.20 (m, 1H, NCH), 3.20–3.10 (m, 1H, NCH), 2.07–1.91 (m, 1H, CH), 1.83–1.67 (m, 3H, CH), 1.45 (s, 9H, CMe_3), 0.04 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6

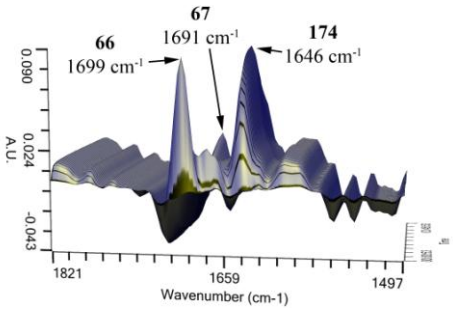
MHz, $CDCl_3$) (mixture of rotamers) δ 154.8 (C=O), 78.7 (*C*Me_3), 47.7 (NCH), 46.9 (NCH_2), 28.6 (C*Me*$_3$), 27.9 (CH_2), 25.5 (CH_2), 2.1 ($SiMe_3$). Spectroscopic data consistent with those reported in the literature.[62]

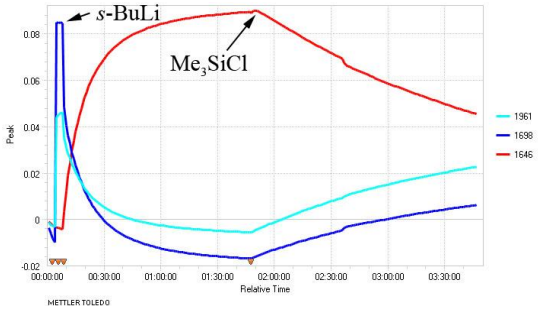
Lab Book Reference: JDF6_542

cis-_tert_-Butyl 4-phenyl-2-(trimethylsilyl)piperidine-1-carboxylate _cis_-67



cis-**67**



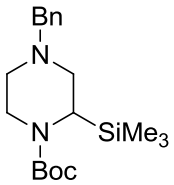


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-4-phenyl piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1699 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-4-phenyl piperidine **66**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1677 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **174**. The solution was stirred at –78 °C for 90 min. Complete lithiation of *N*-Boc-4-phenyl piperidine **66** to give the lithiated intermediate **174** had occurred. Then, Me_3SiCl (217 mg, 253 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1691 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-4-phenyl piperidine *cis*-**67**. The solution was stirred at –78 °C for 2 h. Incomplete trapping of lithiated intermediate **174** to give substituted *N*-

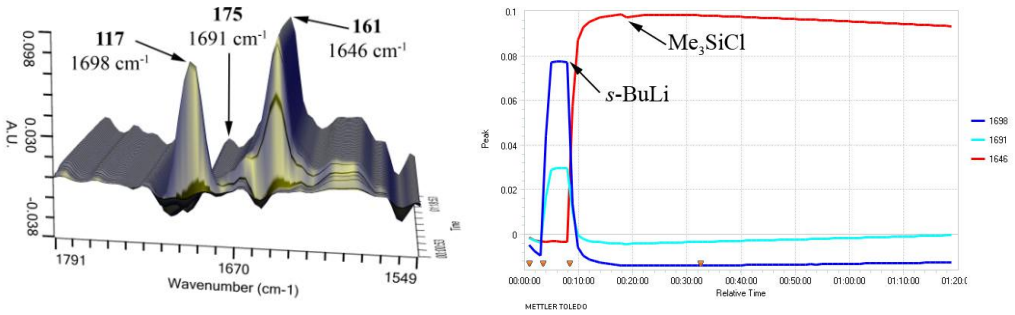
Boc-4-phenyl piperidine **67** and lithiated *N*-Boc-4-phenyl piperidine **174** was observed. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1-1:1 petrol-Et_2O as eluent gave *cis*-*N*-Boc piperidine *cis*-**67** (130 mg, 39%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H, Ph), 7.24-7.18 (m, 3H, Ph), 4.11 (br d, *J* = 13.0 Hz, 1H, NCH), 2.96 (br t, *J* = 12.0 Hz, 1H, NCH), 2.72 (tt, *J* = 12.0, 4.0 Hz, 1H, C*H*Ph), 2.42 (d, *J* = 12.0 Hz, 1H, NCH), 1.88-1.77 (m, 2H, CH), 1.68-1.54 (m, 2H, CH), 1.47 (s, 9H, CMe_3), 0.08 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 155.1 (C=O), 146.2 (*ipso*-Ph), 128.5 (Ph), 126.9 (Ph), 126.2 (Ph), 79.0 (*C*Me_3), 50.0 (NCH), 47.9 (NCH_2), 44.9 (*C*HPh), 34.2 (CH_2), 33.5 (CH_2), 28.4 (C*Me*$_3$), 0.7 ($SiMe_3$) and *N*-Boc-4-phenyl piperidine **66** (129 mg, 49%) as a colourless oil. Spectroscopic data for *cis*-**67** consistent with those reported in the literature.[73]

Lab Book Reference: JDF6_544

tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 175



175

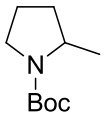


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was

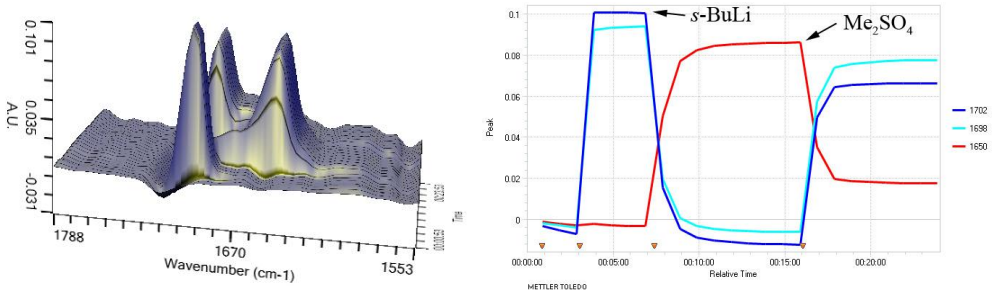
added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 10 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate **161** had occurred. Then, Me_3SiCl (217 mg, 253 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1691 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine **175**. The solution was stirred at –78 °C for 1 h. Incomplete trapping of lithiated intermediate **161** to give substituted *N*-Boc-*N′*-benzyl piperazine **175** and lithiated *N*-Boc-*N′*-benzyl piperazine **161** was observed. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **175** (20 mg, 6%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2977, 2804, 1673 (C=O), 1454, 1420, 1366, 1296, 1168, 1111, 1027, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.32-7.30 (m, 4H, Ph), 7.27-7.22 (m, 1H, Ph) 4.20 (br s, 0.6H, NCH), 3.80 (br s, 0.4H, NCH), 3.61-3.55 (m, 1H, NCH), 3.44 (d, J = 13.0 Hz, 1H, CH_AH_BPh), 3.40 (d, J = 13.0 Hz, 1H, CH_AH_BPh), 3.05 (br s, 0.4H, NCH), 2.92 (br s, 0.6H, NCH), 2.80 (d, J = 12.0 Hz, 1H, NCH), 2.72 (m, 0.6H, NCH), 2.64 (br s, 0.4H, NCH), 2.24 (br s, 1H, NCH), 1.93 (td, J = 12.0, 3.0 Hz, 1H, NCH), 1.46 (s, 9H, CMe_3), 0.12 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 138.3 (*ipso*-Ph), 129.1 (Ph), 128.1 (Ph), 127.0 (Ph), 79.1 (CMe_3), 63.4 (NCH_2), 54.3 (NCH_2), 53.2 (NCH_2), 45.3 (NCH), 41.4 (NCH_2), 28.4 (CMe_3), –0.8 ($SiMe_3$); MS (ESI) *m/z* 349 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{32}N_2O_2Si$ $(M + H)^+$ 349.2306, found 349.2297 (+1.7 ppm error). and *N*-Boc-*N′*-benzyl piperazine **117** (240 mg, 87%) as a colourless oil. Spectroscopic data consistent for **175** with those reported in the literature.[59]

Lab Book Reference: JDF6_543

tert-Butyl 2-methylpyrrolidine-1-carboxylate 33



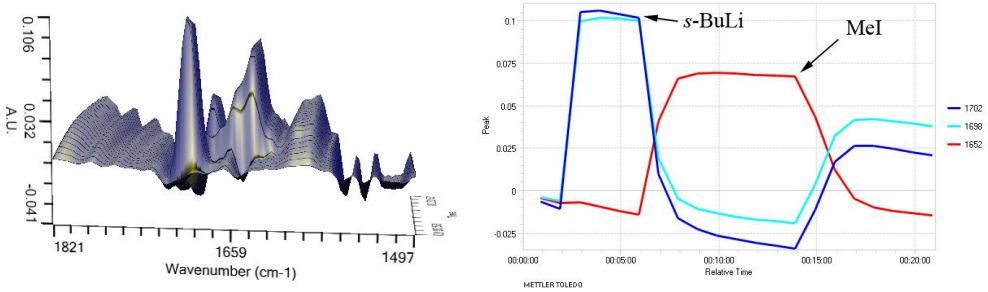
33



Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1650 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 9 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **33**. The solution was stirred at –78 °C for 10 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine **33** was observed within 3 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1 petrol-EtOAc as eluent gave *N*-Boc pyrrolidine **33** (122 mg, 66%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97-3.80 (m, 1H, NCH), 3.42-3.26 (m, 2H, NCH), 2.03-1.92 (m, 1H, CH), 1.91-1.82 (m, 1H, CH), 1.82-1.73 (m, 1H, CH), 1.57-1.46 (m, 1H, CH), 1.45 (s, 9H, CMe_3), 1.14 (d, J = 6.5 Hz, 3H, NCH*Me*); ^{13}C

NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.5 (C=O), 78.8 (CMe_3), 52.7 (NCH), 46.2 (NCH_2), 33.0 (CH_2), 28.5 (CMe_3), 23.2 (CH_2), 20.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[75]

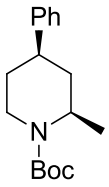
Lab Book Reference: JDF6_545



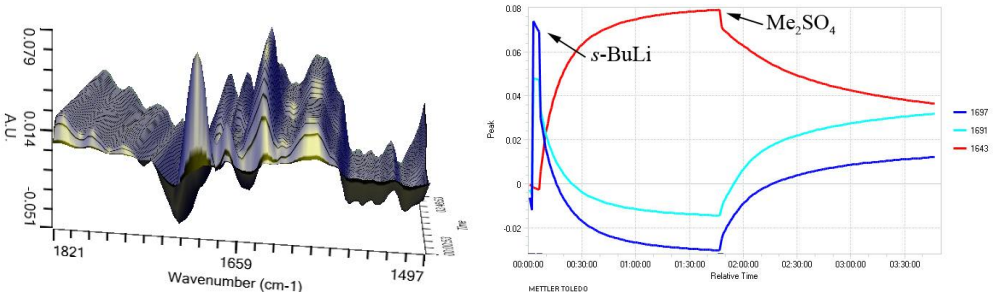
Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1652 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, methyl iodide (284 mg, 195 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **33**. The solution was stirred at –78 °C for 7 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine **33** was observed within 3 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1 petrol-EtOAc as eluent gave *N*-Boc pyrrolidine **33** (60 mg, 33%) as a colourless oil.

Lab Book Reference: JDF6_540

cis-_tert_-Butyl 2-methyl-4-phenylpiperidine-1-carboxylate _cis_-86



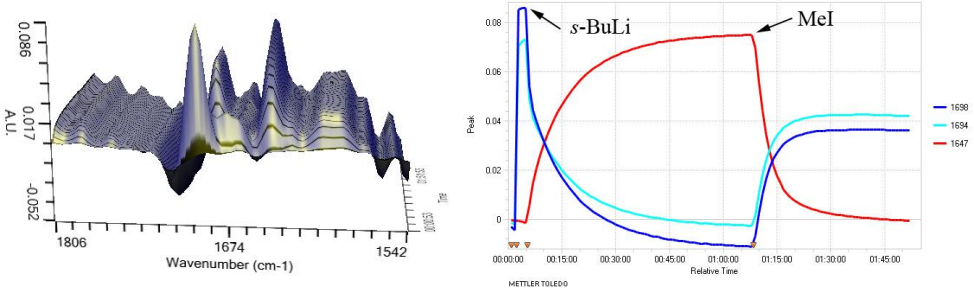
cis-**86**



Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-4-phenyl piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1697 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-4-phenyl piperidine **66**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1676 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 90 min. Complete lithiation of *N*-Boc-4-phenyl piperidine **66** to give the lithiated intermediate had occurred. Then, dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1691 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-4-phenyl piperidine *cis*-**86**. The solution was stirred at –78 °C for 2 h. Incomplete trapping of lithiated intermediate to give substituted *N*-Boc-4-phenyl piperidine *cis*-**86** and *N*-Boc-4-phenyl piperidine **66** was observed. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1 petrol-EtOAc as eluent gave *cis*-*N*-Boc piperidine *cis*-**86** (143 mg, 52%) as a colourless oil, R_F (19:1 petrol-EtOAc) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H, Ph),

7.23-7.17 (m, 3H, Ph), 4.02-3.90 (m, 1H, NCH), 3.81 (ddd, *J* = 14.0, 7.5, 3.0 Hz, 1H, NCH), 3.25 (ddd, *J* = 14.0, 10.0, 6.5 Hz, 1H, NCH), 2.82-2.68 (m, 1H, C*H*Ph), 2.21-2.10 (m, 1H, CH), 1.91 (dddd, *J* = 13.5, 6.0, 3.0, 1.5 Hz, 1H, CH), 1.66-1.55 (m, 2H, CH), 1.49 (s, 9H, CMe_3), 1.20 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (C=O), 146.0 (*ipso*-Ph), 128.5 (Ph), 126.8 (Ph), 126.1 (Ph), 79.2 (*C*Me_3), 50.1 (NCH), 38.0 (*C*HPh), 37.6 (NCH_2), 37.1 (CH_2), 31.3 (CH_2), 28.5 (C*Me*$_3$), 19.9 (CH*Me*). Spectroscopic data consistent with those reported in the literature.[271]

Lab Book Reference: JDF6_547

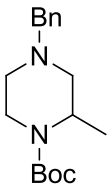


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-4-phenyl piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-4-phenyl piperidine **66**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 60 min. Complete lithiation of *N*-Boc-4-phenyl piperidine **66** to give the lithiated intermediate had occurred. Then, methyl iodide (284 mg, 124 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-4-phenyl piperidine *cis*-**86**. The solution was stirred at –78 °C for 45 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-4-phenyl piperidine *cis*-**86** was observed within 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were

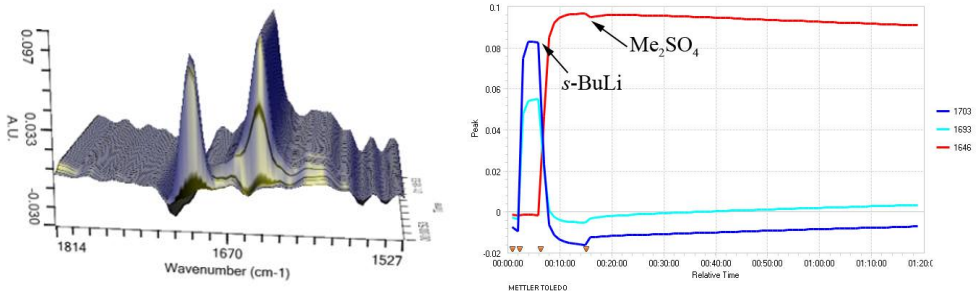
dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-19:1 petrol-EtOAc as eluent gave *cis*-*N*-Boc piperidine *cis*-**86** (192 mg, 70%) as a colourless oil.

Lab Book Reference: JDF6_541

tert-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate 176



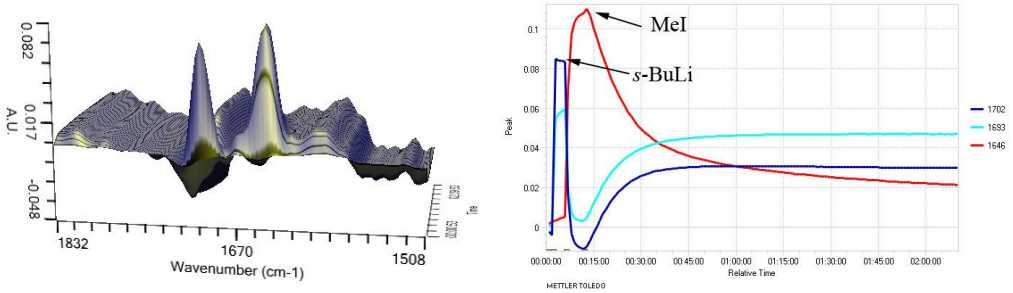
176



Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1703 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 10 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1693 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine **176**. The solution was stirred at –78 °C for 2 h. Incomplete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazine **176** and *N*-Boc-*N′*-benzyl piperazine **117** was

observed. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (11 mg, 4%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.6; IR (ATR) 2973, 1688 (C=O), 1452, 1407, 1392, 1364, 1341, 1322, 1305, 1279, 1247, 1223, 1158, 1107, 1059, 1039, 1028, 740, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 4.18 (br s, 1H, NCH), 3.80 (br d, J = 12.5 Hz, 1H, NCH), 3.53 (d, J = 13.0 Hz, 1H, CH_AH$_B$Ph), 3.40 (d, J = 13.0 Hz, 1H, CH$_A$$H_B$Ph), 3.11 (td, J = 12.5, 3.5 Hz, 1H, NCH), 2.77-2.73 (m, 1H, NCH), 2.59 (dt, J = 11.0, 1.5 Hz, NCH), 2.12 (dd, J = 11.0, 4.0 Hz, 1H, NCH), 2.00 (ddd, J = 12.5, 11.5, 3.5 Hz, 1H, NCH), 1.45 (s, 9H, CMe_3), 1.24 (d, J = 6.5 Hz, 3H, CHMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8 (C=O), 138.4 (*ipso*-Ph), 128.7 (Ph), 128.2 (Ph), 127.0 (Ph), 79.3 (CMe$_3$), 62.8 (NCH$_2$), 57.3 (NCH$_2$), 53.2 (NCH$_2$), 47.0 (NCH), 39.1 (NCH$_2$), 28.4 (CMe_3), 15.9 (Me); MS (ESI) *m/z* 291 $(M + H)^+$. Spectroscopic data consistent with those reported in the literature.[150]

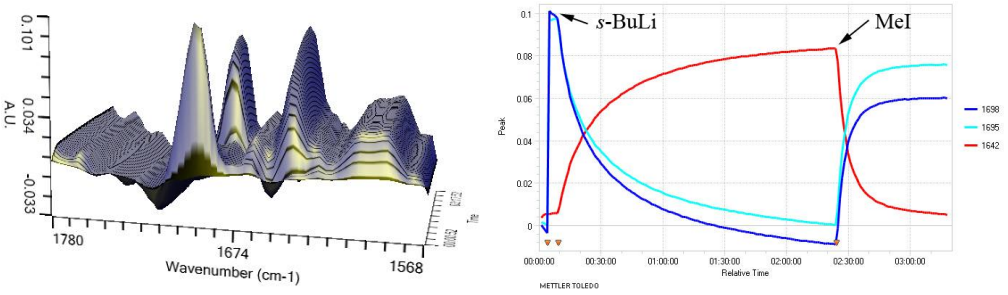
Lab Book Reference: JDF6_554



Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which

was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, methyl iodide (284 mg, 124 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1693 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine **176**. The solution was stirred at –78 °C for 2 h. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazine **176** was observed within 2 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (218 mg, 75%) as a colourless oil.

Lab Book Reference: JDF6_539

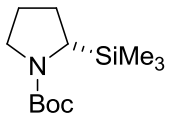


THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1695 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1642 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 210 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, methyl iodide (284 mg, 124 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1695 cm^{-1} was observed which was

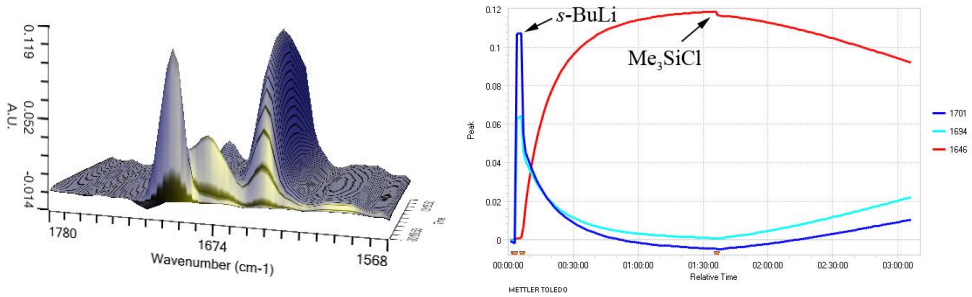
assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine **176**. The solution was stirred at –78 °C for 1 h. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazine **176** was observed within 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (217 mg, 75%) as a colourless oil.

Lab Book Reference: JDF7_604

(*S*)-*tert*-Butyl 2-(trimethylsilyl)pyrrolidine-1-carboxylate (*S*)-13



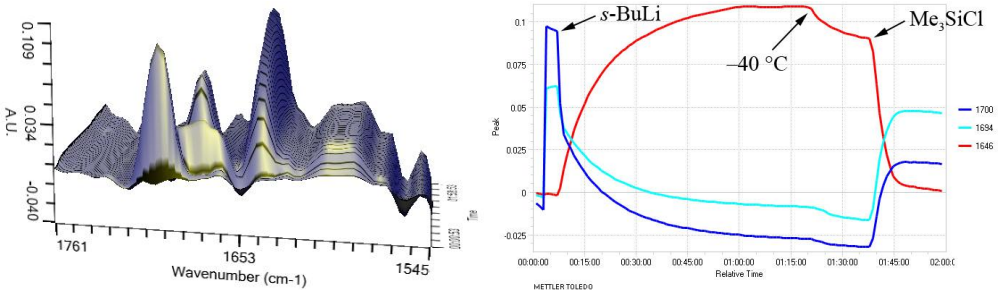
(*S*)-**13**



Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 90 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, Me_3SiCl (217 mg, 254 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1694 cm^{-1} was

observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine (*S*)-**13**. The solution was stirred at –78 °C for 90 min. Incomplete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine (*S*)-**13** and *N*-Boc pyrrolidine **12** was observed. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 4:1-1:1 petrol-Et_2O as eluent gave *N*-Boc pyrrolidine (*S*)-**13** (30 mg, 12%, 98:2 er by CSP-GC) as a pale yellow oil, $[\alpha]_D$ +66.0 (*c* 1.3 in $CHCl_3$) (lit.,[62] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**13** of 98:2 er); CSP-GC: *β*-cyclodextrin (100 °C) (*S*)-**13** 45.7 min, (*R*)-**13** 48.6 min, and *N*-Boc pyrrolidine **12** (144 mg, 84%) as a clear oil.

Lab Book Reference: JDF6_584

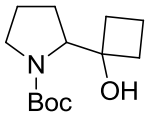


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1700 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1678 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 80 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, the solution warmed to –40 °C and stirred for 10 min (to verify the stability of readout on ReactIR™). Then, Me_3SiCl (217 mg, 254 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-

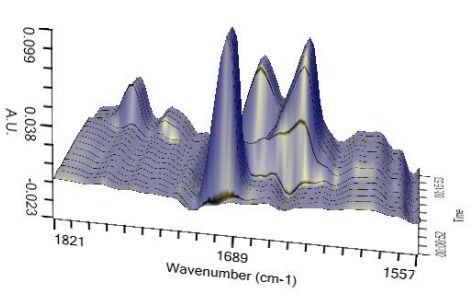
Boc pyrrolidine (*S*)-**13**. The solution was stirred at –40 °C for 25 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine (*S*)-**13** was observed within 10 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 4:1-1:1 petrol-Et_2O as eluent gave *N*-Boc pyrrolidine (*S*)-**13** (178 mg, 73%, 98:2 er by CSP-GC) as a pale yellow oil, $[\alpha]_D$ +71.8 (*c* 1.0 in $CHCl_3$) (lit.,[62] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**13** of 98:2 er); CSP-GC: *β*-cyclodextrin (100 °C) (*S*)-**13** 45.7 min, (*R*)-**13** 48.6 min.

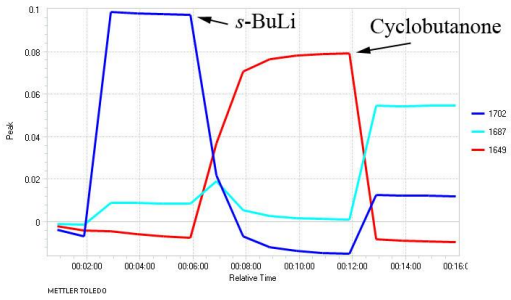
Lab Book Reference: JDF7_602

***tert*-Butyl 2-(1-hydroxycyclobutyl)pyrrolidine-1-carboxylate 177**



177



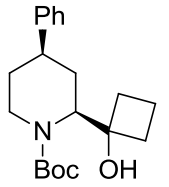


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1649 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 6 min. Complete lithiation

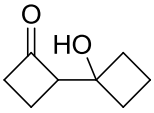
of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, cyclobutanone (140 mg, 149 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1687 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **177**. The solution was stirred at –78 °C for 4 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine **177** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-8:2 petrol-EtOAc as eluent gave *N*-Boc pyrrolidine **177** (180 mg, 74%) as a white solid, mp 104-105 °C; R_F (8:2 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3266 (OH), 2970, 2953, 1639 (C=O), 1453, 1378, 1346, 1199, 1147, 1099, 909, 769, 726, 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (br s, 1H, OH), 3.95 (dd, *J* = 8.0, 5.5 Hz, 1H, NCH), 3.69-3.53 (m, 1H, NCH), 3.33-3.21 (m, 1H, NCH), 2.39-2.25 (m, 1H, CH), 2.15-1.81 (m, 7H, CH), 1.78-1.67 (m, 1H, CH), 1.59-1.50 (m, 1H, CH), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.7 (C=O), 80.0 (C), 78.7 (C), 64.0 (NCH), 48.3 (NCH_2), 34.0 (CH_2), 32.2 (CH_2), 28.4 (CMe_3), 27.7 (CH_2), 24.3 (CH_2), 13.0 (CH_2); MS (ESI) *m/z* 264 [$(M + Na)^+$, 40], 242 [$(M + H)^+$, 100], 186 [$(M – CMe_3)^+$, 70]; HRMS *m/z* calcd for $C_{13}H_{23}NO_3$ $(M + H)^+$ 242.1751, found 242.1748 (+1.5 ppm error) and *N*-Boc pyrrolidine **12** (20 mg, 12%) as a clear oil.

Lab Book Reference: JDF6_551

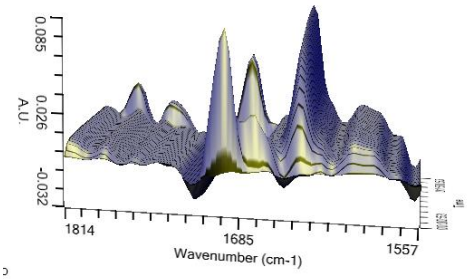
cis-tert-Butyl 2-(1-hydroxycyclobutyl)-4-phenylpiperidine-1-carboxylate _cis_-178 and 1'-hydroxybi(cyclobutan)-2-one 180

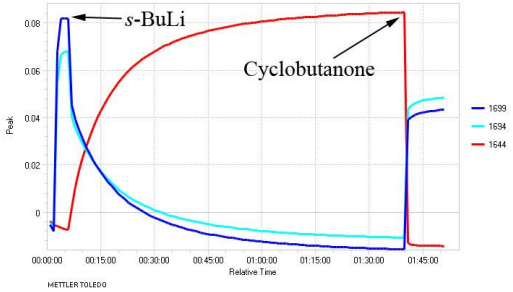


cis-**178**



180



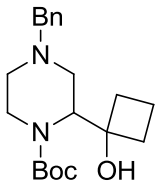


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-4-phenyl piperidine **66** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1699 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-4-phenyl piperidine **66**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 90 min. Complete lithiation of *N*-Boc-4-phenyl piperidine **66** to give the lithiated intermediate had occurred. Then, cyclobutanone (140 mg, 149 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-4-phenyl piperidine *cis*-**178**. The solution was stirred at –78 °C for 10 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-4-phenyl piperidine *cis*-**178** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 8:2-3:7 petrol-Et_2O as eluent gave *cis*-*N*-Boc piperidine *cis*-**178** (185 mg, 56%) as a colourless oil, R_F (7:3

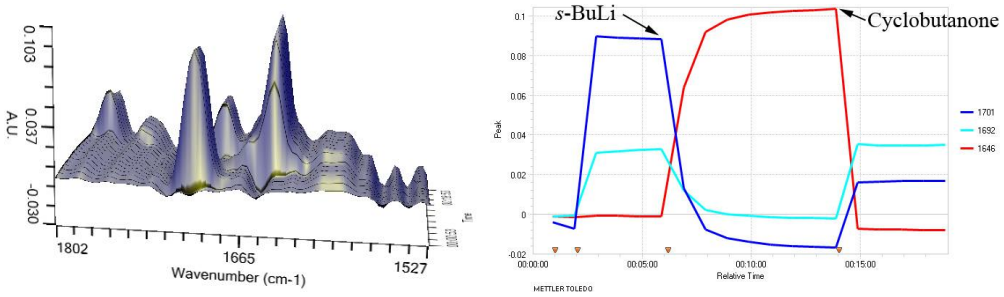
petrol-Et_2O) 0.2; IR ($CHCl_3$) 3281 (OH), 2936, 2894, 1648 (C=O), 1454, 1430, 1402, 1346, 1315, 1268, 1227, 1139, 1046, 1026, 745, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H, Ph), 7.24-7.17 (m, 3H, Ph), 5.36 (br s, 1H, OH), 4.09 (dt, *J* = 13.5, 4.0 Hz, 1H, NCH), 3.41 (dd, *J* = 11.0, 2.5 Hz, 1H, NCH), 3.16-3.04 (m, 1H, NCH), 2.86-2.74 (m, 1H, C*H*Ph), 2.32-2.21 (m, 1H, CH), 2.19-2.01 (m, 2H, CH), 2.00-1.80 (m, 5H, CH), 1.67-1.51 (m, 2H, CH), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 155.7 (C=O), 145.4 (*ipso*-Ph), 128.4 (Ph), 126.8 (Ph), 126.3 (Ph), 80.2 (C), 75.1 (C), 65.8 (NCH), 47.9 (NCH_2), 42.7 (*C*HPh), 34.0 (CH_2), 33.8 (CH_2), 33.5 (CH_2), 28.4 (CMe_3), 12.7 (CH_2); MS (ESI) *m/z* 354 [$(M + Na)^+$, 80], 332 [$(M + H)^+$, 100], 276 [$(M - CMe_3)^+$, 20]; HRMS *m/z* calcd for $C_{20}H_{29}NO_3$ $(M + H)^+$ 332.2220, found 332.2205 (+4.2 ppm error) and hydroxy ketone **180** (44 mg, 24%) as a colourless oil, R_F (7:3 petrol-Et_2O) 0.1; IR ($CHCl_3$) 3425 (OH), 2942, 1747 (C=O), 1365, 1217, 1154, 1071, 1000, 932, 687, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (ddt, *J* = 10.0, 7.0, 2.5 Hz, 1H, CHC=O), 3.07-2.86 (m, 2H, CH_2C=O), 2.35-2.24 (m, 1H, CH), 2.18-1.95 (m, 6H, CH + OH), 1.87-1.75 (m, 1H, CH), 1.63-1.51 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 211.3 (C=O), 74.3 (COH), 67.5 (*C*HC=O), 45.4 (*C*H_2C=O), 35.1 (CH_2), 34.8 (CH_2), 12.7 (CH_2), 12.0 (CH_2); MS (ESI) *m/z* 163 [$(M + Na)^+$, 100], 141 [$(M + H)^+$, 40]; HRMS *m/z* calcd for $C_8H_{12}O_2$ $(M + H)^+$ 141.0910, found 141.0911 (–1.1 ppm error) and *N*-Boc-4-phenyl piperidine **66** (80 mg, 31%) as a clear oil.

Lab Book Reference: JDF6_553

tert-Butyl 4-benzyl-2-(1-hydroxycyclobutyl)piperazine-1-carboxylate 179



179

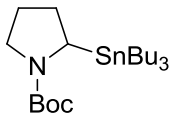


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N*′-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N*′-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N*′-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, cyclobutanone (140 mg, 149 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1692 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N*′-benzyl piperazine **179**. The solution was stirred at –78 °C for 6 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N*′-benzyl piperazine **179** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **179** (206 mg, 59%) as a colourless oil, R_F (8:2 petrol-EtOAc) 0.2; IR

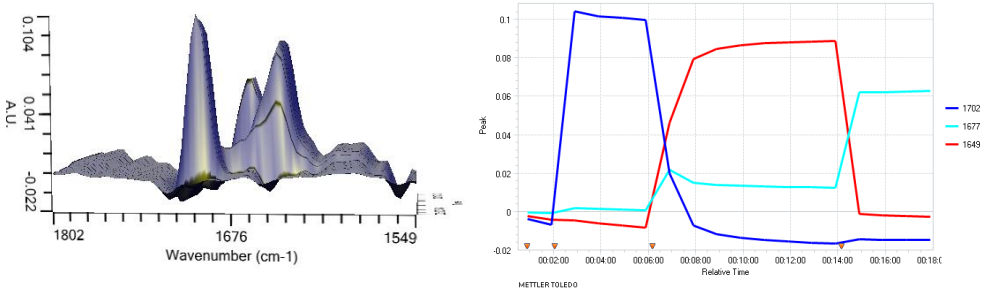
($CHCl_3$) 2973, 1653 (C=O), 1394, 1354, 1274, 1197, 1151, 1106, 1015, 749, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.35-7.23 (m, 5H, Ph), 6.82 (br s, 1H, OH), 4.28 (br s, 0.4H, NCH), 4.13-4.04 (m, 1.2H, NCH), 3.90 (br d, *J* = 12.5 Hz, 0.4H, NCH), 3.60-3.35 (m, 3H, NCH), 3.18-3.06 (m, 1H, NCH), 2.85-2.71 (m, 1H, NCH), 2.40-2.28 (m, 1H, NCH), 2.15-2.02 (m, 2H, NCH + CH), 2.01-1.83 (m, 3H, CH), 1.72-1.61 (m, 1H, CH), 1.61-1.49 (m, 1H, CH), 1.47 (s, 5.4H, CMe_3), 1.45 (s, 3.6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 155.2 (C=O), 154.8 (C=O), 136.4 (*ipso*-Ph), 136.3 (*ipso*-Ph), 129.0 (Ph), 128.5 (Ph), 127.6 (Ph), 80.4 (C), 80.3 (C), 79.7 (C), 62.8 (NCH_2Ph), 53.3 (NCH), 52.9 (NCH_2), 52.8 (NCH_2), 52.3 (NCH), 52.2 (NCH_2), 52.0 (NCH_2), 41.6 (NCH_2), 40.3 (NCH_2), 36.3 (CH_2), 36.1 (CH_2), 32.7 (CH_2), 28.4 (CMe_3), 28.3 (CMe_3), 11.3 (CH_2), 11.2 (CH_2); MS (ESI) *m/z* 347 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{30}N_2O_3$ $(M + H)^+$ 347.2329, found 347.2328 (+0.1 ppm error) and *N*-Boc-*N′*-benzyl piperazine **117** (81 mg, 29%) as a white solid.

Lab Book Reference: JDF6_552

tert-Butyl 2-(tributylstannyl)pyrrolidine-1-carboxylate 21



21

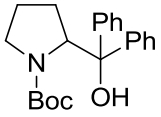


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new

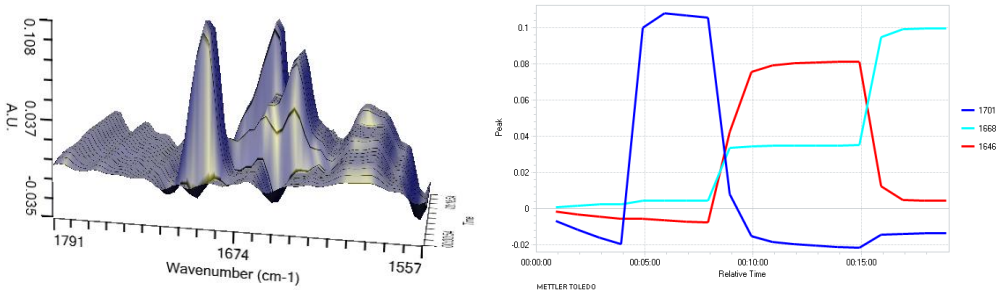
peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1649 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, tributyltin chloride (650 mg, 542 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1677 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **21**. The solution was stirred at –78 °C for 4 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine **21** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 98:2 petrol-EtOAc as eluent gave *N*-Boc pyrrolidine **21** (276 mg, 60%) as a pale yellow oil, R_F (98:2 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 3.73-3.69 (m, 0.3H, NCH), 3.42-3.27 (m, 1.7H, NCH), 3.20-3.12 (m**,** 1H, NCH), 2.24-2.04 (m, 1H, CH), 1.95-1.73 (m, 3H, CH), 1.55-1.40 (m, 6H, CH), 1.48 (s, 2.7H, CMe_3), 1.44 (s, 6.3H, CMe_3), 1.31-1.24 (m, 6H, CH_2), 0.93-0.81 (m, 15H, CH_2 + Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.1 (C=O), 78.2 (CMe_3), 46.7 (NCH), 46.4 (NCH), 30.4 (NCH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.7 (CMe_3), 28.6 (CMe_3), 27.9 (CH_2), 27.7 (CH_2), 27.2 (CH_2), 13.8 (Me), 10.0 (CH_2), 9.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[62]

Lab Book Reference: JDF6_571

tert-Butyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate 36



36

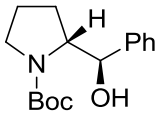


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added dropwise. A new peak at 1668 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine **36**. The solution was stirred at –78 °C for 5 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine **36** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc pyrrolidine **36** (241 mg, 68%) as a white solid, mp 106-108 °C (lit.,[272] 101-103 °C); R_F (7:3 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 4H, Ph), 7.34-7.23 (m, 6H, Ph), 6.44 (br s, 1H, OH), 4.90 (dd, J = 9.0, 3.5 Hz, 1H, NCH), 3.42-3.26 (m, 1H, NCH), 2.86 (br s, 1H, NCH),

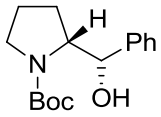
2.16-2.03 (m, 1H, CH), 1.96-1.88 (m, 1H, CH), 1.48-1.42 (m, 1H, CH), 1.44 (s, 9H, CMe_3), 0.76 (br s, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 157.8 (C=O), 146.4 (*ipso*-Ph), 143.7 (*ipso*-Ph), 128.5 (Ph), 128.2 (Ph), 127.8 (Ph), 127.7 (Ph), 127.3 (Ph), 127.1 (Ph), 127.0 (Ph), 126.5 (Ph), 81.6 (Ph_2COH), 80.6 (CMe_3), 65.7 (NCH), 47.8 (NCH_2), 29.7 (CH_2), 28.5 (CMe_3), 28.3 (CMe_3), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[272]

Lab Book Reference: JDF6_567

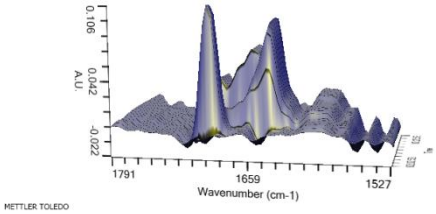
2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-31 and *anti*-32

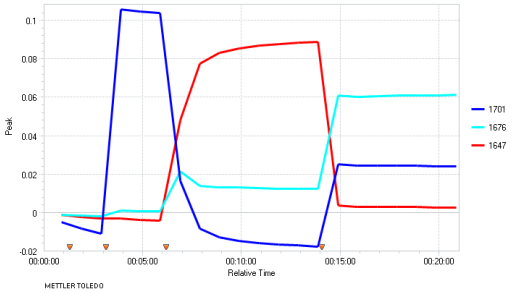


syn-**31**



anti-**32**



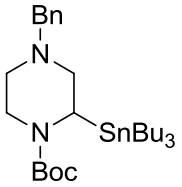


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, benzaldehyde (212 mg, 203 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1676 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc

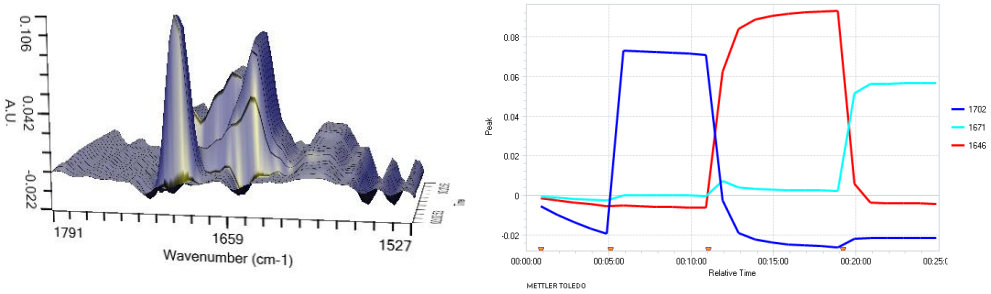
pyrrolidines *syn*-**31** and *anti*-**32**. The solution was stirred at –78 °C for 10 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidines *syn*-**31** and *anti*-**32** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 98:2 CH_2Cl_2-acetone as eluent gave *N*-Boc pyrrolidine *syn*-**31** (165 mg, 59%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, Ph), 4.69 (br s, 1H, CHO*H*), 4.54 (d, *J* = 9.0 Hz, 1H, C*H*OH), 4.11-4.06 (m, 1H, NCH), 3.49-3.43 (m, 1H, NCH), 3.40-3.26 (m, 1H, NCH), 1.76-1.64 (m, 2H, CH), 1.64-1.45 (m, 1H, CH), 1.52 (s, 9H, CMe_3), 1.36-1.25 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 158.3 (C=O), 142.4 (*ipso*-Ph), 128.3 (Ph), 127.7 (Ph), 127.2 (Ph), 80.7 (*C*Me_3), 76.3 (CHOH), 64.0 (NCH), 47.5 (NCH_2), 28.6 (CH_2), 28.5 (C*Me*$_3$), 23.6 (CH_2) and *N*-Boc pyrrolidine *anti*-**32** (94 mg, 34%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H, Ph), 4.94 (br s, 1H, C*H*OH), 4.23 (br s, 1H, NCH), 3.81 (br s, 1H, CHO*H*), 3.39-3.33 (m, 1H, NCH), 2.94 (br s, 1H, NCH), 1.94-1.72 (m, 2H, CH), 1.63-1.47 (m, 2H, CH), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 157.1 (C=O), 141.2 (*ipso*-Ph), 128.0 (Ph), 127.3 (Ph), 126.7 (Ph), 80.3 (*C*Me_3), 76.2 (CHOH), 63.3 (NCH), 47.7 (NCH_2), 28.5 (C*Me*$_3$), 26.9 (CH_2), 23.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[67] The total yield of *syn*-**31** and *anti*-**32** was 93%.

Lab Book Reference: JDF6_566

tert-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate 181



181

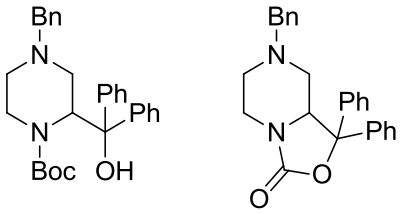


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N*′-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N*′-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1675 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N*′-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, tributyltin chloride (650 mg, 542 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1671 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N*′-benzyl piperazine **181**. The solution was stirred at –78 °C for 6 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N*′-benzyl piperazine **181** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **181** (324 mg, 57%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; IR

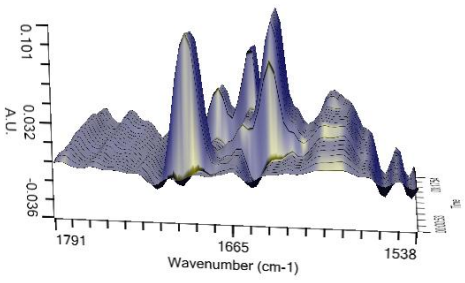
($CHCl_3$) 2961, 2911, 2881, 2827, 1647 (C=O), 1433, 1395, 1395, 1344, 1278, 1231, 1151, 1088, 1055, 1007, 850, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.38–7.21 (m, 5H, Ph), 4.13 (s, 0.5H, NCH), 4.03 (br d, *J* = 13.0 Hz, 0.5H, NCH), 3.80–3.16 (m, 4H, NCH), 2.82–2.37 (m, 3H, NCH), 2.21 (br s, 0.5H, NCH), 1.96–1.80 (m, 0.5H, NCH), 1.55–1.35 (m, 15H, CH_2 + CMe_3), 1.35–1.23 (m, 6H, CH_2), 0.99–0.78 (m, 15H, CH_2 + Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.6 (C=O), 154.2 (C=O), 138.2 (*ipso*-Ph), 129.4 (Ph), 128.3 (Ph), 127.2 (Ph), 79.5 (CMe_3), 79.4 (CMe_3), 63.3 (NCH_2), 58.1 (NCH_2), 53.2 (NCH_2), 53.0 (NCH_2), 46.5 (NCH), 45.5 (NCH), 44.8 (NCH_2), 42.6 (NCH_2), 29.3 (CH_2), 29.3 (CH_2), 28.5 (CMe_3), 27.9 (CH_2), 27.7 (CH_2), 13.8 (Me), 11.1 (CH_2), 10.4 (CH_2); MS (ESI) *m/z* 567 $(M + H)^+$; HRMS *m/z* calcd for $C_{28}H_{50}N_2O_2Sn$ $(M + H)^+$ 567.2972, found 567.2945 (+3.9 ppm error).

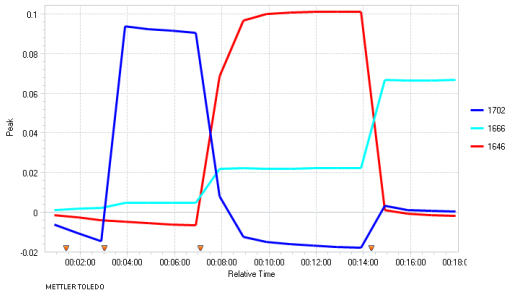
Lab Book Reference: JDF6_572

tert-Butyl 4-benzyl-2-(hydroxydiphenylmethyl)piperazine-1-carboxylate 182 and 7-benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 183



182 **183**





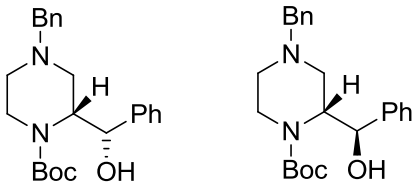
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of

readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1676 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added dropwise. A new peak at 1666 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine **182** and oxazolidinone **183**. The solution was stirred at –78 °C for 4 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazine **182** and oxazolidinone **183** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine **182** (230 mg, 50%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3117 (OH), 2960, 2782, 1654 (C=O), 1430, 1394, 1345, 1320, 1282, 1197, 1150, 1107, 1049, 1002, 849, 746, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.77 (br s, 0.5H, OH), 7.67-7.43 (m, 4.5H, Ph + OH), 7.36-7.04 (m, 11H, Ph), 5.17 (d, *J* = 3.0 Hz, 0.5H, NCH), 4.85 (d, *J* = 3.0 Hz, 0.5H, NCH), 4.16 (dd, *J* = 13.5, 3.5 Hz, 0.5H, NCH), 3.90-3.70 (m, 1.5H, NCH), 3.45-3.27 (m, 2H, NCH), 3.00 (dd, *J* = 11.5, 6.0 Hz, 1H, NCH), 2.94 (d, *J* = 11.5Hz, 0.5H, NCH), 2.85 (d, *J* = 11.5 Hz, 0.5H, NCH), 2.36-2.25 (m, 1H, NCH), 2.21-2.07 (m, 1H, NCH), 1.26 (s, 4.5H, CMe_3), 1.20 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.6 (C=O), 154.2 (C=O), 147.1 (*ipso*-Ph), 146.5 (*ipso*-Ph), 144.8 (*ipso*-Ph), 144.5 (*ipso*-Ph), 136.1 (*ipso*-Ph), 129.2 (Ph), 129.1 (Ph), 128.5 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 127.6 (Ph), 127.3 (Ph), 126.8 (Ph), 126.7 (Ph), 126.6 (Ph), 126.5 (Ph), 126.4 (Ph), 126.3 (Ph), 126.1 (Ph), 125.8 (Ph), 83.6 (Ph_2COH), 83.5 (Ph_2COH), 79.8 (CMe_3), 62.8 (NCH_2Ph), 55.6 (NCH), 54.5 (NCH_2), 53.9 (NCH), 53.7 (NCH_2), 52.6 (NCH_2), 52.5 (NCH_2), 41.6 (NCH_2), 40.6 (NCH_2), 28.2 (CMe_3), 27.9 (CMe_3); MS (ESI) *m/z* 459 $(M + H)^+$; HRMS *m/z* calcd for $C_{29}H_{34}N_2O_3$ $(M + H)^+$ 459.2642, found 459.2626 (+3.9 ppm error) and oxazolidinone **183** (40 mg, 10%) as a white solid, mp 146-149 °C; R_F (7:3 petrol-Et_2O) 0.2; IR

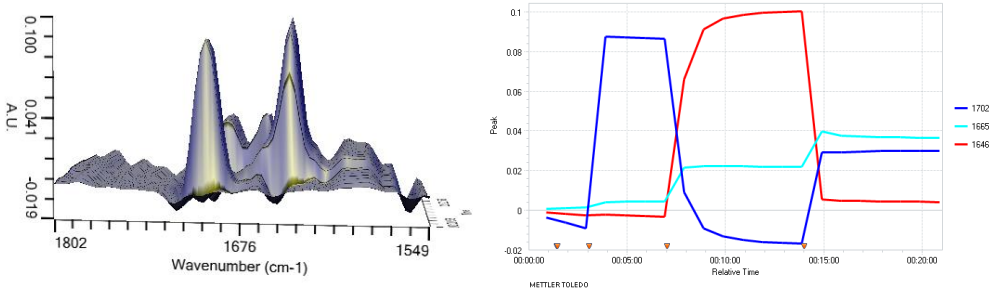
($CHCl_3$) 3020, 2400, 1751 (C=O), 1422, 1215, 929, 759, 669 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H, Ph), 7.40-7.21 (m, 13H, Ph), 4.54 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.80 (ddd, *J* = 13.0, 3.5, 1.5 Hz, 1H, NCH), 3.50 (d, *J* = 13.0 Hz, 1H, CH_AH$_B$Ph), 3.31 (d, *J* = 13.0 Hz, 1H, CH$_A$$H_B$Ph), 3.09 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.70-2.66 (m, 1H, NCH), 2.55 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, NCH), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.57 (t, *J* = 11.0 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5 (C=O), 142.7 (*ipso*-Ph), 139.1 (*ipso*-Ph), 137.6 (*ipso*-Ph), 129.1 (Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.6 (Ph), 126.2 (Ph), 126.0 (Ph), 85.3 (Ph_2CO), 62.9 (NCH_2), 61.1 (NCH), 55.7 (NCH_2), 50.7 (NCH_2), 41.5 (NCH_2); MS (ESI) *m/z* 385 $(M + H)^+$; HRMS *m/z* calcd for $C_{25}H_{24}N_2O_2$ $(M + H)^+$ 385.1911, found 385.1899 (+3.6 ppm error). Spectroscopic data consistent with those reported in the literature.[59] The total yield of **182** and **183** was 60%.

Lab Book Reference: JDF6_569

tert-Butyl 4-benzyl-2-(hydroxy(phenyl)methyl)piperazine-1-carboxylate _anti_-185 and _syn_-184



anti-**185** *syn*-**184**



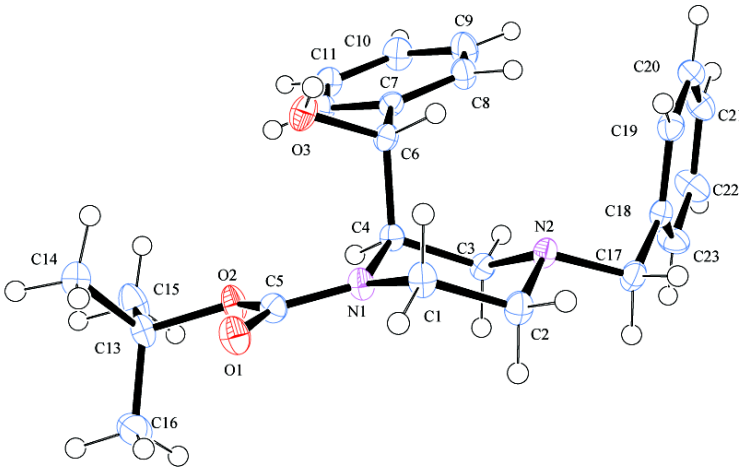
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of

readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, benzaldehyde (212 mg, 203 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peaks at 1665 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazines *anti*-**185** and *syn*-**184**. The solution was stirred at –78 °C for 7 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazines *anti*-**185** and *syn*-**184** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 19:1-7:3 Et_2O-CH_2Cl_2 as eluent gave *N*-Boc piperazine *anti*-**185** (45 mg, 12%) as a white solid, mp 100-102 °C; R_F (9:1 Et_2O-CH_2Cl_2) 0.3; IR ($CHCl_3$) 3215 (OH), 2971, 2783, 1658 (C=O), 1429, 1385, 1345, 1302, 1197, 1151, 1101, 1000, 744, 691, 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 3H, Ph), 7.36-7.31 (m, 2H, Ph), 7.21-6.99 (m, 5H, Ph), 6.42 (br s, 1H, CHO*H*), 5.08 (br s, 1H, C*H*OH), 4.01-3.85 (m, 1H, NCH), 3.80-3.67 (m, 1H, NCH), 3.63 (d, *J* = 12.5 Hz, 1H, C$H_A$$H_B$Ph), 3.28 (d, *J* = 12.0 Hz, 1H, NCH_2), 3.08-2.94 (m, 1H, NCH_2), 2.95 (d, *J* = 12.5 Hz, 1H, $CH_A$$H_B$Ph), 2.33-2.16 (m, 1H, NCH), 2.00 (dd, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.70-1.55 (m, 1H, NCH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 155.0 (C=O), 154.8 (C=O), 143.2 (*ipso*-Ph), 136.3 (*ipso*-Ph), 129.7 (Ph), 128.7 (Ph), 128.0 (Ph), 127.8 (Ph), 126.6 (Ph), 126.5 (Ph), 125.5 (Ph), 125.5 (Ph), 80.3 (*C*Me_3), 80.1 (*C*Me_3), 79.0 (CHOH), 63.0 (N*C*H_2Ph), 55.6 (NCH), 54.8 (NCH), 53.0 (NCH_2), 50.5 (NCH_2), 42.3 (NCH_2), 41.2 (NCH_2), 28.5 (CMe_3); MS (ESI) *m/z* 383 $(M + H)^+$; HRMS *m/z* calcd for $C_{23}H_{30}N_2O_3$ $(M + H)^+$ 383.2329, found 383.2319 (+3.0 ppm error) and *N*-Boc piperazine *syn*-**184** (151 mg, 40%) as a white solid, mp 118-119 °C; R_F (9:1 Et_2O-CH_2Cl_2) 0.2; IR ($CHCl_3$) 2963, 1656 (C=O), 1431, 1393, 1345, 1281, 1229, 1196, 1150, 1109, 1000, 848, 744, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.43-7.14 (m, 10H, Ph), 6.01 (br s, 1H, OH), 5.28-4.97 (m, 1H, C*H*OH),

4.31 (s, 0.45H, NCH), 4.20-4.09 (m, 1.1H, NCH), 3.89 (d, *J* = 13.5 Hz, 0.45H, NCH), 3.72-3.43 (m, 3H, NCH + C*H*$_2$Ph), 3.12 (d, *J* = 11.5 Hz, 0.55H, NCH$_2$), 3.01-2.80 (m, 1.45H, NCH$_2$), 2.43 (dd, *J* = 11.5, 3.5 Hz, 0.55H, NCH), 2.29 (d, *J* = 11.5 Hz, 0.45H, NCH), 2.24-2.07 (m, 1H, NCH), 1.30 (s, 4H, CMe$_3$), 1.08 (s, 5H, CMe$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) (mixture of rotamers) δ 154.5 (C=O), 141.6 (*ipso*-Ph), 137.0 (*ipso*-Ph), 136.6 (*ipso*-Ph), 129.2 (Ph), 128.6 (Ph), 128.5 (Ph), 128.2 (Ph), 128.0 (Ph), 127.7 (Ph), 127.4 (Ph), 127.2 (Ph), 126.6 (Ph), 126.5 (Ph), 79.9 (*C*Me$_3$), 79.6 (CHOH), 63.0 (N*C*H$_2$Ph), 56.4 (NCH$_2$), 54.8 (NCH), 54.5 (NCH), 52.6 (NCH$_2$), 52.5 (NCH$_2$), 41.7 (NCH$_2$), 40.9 (NCH$_2$), 28.2 (CMe$_3$), 27.8 (CMe$_3$); MS (ESI) *m/z* 383 (M + H)$^+$; HRMS *m/z* calcd for $C_{23}H_{30}N_2O_3$ (M + H)$^+$ 383.2329, found 383.2315 (+3.9 ppm error). The total yield of *anti*-**185** and *syn*-**184** was 52%.

Lab Book Reference: JDF6_568

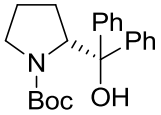
tert-Butyl 4-benzyl-2-(hydroxy(phenyl)methyl)piperazine-1-carboxylate _syn_-184



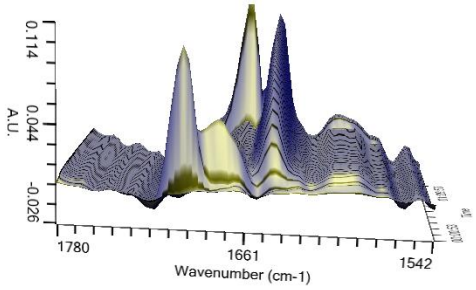
Crystal data and structure refinement for _syn_-**184**

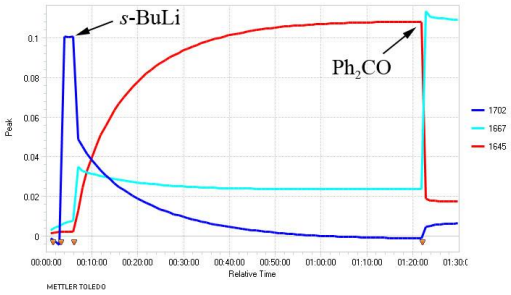
Identification code	paob1204
Empirical formula	$C_{23}H_{30}N_2O_3$
Formula weight	382.49
Temperature/K	110.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.2272(3)
b/Å	10.4025(3)
c/Å	11.5915(4)
α/°	102.908(3)
β/°	98.613(3)
γ/°	96.263(3)
Volume/Å^3	1060.48(6)
Z	2
ρ_{calc} mg/mm^3	1.198
m/mm^{-1}	0.079
F(000)	412.0
Crystal size/mm^3	0.3921 × 0.2964 × 0.1735
2Θ range for data collection	6.1 to 64.44°
Index ranges	$-13 \leq h \leq 13$, $-14 \leq k \leq 15$, $-17 \leq l \leq 17$
Reflections collected	52490
Independent reflections	7110[R(int) = 0.0404]
Data/restraints/parameters	7110/0/266
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0424, wR_2 = 0.1068
Final R indexes [all data]	R_1 = 0.0520, wR_2 = 0.1144
Largest diff. peak/hole / e Å^{-3}	0.41/-0.23

(*R*)-*tert*-Butyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (*R*)-36



(*R*)-**36**



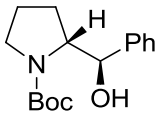


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 80 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added dropwise. A new peak at 1667 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidine (*R*)-**36**. The solution was stirred at –78 °C for 10 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidine (*R*)-**36** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-17:3 petrol-Et_2O as eluent gave *N*-Boc pyrrolidine (*R*)-**36** (260 mg, 74%, 94:6 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +121.5 (*c* 1.0 in $CHCl_3$) (lit.,[62] $[\alpha]_D$ +132.1 (*c* 1.97 in $CHCl_3$) for (*R*)-**36** of 95:5 er); CSP-

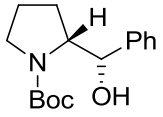
HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**36** 12.8 min, (*S*)-**36** 15.6 min.

Lab Book Reference: JDF6_587

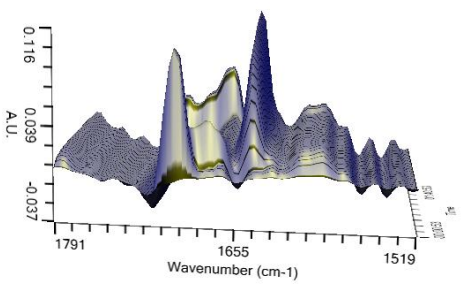
(*R*)-*tert*-Butyl 2-((*R*)-hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (*R,R*)-31 and (*R*)-*tert*-butyl 2-((*S*)-hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (*R,S*)-32

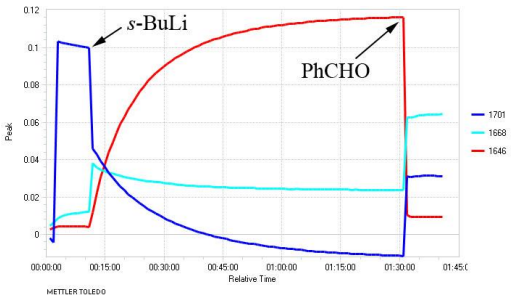


(*R,R*)-**31**



(*R,S*)-**32**



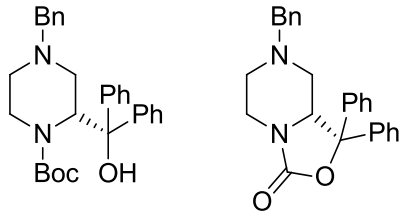


Et_2O (14 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by *N*-Boc-pyrrolidine **12** (171 mg, 175 µL, 1.0 mmol, 1.0 eq.). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). A peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-pyrrolidine **12**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 75 min. Complete lithiation of *N*-Boc-pyrrolidine **12** to give the lithiated intermediate had occurred. Then, benzaldehyde (212 mg, 203 µL, 2.0 mmol, 2.0 eq.) was added dropwise. A new peak at 1668 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc pyrrolidines (*R,R*)-**31** and (*R,S*)-**32**. The solution was stirred at –78 °C for 10 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc pyrrolidines (*R,R*)-**31** and (*R,S*)-**32** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL)

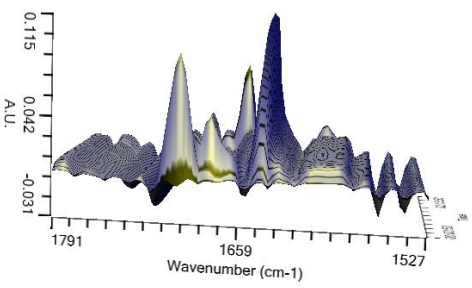
was added at –78 °C. After warming to rt, the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave *N*-Boc pyrrolidine (*R*,*R*)-**31** (181 mg, 66%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –0.3 (*c* 1.0 in $CHCl_3$) (lit.,[67] $[\alpha]_D$ –1.9 (*c* 1.0 in $CHCl_3$) for (*R*,*R*)-**31** of 95:5 er); CSP-HPLC: Chiralcel OD (98:2 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*,*R*)-**31** 23.9 min, (*S*,*S*)-**32** 30.4 min and (*R*,*S*)-**32** (58 mg, 21%, 92:8 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +85.8 (*c* 1.0 in $CHCl_3$) (lit.,[67] $[\alpha]_D$ +95.3 (*c* 1.0 in $CHCl_3$) for (*R*,*S*)-**32** of 97:3 er); CSP-HPLC: Chiralcel OD (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*,*S*)-**32** 40.6 min, (*S*,*R*)-**32** 46.6 min. The total yield of (*R*,*R*)-**31** and (*R*,*S*)-**32** was 87%.

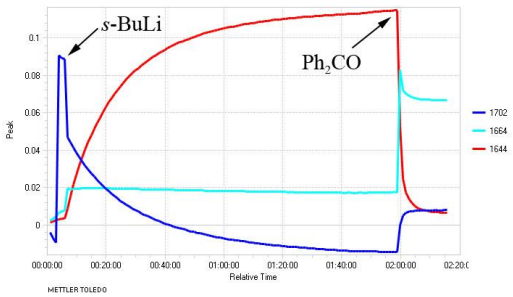
Lab Book Reference: JDF6_589

(*S*)-*tert*-Butyl 4-benzyl-2-(hydroxydiphenylmethyl)piperazine-1-carboxylate (*R*)-182 and (*R*)-7-benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*)-183



(*R*)-**182** (*R*)-**183**





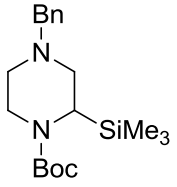
Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N*′-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability

of readout on ReactIR™). A peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$ of *N*-Boc-*N′*-benzyl piperazine **117**. Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. A new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The solution was stirred at –78 °C for 8 min. Complete lithiation of *N*-Boc-*N′*-benzyl piperazine **117** to give the lithiated intermediate had occurred. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added dropwise. A new peaks at 1664 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the substituted *N*-Boc-*N′*-benzyl piperazine (*S*)-**182** and oxazolidinone (*R*)-**183**. The solution was stirred at –78 °C for 15 min. Complete trapping of lithiated intermediate to give substituted *N*-Boc-*N′*-benzyl piperazine (*R*)-**182** and oxazolidinone (*R*)-**183** was observed within 1 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added at –78 °C. After warming to rt, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**182** (176 mg, 38%) as a colourless oil, and oxazolidinone (*R*)-**183** (52 mg, 14%, 81:19 er by CSP-HPLC) as a white solid; CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**183** 12.3 min, (*R*)-**183** 16.3 min.

Lab Book Reference: JDF6_585

6.4 Experimental for Chapter Three

tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 175

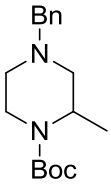


175

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-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and Me_3SiCl (217 mg, 254 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **175** (236 mg, 68%) as a colourless oil.

Lab Book Reference: JDF3_211

tert-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate 176



176

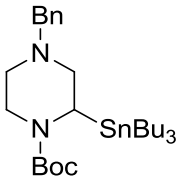
Using general procedure A, *s*-BuLi (3.0 mL of a 1.3 M solution in hexanes, 3.9 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (829 mg, 3.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and methyl iodide (852 mg, 374 µL, 6.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (20 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (645 mg, 74%) as a colourless oil.

Lab Book Reference: JDF3_205

Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (415 mg, 1.5 mmol, 1.0 eq.) in THF (7 mL) for 1 h, and dimethyl sulfate (378 mg, 284 µL, 3.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (300 mg, 69%) as a colourless oil.

Lab Book Reference: JDF1_36

tert-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate 181

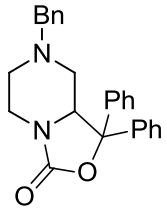


181

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-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and Bu_3SnCl (650 mg, 542 µL, 2.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **181** (387 mg, 68%) as a colourless oil.

Lab Book Reference: JDF5_445

7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 183

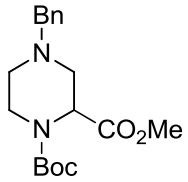


183

Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), *N*-Boc-*N*′-benzyl piperazine **117** (415 mg, 1.5 mmol, 1.0 eq.) in THF (7 mL) for 1 h and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in THF (1 mL), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-7:3 petrol-EtOAc as eluent gave oxazolidinone **183** (520 mg, 90%) as a white solid.

Lab Book Reference: JDF1_13

1-*tert*-Butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate 208



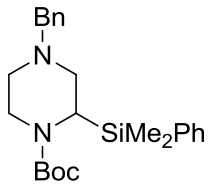
208

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-*N*′-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and methyl chloroformate (190 mg, 155 µL, 2.0 mmol, 2.0 eq.) worked up saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine **208** (200 mg, 60%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.7; IR ($CHCl_3$) 2979, 1744 (C=O, CO_2Me), 1691 (C=O, Boc), 1408, 1366, 1301, 1169, 1119, 1046, 976, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.32-7.24 (m, 5H, Ph), 4.71 (br s, 0.55H, NCH), 4.54 (br s, 0.45H, NCH), 3.85 (br d, J = 13.0 Hz, 0.55H, NCH), 3.77-3.75 (m, 0.45H, NCH), 3.73 (s, 1.35H, OMe), 3.71 (s, 1.65H, OMe), 3.58

(d, *J* = 13.0 Hz, 0.45H, C*H*$_A$H$_B$Ph), 3.58 (d, *J* = 13.0 Hz, 0.55H, C*H*$_A$H$_B$Ph), 3.45 (d, *J* = 13.0 Hz, 0.55H, CH$_A$*H*$_B$Ph), 3.41 (d, *J* = 13.0 Hz, 0.45H, CH$_A$*H*$_B$Ph), 3.34-3.27 (m, 1.55H, NCH), 3.18 (td, *J* = 13.0, 3.0 Hz, 0.45H, NCH), 2.79 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.74 (d, *J* = 11.0 Hz, 0.55H, NCH), 2.18 (td, *J* = 11.0, 4.0 Hz, 1H, NCH), 2.11 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.11 (br d, *J* = 11.0 Hz, 0.45H, NCH), 1.47 (s, 4.9H, CMe$_3$), 1.42 (s, 4.1H, CMe$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) (mixture of rotamers) δ 171.3 (*C*O$_2$Me), 171.1 (*C*O$_2$Me), 155.8 (NC=O), 155.3 (NC=O), 137.6 (*ipso*-Ph), 128.7 (Ph), 128.1 (Ph), 127.2 (Ph), 80.2 (CMe$_3$), 62.3 (NCH$_2$), 55.5 (NCH), 54.3 (NCH), 53.5 (NCH$_2$), 52.4 (NCH$_2$), 52.3 (NCH$_2$), 51.9 (OMe), 42.0 (NCH$_2$), 41.0 (NCH$_2$), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 335 (M + H)$^+$; HRMS *m/z* calcd for C$_{18}$H$_{26}$N$_2$O$_4$ (M + H)$^+$ 335.1965, found 335.1974 (–2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab Book Reference: JDF2_117

tert-Butyl 4-benzyl-2-(dimethyl(phenyl)silyl)piperazine-1-carboxylate 242



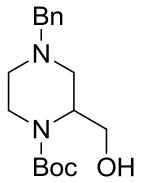
242

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-*N*′-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and PhMe$_2$SiCl (341 mg, 335 μL, 2.0 mmol, 2.0 eq.) worked up with 20% NaOH$_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **242** (190 mg, 46%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; IR (CHCl$_3$) 3019, 2400, 1679 (C=O), 1421, 1366, 1294, 1215, 759, 669 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) (60:40 mixture of rotamers) δ 7.53-7.44 (m, 2H, Ph), 7.35-7.28 (m, 8H, Ph), 4.05 (br d, *J* = 12.0 Hz, 0.6H, NCH), 3.87 (br s, 0.4H, NCH), 3.76 (br s, 1H, NCH), 3.40 (d, *J* = 13.0 Hz, 1H, C*H*$_A$H$_B$Ph), 3.36 (d, *J* = 13.0 Hz, 1H, CH$_A$*H*$_B$Ph), 3.00-3.90 (m, 1H, NCH), 2.79-2.72 (m, 1.6H, NCH), 2.62 (br s, 0.4H, NCH), 2.25-2.16 (m, 1H, NCH), 1.92 (td, *J* = 11.5,

3.5 Hz, 1H, NCH), 1.42 (s, 9H, CMe_3), 0.48 (s, 3H, SiMe), 0.37 (br s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.5 (C=O), 138.2 (*ipso*-Ph), 138.0 (*ipso*-Ph), 133.9 (Ph), 129.3 (Ph), 129.0 (Ph), 128.1 (Ph), 127.7 (Ph), 127.1 (Ph), 79.3 (CMe_3), 66.4 (NCH_2), 54.2 (NCH_2), 53.1 (NCH_2), 46.1 (NCH), 41.4 (NCH_2), 28.3 (CMe_3), –1.6 (SiMe), –2.8 (SiMe); MS (ESI) *m/z* 411 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{34}N_2O_2Si$ $(M + H)^+$ 411.2462, found 411.2472 (–0.4 ppm error).

Lab Book Reference: JDF3_252

tert-Butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate 243

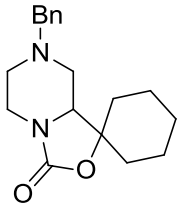


243

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-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (6 mL) for 1 h and a suspension of paraformaldehyde (60 mg, 2.0 mmol, 2.0 eq.) in THF (1 mL) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **243** (197 mg, 64%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3280 (OH), 2971, 2913, 2781 1658 (C=O), 1433, 1390, 1345, 1302, 1197, 1152, 1103, 1060, 1035, 997, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H, Ph), 4.07 (br s, 1H, NCH), 3.96-3.81 (m, 3H, CH_2O + NCH), 3.51 (d, *J* = 13.0 Hz, 1H, C$H_A$$H_B$Ph), 3.47 (d, *J* = 13.0 Hz, 1H C$H_A$$H_B$Ph), 3.40 (br s, 1H, NCH), 2.98 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.83 (br d, *J* = 10.0 Hz, 1H, NCH), 2.31 (ddd, *J* = 11.5, 4.0, 1.0 Hz, 1H, NCH), 2.09 (ddd, *J* = 12.5, 11.5, 4.0 Hz, 1H, NCH), 1.45 (CMe_3), OH not resolved; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 137.0 (*ipso*-Ph), 129.0 (Ph), 128.5 (Ph), 127.5 (Ph), 80.0 (CMe_3), 66.7 (CH_2OH), 63.0 (CH_2Ph), 55.1 (NCH_2), 52.5 (NCH_2), 51.1 (NCH), 41.4 (NCH_2), 28.4 (CMe_3); MS (ESI) *m/z* 307 $(M + H)^+$; HRMS *m/z* calcd for $C_{17}H_{26}N_2O_3$ $(M + H)^+$ 307.2016, found 307.2023 (–2.2 ppm error). Spectroscopic data consistent with those reported in the literature.[273]

Lab Book Reference: JDF5_481

7'-Benzyltetrahydrospiro[cyclohexane-1,1'-oxazolo[3,4-a]pyrazin]-3'(5'H)-one 244

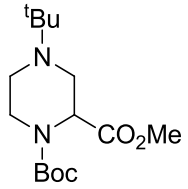


244

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-*N'*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 1 h and cyclohexanone (196 mg, 207 µL 2.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave oxazolidinone **244** (131 mg, 44%) as a white solid, mp 64-66 °C; R_F (1:1 petrol-EtOAc) 0.1; IR ($CHCl_3$) 2896, 1710 (C=O), 1428, 1331, 1286, 1074, 1025, 961, 890, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H, Ph), 3.76 (dd, *J* = 13.0, 3.5 Hz, 1H, NCH), 3.61-3.49 (m, 2H, C*H*$_2$Ph), 3.39 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.05 (td, *J* = 12.5, 3.5 Hz, 1H, NCH), 2.77-2.73 (m, 2H, NCH), 2.05-1.97 (m, 2H, NCH), 1.89-1.20 (m, 10H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.4 (C=O), 137.3 (*ipso*-Ph), 128.8 (Ph), 128.3 (Ph), 127.3 (Ph), 80.7 (CO), 63.0 (NCH_2), 61.7 (NCH), 52.8 (NCH_2), 51.7 (NCH_2), 41.0 (NCH_2), 36.7 (CH_2), 30.7 (CH_2), 28.3 (CH_2), 25.0 (CH_2), 21.9 (CH_2); MS (ESI) *m/z* 301 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{25}N_2O_2$ $(M + H)^+$ 301.1905, found 301.1911 (+1.6 ppm error).

Lab Book Reference: JDF4_482

1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate 245

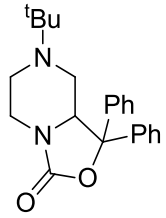


245

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-*N'*-*t*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.), TMEDA (232 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and methyl chloroformate (189 mg, 155 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine **245** (135 mg, 45%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2976, 1745 (C=O, CO_2Me), 1689 (C=O, Boc), 1455, 1393, 1367, 1304, 1253, 1170, 1119, 1041, 965, 865, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.70 (br s, 0.5H, NCH), 4.53 (br s, 0.5H, NCH), 3.83 (br d, J = 12.5 Hz, 0.5H, NCH), 3.75-3.73 (m, 0.5H, NCH), 3.73 (s, 1.5H, OMe), 3.72 (s, 1.5H, OMe), 3.52-3.45 (m, 1H, NCH), 3.13 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 3.03 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 2.92 (br d, J = 11.0 Hz, 0.5H, NCH), 2.84 (br d, J = 11.0 Hz, 0.5H, NCH), 2.28-2.23 (m, 1H, NCH), 2.11 (td, J = 11.0, 3.5 Hz, 1H, NCH), 1.46 (s, 4.5H, $OCMe_3$), 1.42 (s, 4.5H, $OCMe_3$), 0.96 (s, 9H, $NCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.6 (CO_2Me), 171.3 (CO_2Me), 155.8 (NC=O), 155.4 (NC=O), 80.0 ($OCMe_3$), 56.3 (NCH), 55.0 (NCH), 53.3 ($NCMe_3$), 51.9 (OMe), 47.6 (NCH_2), 45.2 (NCH_2), 42.9 (NCH_2), 42.0 (NCH_2), 28.3 (CMe_3), 25.8 (CMe_3); MS (ESI) *m/z* 301 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{28}N_2O_4$ $(M + H)^+$ 301.2122, found 301.2122 (+0.3 ppm error).

Lab Book Reference: JDF2_123

7-*tert*-Butyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 246

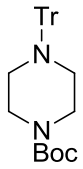


246

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-*N′*-*t*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.), TMEDA (232 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in THF (1 mL) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-98:2 CH_2Cl_2-MeOH as eluent gave oxazolidinone **246** (200 mg, 57%) as a white solid, mp 193-195 °C; R_F (99:1 CH_2Cl_2-MeOH) 0.2; IR ($CHCl_3$) 2975, 1750 (C=O), 1449, 1363, 1302, 1255, 1203, 1036, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H, Ph), 7.39-7.24 (m, 8H, Ph), 4.43 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.85 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.08 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.92-2.88 (m, 1H, NCH), 2.62 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.06 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.51 (t, *J* = 11.0 Hz, 1H, NCH), 0.93 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 142.4 (*ipso*-Ph), 138.8 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.2 (Ph), 127.8 (Ph), 126.0 (Ph), 125.7 (Ph), 85.4 (Ph_2CO), 61.9 (NCH), 54.3 (CMe_3), 48.8 (NCH_2), 44.8 (NCH_2), 42.6 (NCH_2), 26.0 (CMe_3); MS (ESI) *m/z* 351 $(M + H)^+$; HRMS *m/z* calcd for $C_{23}H_{26}N_2O_2$ $(M + H)^+$ 351.2067, found 351.2062 (+0.7 ppm error).

Lab Book Reference: JDF4_327

4-Tritylpiperazine-1-carboxylic acid *tert*-butyl ester 203

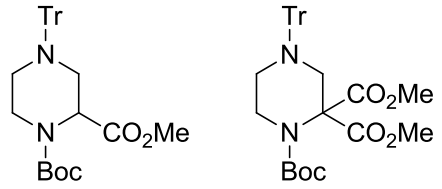


203

Triphenylmethyl chloride (2.06 g, 7.4 mmol 1.1 eq.) was added to a stirred solution of Et_3N (748 mg, 1.03 mL, 7.4 mmol, 1.1 eq.) and *N*-Boc piperazine **257** (1.25 g, 6.7 mmol, 1.0 eq.) in $CHCl_3$ (40 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, saturated $NaHCO_{3(aq)}$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 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 9:1 petrol-Et_2O as eluent gave *N*-Boc-*N′*-trityl piperazine **203** (2.29 g, 80%) as a white solid, mp 137-140 °C, R_F (9:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 1693 (C=O), 1410, 1364, 1169, 1115, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 6H, Ph), 7.37-7.21 (m, 6H, Ph), 7.15 (t, *J* = 7.5 Hz, 3H, *p*-Ph), 3.54 (br s, 4H, NCH_2), 2.25 (br s, 4H, NCH), 1.38 (s, 9H, CMe_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.9 (C=O), 146.9 (*ipso*-Ph), 127.9 (Ph), 127.6 (Ph), 126.1 (Ph), 79.4 (*C*Me_3), 76.9 (*C*Ph_3), 47.8 (NCH_2), 44.4 (NCH_2), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 451 $(M + na)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{32}N_2O_2$ $(M + Na)^+$ 451.2355, found 451.2356.

Lab Book Reference: JDF5_433

1-*tert*-Butyl 2-methyl 4-tritylpiperazine-1,2-dicarboxylate 247 and 1-*tert*-Butyl 2,2-dimethyl 4-tritylpiperazine-1,2,2-tricarboxylate 248



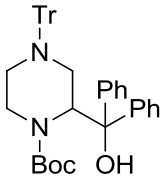
247 **248**

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave *N*-Boc piperazine **247** (86 mg, 35%) as a white solid, mp 189-192 °C; R_F (4:1 petrol-Et_2O) 0.3; IR ($CHCl_3$) 3020, 2399, 1746 (C=O, CO_2Me), 1688 (C=O, Boc), 1410, 1215, 1120, 1010, 762, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.42 (br s, 6H, Ph), 7.29-7.20 (m, 6H, Ph), 7.17 (br s, 3H, Ph), 4.61 (br s, 0.6H, NCH), 4.46 (br s, 0.4H, NCH), 3.92 (s, 3H, OMe), 3.82 (d, J = 12.0 Hz, 0.4H, NCH), 3.74-3.62 (m, 1.6H, NCH), 3.59-3.44 (m, 2H, NCH), 3.09 (d, J = 11.0 Hz, 0.4H, NCH), 3.02 (d, J = 11.0 Hz, 0.6H, NCH), 1.88-1.80 (m, 1H, NCH), 1.43 (s, 5.4H, CMe_3), 1.39 (s, 3.6H, CMe_3); ^{13}C NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 171.9 (CO_2Me), 155.8 (NC=O), 155.2 (NC=O), 137.9 (*ipso*-Ph), 129.2 (Ph), 127.5 (Ph), 126.3 (Ph), 80.2 (CMe_3), 76.9 (CPh_3), 55.4 (NCH or OMe), 54.2 (NCH or OMe), 51.9 (NCH or OMe), 48.9 (NCH_2), 47.8 (NCH_2), 44.2 (NCH_2), 42.5 (NCH_2), 41.5 (NCH_2), 28.3 (CMe_3); MS (ESI) *m/z* 509 $(M + Na)^+$; MS (ESI) *m/z* 509 $(M + Na)^+$; HRMS *m/z* calcd for $C_{30}H_{33}N_2O_4Na$ $(M + Na)^+$ 509.2411, found 509.2417 (–0.9 ppm error) and *N*-Boc piperazine **248** (80 mg, 29%) as a white solid, mp 83-86 °C; R_F (4:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2971, 1743 (C=O, CO_2Me) 1660 (C=O, Boc), 1465, 1425, 1380, 1346, 1262, 1200, 1150, 1102, 1065, 1008, 920, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (br s, 6H, Ph), 7.32-7.20 (m, 6H, Ph), 7.22-7.10 (m, 3H, Ph), 4.02 (br s, 1H, NCH), 3.88 (s, 3H, CO_2Me), 3.80 (br s, 1H, NCH), 3.68 (s, 3H, CO_2Me), 3.25 (br s, 1H, NCH), 3.01 (br s, 1H, NCH), 1.82-1.50 (m, 2H, NCH), 1.36 (s, 9H, CMe_3); ^{13}C NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 153.2 (br, NC=O), 152.6 (br, NC=O), 146.5 (*ipso*-Ph), 142.0 (br, *ipso*-Ph), 129.4 (Ph), 127.6 (Ph), 126.2 (Ph), 80.2 (CMe_3), 77.1 (CPh_3), 58.1

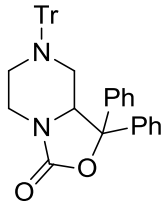
(CO_2*Me*), 55.5 (CO_2*Me*), 48.1 (NCH_2), 46.6 (NCH_2), 44.7 (NCH_2), 28.1 (C*Me*$_3$), 28.0 (C*Me*$_3$) (*C*O_2Me and *C*CO_2Me not resolved); MS (ESI) *m/z* 567 $(M + Na)^+$; HRMS *m/z* calcd for $C_{32}H_{36}N_2O_6$ $(M + Na)^+$ 567.2466, found 567.2460 (+0.6 ppm error).

Lab Book Reference: JDF5_496

tert-Butyl 2-(hydroxydiphenylmethyl)-4-tritylpiperazine-1-carboxylate 250 and 1,1-Diphenyl-7-trityltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 249



250



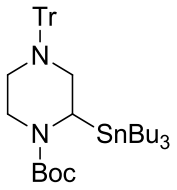
249

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and , a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-6:4 petrol-Et_2O as eluent gave *N*-Boc piperazine **250** (35 mg, 11%) as a white solid, mp 105-108 °C; R_F (8:2 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2963, 1654 (C=O), 1468, 1425, 1396, 1345, 1328, 1286, 1266, 1218, 1150, 1099, 967, 892, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 8.26 (s, 0.55H, OH), 8.03 (s, 0.45H, OH), 7.74-7.69 (m, 1H, Ph), 7.66-7.56 (m, 2H, Ph), 7.54-7.06 (m, 19H, Ph), 6.91-6.68 (m, 3H, Ph), 5.23 (d, *J* = 3.0 Hz, 1H, NCH), 4.93 (d, *J* = 3.0 Hz, 1H, NCH), 4.26-4.06 (m, 1.45H, NCH), 3.79 (d, *J* = 12.0 Hz, 0.55H, NCH), 3.68 (d, *J* = 12.0 Hz, 1H, NCH), 3.11 (d, *J* = 12.0 Hz, 0.45H, NCH), 3.05 (d, *J* = 12.0 Hz, 0.55H, NCH), 2.27 (dd, *J* = 12.0, 4.0 Hz, 0.55H, NCH), 2.14 (dd, *J* = 12.0, 4.0 Hz, 0.45H, NCH), 1.25-1.21 (m, 1H, NCH), 1.08 (s, 5H, CMe_3), 1.06 (s, 4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.0 (C=O), 153.8 (C=O), 146.7 (*ipso*-Ph), 146.6 (*ipso*-Ph), 145.3 (*ipso*-Ph), 145.0 (*ipso*-Ph), 144.5 (*ipso*-Ph), 143.4 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.4 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.5 (Ph), 127.2 (Ph), 127.0 (Ph), 126.8 (Ph), 126.7 (Ph), 126.5 (Ph), 126.5 (Ph), 126.4 (Ph), 126.3 (Ph), 126.1 (Ph), 84.0 (COH), 79.7

(*C*Me_3 or *C*Ph_3), 79.6 (*C*Me_3 or *C*Ph_3), 78.7 (*C*Me_3 or *C*Ph_3), 55.0 (NCH), 53.3 (NCH), 49.8 (NCH_2), 49.4 (NCH_2), 49.1 (NCH_2), 41.8 (NCH_2), 40.5 (NCH_2), 28.0 (C*Me*$_3$), 27.8 (C*Me*$_3$); MS (ESI) *m/z* 611 $(M + H)^+$; HRMS *m/z* calcd for $C_{41}H_{42}N_2O_3$ $(M + H)^+$ 611.3268, found 611.3284 (–3.1 ppm error) and oxazolidinone **249** (132 mg, 50%) as a white solid, mp 238-241 °C (decomposed); R_F (8:2 petrol-Et_2O) 0.1; IR ($CHCl_3$) 2964, 1743 (C=O), 1467, 1426, 1398, 1341, 1280, 1214, 1164, 1107, 1017, 973, 929, 889, 747, 700, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 2H, Ph), 7.44-7.28 (m, 9H, Ph), 7.25-7.20 (m, 6H, Ph), 7.18-7.12 (m, 6H, Ph), 7.05-702 (m, 2H, Ph), 4.74 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.86-3.75 (m, 1H, NCH), 3.38 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 3.10-3.01 (m, 1H, NCH), 2.88-2.81 (m, 1H, NCH), 1.38 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 0.82-0.74 (m, 1H, NCH); NMR (100.6 MHz, $CDCl_3$) *δ* 156.1 (C=O), 142.2 (*ipso*-Ph), 138.6 (*ipso*-Ph), 128.8 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 127.7 (Ph), 127.7 (Ph), 126.4 (Ph), 126.0 (Ph), 125.6 (Ph), 85.3 (Ph_2CO), 77.2 (*C*Ph_3), 62.0 (NCH), 52.0 (NCH_2), 47.0 (NCH_2), 42.0 (NCH_2); MS (ESI) *m/z* 559 $(M + Na)^+$; HRMS *m/z* calcd for $C_{37}H_{32}N_2O_2$ $(M + Na)^+$ 559.2356, found 559.2376 (–3.6 ppm error).

Lab Book Reference: JDF5_497

tert-Butyl 2-(tributylstannyl)-4-tritylpiperazine-1-carboxylate 251



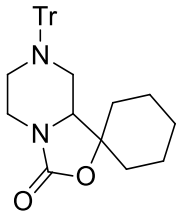
251

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 petrol-Et_2O as eluent gave *N*-Boc piperazine **251** (308 mg, 86%) as a pale yellow oil, R_F (19:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2911, 2879, 1646 (C=O), 1465, 1428, 1402, 1344, 1277, 1232, 1196, 1134, 1092, 987, 744, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of

rotamers) δ 7.46 (br s, 6H, Ph), 7.32-7.20 (m, 6H, Ph), 7.20-7.06 (m, 3H, Ph), 4.06 (s, 0.25H, NCH), 3.82 (s, 0.75H, NCH), 3.50-2.46 (m, 4H, NCH), 2.09-1.48 (m, 2H, NCH), 1.49-1.29 (m, 15H, CH_2 + CMe_3), 1.29-1.14 (m, 6H, CH_2), 0.95-0.61 (m, 15H, CH_2 + Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 142.8 (*ipso*-Ph), 129.3 (Ph), 127.4 (Ph), 126.0 (Ph), 79.3 (*C*Me_3), 77.1 (*C*Ph_3), 52.4 (NCH_2), 48.5 (NCH_2), 46.6 (NCH_2), 45.4 (NCH), 29.2 (CH_2), 28.2 (C*Me*$_3$), 27.6 (CH_2), 13.7 (Me), 11.9 (CH_2); MS (ESI) *m/z* 719 $(M + H)^+$; HRMS *m/z* calcd for $C_{40}H_{58}N_2O_2Sn$ $(M + H)^+$ 719.3601, found 719.3605 (–0.6 ppm error).

Lab Book Reference: JDF5_499

7'-Trityltetrahydrospiro[cyclohexane-1,1'-oxazolo[3,4-a]pyrazin]-3'(5'H)-one 252



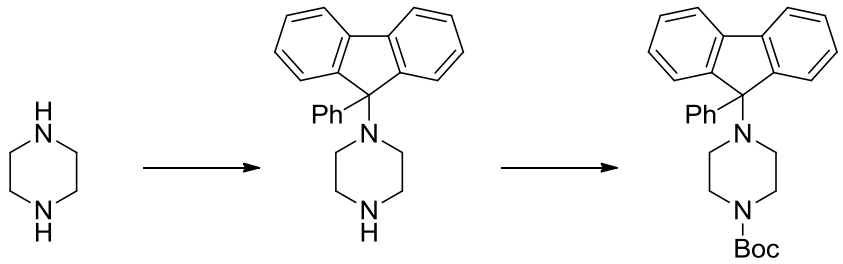
252

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and cyclohexanone (98 mg, 104 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2-4:6 petrol-Et_2O as eluent gave *N*-Boc piperazine **252** (84 mg, 37%) as a white solid, mp 74-76 °C; R_F (8:2 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2973, 1709 (C=O), 1466, 1426, 1341, 1288, 1262, 1197, 1053, 1018, 992, 967, 914, 895, 748 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.44 (br s, 6H, Ph), 7.30-7.26 (m, 6H, Ph), 7.20-7.16 (m, 3H, Ph), 3.77-3.73 (m, 1H, NCH), 3.69 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH), 3.31 (td, *J* = 12.5, 3.5 Hz, 1H, NCH), 3.07-3.04 (m, 2H, NCH), 1.94-1.91 (m, 1H, NCH), 1.75-1.71 (m, 1H, NCH), 1.62-1.31 (m, 10H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5 (C=O), 129.0 (Ph), 127.8 (Ph), 126.4 (Ph), 80.8 (CO), 77.4 (*C*Ph_3), 62.6 (NCH), 48.8 (NCH_2), 47.6 (NCH_2), 41.7 (NCH_2), 36.9 (CH_2), 30.6 (CH_2), 25.0 (CH_2), 22.0 (CH_2), 21.9 (CH_2) (*ipso*-Ph not resolved); MS

(ESI) *m/z* 453 $(M + H)^+$; HRMS *m/z* calcd for $C_{30}H_{32}N_2O_2$ $(M + H)^+$ 453.2537, found 453.2536 (–0.4 ppm error).

Lab Book Reference: JDF6_509

tert-Butyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1-carboxylate 240



253 **254** **240**

A mixture of 9-bromo-9-phenyl fluorene (3.21 g, 10 mmol, 1.0 eq.), piperazine **253** (4.31 g, 50 mmol, 5.0 eq.), $Pb(NO_3)_2$ (3.97 g, 12 mmol, 1.2 eq.) and K_3PO_4 (3.18 g, 15 mmol, 1.5 eq.) in MeCN (40 mL) was stirred at rt under Ar for 48 h. The solids were removed by filtration through Celite® and washed with MeCN (50 mL), EtOAc (100 mL) and CH_2Cl_2 (100 mL). The filtrate was evaporated under reduced pressure. Then, CH_2Cl_2 (50 mL) and water (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude *N*-fluorophenyl piperazine **254** (2.70 g, 83%) as a beige solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H, Ar), 7.51 (br s, 2H, Ar), 7.41-7.32 (m, 5H, Ar), 7.27-7.22 (m, 4H, Ar), 2.84 (t, *J* = 5.0 Hz, 4H, NCH_2), 2.42 (br s, 4H, NCH_2), 1.72 (br s, 1H, NH). The crude product was used in the next step without further purification (≥95% purity by ^{1}H NMR spectroscopy).

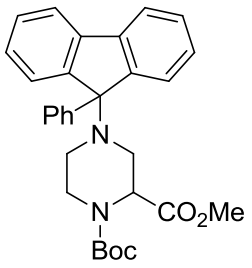
Lab Book Reference: JDF6_528

A solution of di-*tert*-butyl dicarbonate (2.17 g, 9.93 mmol, 1.2 eq.) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of crude *N*-fluorophenyl piperazine **254** (2.0 g, 8.27 mmol, 1.0 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was

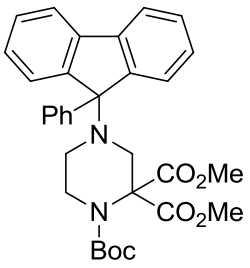
allowed to warm to rt and stirred for at rt for 16 h. Then, water (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 as eluent gave *N*-Boc piperazine **240** (3.24 g, 92%) as a white solid, mp 198-201 °C; R_F (9:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3008, 1681 (C=O), 1451, 1429, 1429, 1366, 1287, 1253, 1169, 1129, 1000, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2H, Ar), 7.49 (br s, 2H, Ar), 7.39-7.34 (m, 4H, Ar), 7.28-7.23 (m, 5H, Ar), 3.39 (br s, 4H, NCH_2), 2.40 (br s, 4H, NCH_2), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 146.6 (*ipso*-Ar), 142.6 (*ipso*-Ar), 140.6 (*ipso*-Ar), 128.4 (Ar), 128.2 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 126.1 (Ar), 119.9 (Ar), 79.3 (C*Me*$_3$ or N*C*Ph), 77.9 (C*Me*$_3$ or N*C*Ph), 47.3 (NCH_2), 28.4 (C*Me*$_3$) (one NCH_2 resonance not resolved); MS (ESI) *m/z* 427 $(M + H)^+$; HRMS *m/z* calcd for $C_{28}H_{30}N_2O_2$ $(M + H)^+$ 427.2380, found 427.2391 (–1.7 ppm error).

Lab Book Reference: JDF6_529

1-*tert*-Butyl 2-methyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2-dicarboxylate 255 and 1-*tert*-Butyl 2,2-dimethyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2,2-tricarboxylate 256



255



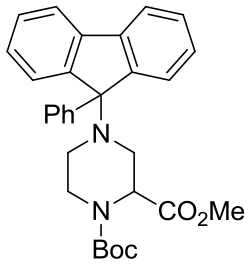
256

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **240** (213 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine **255** (86 mg, 36%) as a white solid mp, 165-167 °C; R_F

(7:3 petrol-Et_2O) 0.2; IR ($CHCl_3$) 3018, 2980, 1745 (C=O, CO_2Me), 1691 (C=O, Boc), 1451, 1408, 1367, 1304, 1216, 1170, 1119, 746, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.72-7.67 (m, 2H, Ar), 7.40-7.35 (m, 4H, Ar), 7.30-7.22 (m, 7H, Ar), 4.56 (br s, 0.6H, NCH), 4.39 (br s, 0.4H, NCH), 3.83-3.78 (m, 0.4H, NCH), 3.80 (s, 3H, OMe), 3.70 (br d, *J* = 12.5 Hz, 0.6H, NCH), 3.41 (td, *J* = 12.5, 3.5 Hz, 0.6H, NCH), 3.30 (td, *J* = 12.5, 3.5 Hz, 0.4H, NCH), 3.15 (br d, *J* = 11.5 Hz, 0.6H, NCH), 3.07 (br d, *J* = 11.5 Hz, 0.4H, NCH), 2.94 (br d, *J* = 11.0 Hz, 0.4H, NCH), 2.84 (br d, *J* = 11.0 Hz, 0.6H, NCH), 2.26-2.16 (m, 2H, NCH), 1.42 (s, 5.4H, CMe_3), 1.37 (s, 3.6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.4 (*C*O_2Me), 155.9 (NC=O), 155.3 (NC=O), 156.6 (*ipso*-Ar), 155.7 (*ipso*- Ar), 142.3 (*ipso*- Ar), 141.1 (*ipso*- Ar), 140.3 (*ipso*- Ar), 128.5 (Ar), 128.4 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 126.4 (Ar), 126.2 (Ar), 126.1 (Ar), 126.0 (Ar), 120.2 (Ar), 120.0 (Ar), 80.1 (*C*Me_3), 77.6 (N*C*Ph), 55.7 (NCH or OMe), 54.6 (NCH or OMe), 51.8 (NCH or OMe), 48.6 (NCH_2), 47.3 (NCH_2), 42.7 (NCH_2), 41.7 (NCH_2), 28.3 (*C*Me_3), 28.2 (*C*Me_3); MS (ESI) *m/z* 485 $(M + H)^+$; HRMS *m/z* calcd for $C_{30}H_{32}N_2O_4$ $(M + H)^+$ 485.2435, found 485.2442 (–1.4 ppm error), and *N*-Boc piperazine **256** (46 mg, 17%), R_F (8:2 petrol-Et_2O) 0.1; IR ($CHCl_3$) 3014, 2931, 1754, (C=O, CO_2Me), 1662 (C=O, Boc), 1427, 1380, 1345, 1261, 1150, 1104, 1078, 1012, 974, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ δ 7.70 (d, *J* = 7.5 Hz, 2H, Ar), 7.66-7.43 (m, 2H, Ar), 7.43-7.32 (m, 4H, Ar), 7.32-7.15 (m, 5H, Ar), 3.99 (br s, 0.5H, NCH), 3.85 (s, 3H, CO_2Me), 3.90-3.71 (m, 1.5H, NCH), 3.55 (br s, 3H, CO_2Me), 3.05 (br s, 1H, NCH), 2.79 (br s, 1H, NCH), 2.36 (br s, 1H, NCH), 2.23 (br s, 1H, NCH), 1.37 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.2 (*C*O_2Me), 171.0 (*C*O_2Me), 155.8 (NC=O), 155.3 (NC=O), 143.4 (*ipso*-Ar), 143.2 (*ipso*-Ar), 128.1 (Ar), 127.4 (Ar), 127.0 (Ar), 80.1 (*C*Me_3), 77.6 (N*C*Ph), 64.1 (OMe), 55.6 (OMe), 54.4 (OMe), 53.4 (*C*CO_2Me), 51.7 (NCH_2), 51.5 (NCH_2), 49.2 (NCH_2), 42.2 (NCH_2), 41.2 (NCH_2), 28.3 (C*Me*$_3$), 28.2 (C*Me*$_3$) (several Ar signals not resolved); MS (ESI) *m/z* 543 $(M + H)^+$; HRMS *m/z* calcd for $C_{32}H_{34}N_2O_6$ $(M + H)^+$ 543.2490, found 543.2470 (+3.7 ppm error), and *N*-Boc piperazine **240** (92 mg, 43%) as a white solid.

Lab Book Reference: JDF6_520

1-*tert*-Butyl 2-methyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2-dicarboxylate 255



255

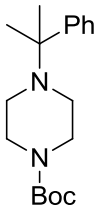
Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **240** (213 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in MTBE (7 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine **255** (140 mg, 58%) as a white solid and *N*-Boc piperazine **240** (43 mg, 20%) as a white solid.

Lab Book Reference: JDF6_521

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **240** (213 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in toluene (5 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine **255** (186 mg, 77%) as a white solid and *N*-Boc piperazine **240** (49 mg, 23%) as a white solid.

Lab Book Reference: JDF6_522

***tert*-Butyl 4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 241**

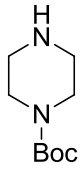


241

Phenyl magnesium chloride (26.6 mL of a 2.0 in THF, 53.3 mmol, 3.0 eq.) was added dropwise to a stirred solution of nitrile **258** (4.5 g, 17.8 mmol, 1.0 eq.) in THF (100 mL) at 0 °C under Ar. The reaction was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was cooled to 0 °C and water (20 mL) was added dropwise. The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 Et_2O-petrol and then with 98:2-94:6 CH_2Cl_2-MeOH as eluent gave *N*-Boc-*N′*-cumyl piperazine **241** (4.2 g, 77%) as a colourless viscous oil, R_F (8:2 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2932, 1655 (C=O), 1404, 1370, 1345, 1283, 1268, 1245, 1228, 1152, 1109, 989, 949, 850, 745, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2H, Ph), 7.34–7.27 (m, 2H, Ph), 7.24–7.17 (m, 1H, Ph), 3.36 (t, *J* = 4.5 Hz, 4H, NCH_2), 2.41 (br s, 4H, NCH_2), 1.44 (s, 9H, CMe_3), 1.33 (s, 6H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.8 (C=O), 148.8 (*ipso*-Ph), 128.0 (Ph), 126.2 (Ph), 126.0 (Ph), 79.3 (*C*Me_3), 59.7 (*C*Me_2Ph), 46.0 (NCH_2), 44.3 (NCH_2), 28.4 (C*Me*$_3$), 24.0 (C*Me*$_2$Ph); MS (ESI) *m/z* 305 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{28}N_2O_2$ $(M + H)^+$ 305.2224, found 305.2230 (–1.1 ppm error).

Lab Book Reference: JDF7_623

***tert*-Butyl piperazine-1-carboxylate 257**

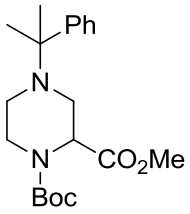


257

10% Pd/C (10 mg) was added to a stirred solution of *N*-Boc-*N′*-cumyl piperazine **241** (50 mg, 0.16 mmol, 1.0 eq.) in MeOH (5 mL). Then, the reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 48 h. The mixture was filtered through Celite® and washed with Et_2O (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine **257** (30 mg, 98%) as a white solid.

Lab Book Reference: JDF6_596

1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate 259



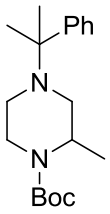
259

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 97:3-8:2 CH_2Cl_2-Et_2O as eluent gave *N*-Boc piperazine **259** (119 mg, 66%) as a pale yellow oil, R_F (19:1 CH_2Cl_2-Et_2O) 0.2; IR ($CHCl_3$) 2972, 2933, 1718 (C=O, CO_2Me), 1662 (C=O, Boc), 1469, 1452, 1391, 1369, 1346, 1331, 1310, 1284, 1195, 1155, 1101, 1016, 951, 736, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.42–7.37 (m, 2H, Ph), 7.31–7.25 (m, 2H, Ph), 7.23–7.17 (m, 1H, Ph), 4.66 (br s, 0.55H, NCH),

4.50 (br s, 0.45H, NCH), 3.80 (d, *J* = 11.0 Hz, 0.55H, NCH), 3.72 (s, 1.35H, OMe), 3.70 (s, 1.65H, OMe), 3.72-3.69 (m, 0.45H, NCH), 3.35–3.19 (m, 1.55H, NCH), 3.13 (td, *J* = 12.0, 3.0 Hz, 0.45H, NCH), 2.74 (d, *J* = 10.5 Hz, 0.45H, NCH), 2.67 (d, *J* = 10.5 Hz, 0.55H, NCH), 2.37 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.18 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.46 (s, 5H, CMe_3), 1.41 (s, 4H, CMe_3), 1.31 (s, 6H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.6 (*C*O_2Me), 171.4 (*C*O_2Me), 156.0 (NC=O), 155.4 (NC=O), 148.4 (*ipso*-Ph), 148.3 (*ipso*-Ph), 127.9 (Ph), 126.3 (Ph), 125.9 (Ph), 80.1 (*C*Me_3), 59.2 (*C*Me_2Ph), 56.0 (NCH), 54.9 (NCH), 51.8 (OMe), 47.8 (NCH_2), 45.7 (NCH_2), 42.7 (NCH_2), 41.7 (NCH_2), 28.3 (C*Me*$_3$), 28.2 (C*Me*$_3$), 24.0 (C*Me*$_2$Ph), 23.9 (C*Me*$_2$Ph), 23.7 (C*Me*$_2$Ph); MS (ESI) *m/z* 363 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{30}N_2O_4$ $(M + H)^+$ 363.2278, found 363.2277 (0.0 ppm error).

Lab Book Reference: JDF6_600

tert-Butyl 2-methyl-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 260



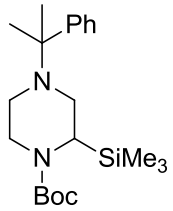
260

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N*′-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl iodide (142 mg, 62 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave *N*-Boc piperazine **260** (152 mg, 95%) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2931, 1652 (C=O), 1427, 1393, 1345, 1300, 1263, 1214, 1152, 1093, 1005, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H, Ph), 7.33-7.27 (m, 2H, Ph), 7.23-7.18 (m, 1H, Ph), 4.12 (br s, 1H, NCH), 3.75 (br d, *J* = 13.0 Hz, 1H, NCH), 3.04 (td, *J* = 12.5, 3.5 Hz, 1H, NCH), 2.76-2.67 (m, 1H, NCH), 2.52 (dt, *J* = 11.0, 2.0 Hz, 1H, NCH), 2.31 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 2.14 (td, *J* = 12.5, 3.5 Hz, 1H, NCH), 1.44 (s, 9H, CMe_3), 1.33 (s, 3H, C*Me*$_2$Ph), 1.30 (s, 3H, C*Me*$_2$Ph), 1.22

(d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 149.2 (*ipso*-Ph), 128.0 (Ph), 126.3 (Ph), 126.2 (Ph), 79.3 (*C*Me_3), 59.4 (*C*Me_2Ph), 50.8 (NCH_2), 47.6 (NCH), 46.5 (NCH_2), 39.9 (NCH_2), 28.5 (C*Me*$_3$), 24.3 (C*Me*$_2$Ph), 23.6 (C*Me*$_2$Ph), 15.8 (CH*Me*); MS (ESI) *m/z* 319 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{30}N_2O_2$ $(M + H)^+$ 319.2380, found 319.2369 (+3.5 ppm error).

Lab Book Reference: JDF7_655

tert-Butyl 4-(2-phenylpropan-2-yl)-2-(trimethylsilyl)piperazine-1-carboxylate 261

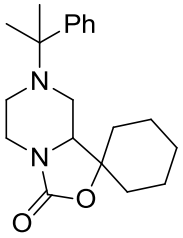


261

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N*′-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and Me_3SiCl (109 mg, 127 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave *N*-Boc piperazine **261** (184 mg, 98%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2965, 2931, 1645 (C=O), 1428, 1399, 1344, 1277, 1261, 1228, 1197, 1154, 1094, 916, 825, 749, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.52-7.47 (m, 2H, Ph), 7.34-7.28 (m, 2H, Ph), 7.24-7.18 (m, 1H, Ph), 3.95 (br s, 0.6H, NCH), 3.72 (br s, 0.4H, NCH), 3.63-3.56 (br m, 1H, NCH), 2.95 (dt, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.93 (br s, 0.4H, NCH), 2.84 (br s, 0.6H, NCH), 2.45 (br s, 2H, NCH), 2.03 (td, *J* = 11.5, 3.0 Hz, 1H, NCH), 1.43 (s, 9H, CMe_3), 1.35 (s, 6H, C*Me*$_2$Ph), 0.13 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.5 (C=O), 154.4 (C=O), 148.4 (*ipso*-Ph), 127.9 (Ph), 126.3 (Ph), 126.3 (Ph), 79.1 (*C*Me_3), 59.9 (*C*Me_2Ph), 47.1 (NCH_2), 46.9 (NCH_2), 46.5 (NCH_2), 45.7 (NCH), 44.7 (NCH), 43.7 (NCH_2), 42.0 (NCH_2), 28.4 (C*Me*$_3$), 26.7 (C*Me*$_2$Ph), 20.4 (C*Me*$_2$Ph), –0.6 ($SiMe_3$); MS (ESI) *m/z* 377 $(M + H)^+$; HRMS *m/z* calcd for $C_{21}H_{36}N_2O_2Si$ $(M + H)^+$ 377.2619, found 377.2601 (+4.3 ppm error).

Lab Book Reference: JDF7_656

7'-(2-Phenylpropan-2-yl)tetrahydrospiro[cyclohexane-1,1'-oxazolo[3,4-a]pyrazin]-3'(5'H)-one 262

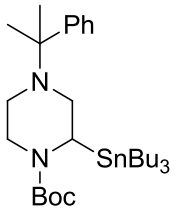


262

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and cyclohexanone (97 mg, 104 µL 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-EtOAc as eluent gave oxazolidinone **262** (95 mg, 58%) as a pale yellow oil, R_F (8:2 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2972, 2930, 2895, 1708 (C=O), 1497, 1425, 1404, 1342, 1263, 1199, 1162, 913, 771, 726, 691, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H, Ph), 7.31 (t, *J* = 7.5 Hz, 2H, Ph), 7.22 (t, *J* = 7.5 Hz, 1H, Ph), 3.73 (dd, *J* = 13.0, 2.0 Hz, 1H, NCH), 3.31 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 2.97 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 2.76-2.67 (m, 2H, NCH), 2.19-2.06 (m, 2H, NCH), 1.91-1.40 (m, 10H, CH_2), 1.33 (s, 6H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.5 (C=O), 148.5 (*ipso*-Ph), 128.2 (Ph), 126.4 (Ph), 125.8 (Ph), 80.8 (CO), 62.7 (NCH), 60.3 (*C*Me$_2$Ph), 46.7 (NCH_2), 45.4 (NCH_2), 41.9 (NCH_2), 36.8 (CH_2), 30.7 (CH_2), 25.0 (CH_2), 24.4 (C*Me*$_2$Ph), 24.1 (C*Me*$_2$Ph), 22.0 (CH_2), 21.9 (CH_2); MS (ESI) *m/z* 329 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{28}N_2O_2$ $(M + H)^+$ 329.2224, found 329.2207 (+4.6 ppm error).

Lab Book Reference: JDF7_642

***tert*-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannyl)piperazine-1-carboxylate 263**

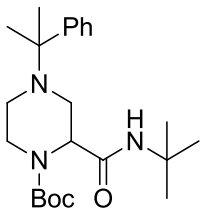


263

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **263** (260 mg, 80%) as a pale yellow oil, R_F (19:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2971, 2913, 2881, 2827, 1645 (C=O), 1432, 1397, 1344, 1280, 1197, 1152, 1090, 1002, 947, 908, 849, 743, 691, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.49 (d, *J* = 7.5 Hz, 2H, Ph), 7.29 (t, *J* = 7.5 Hz, 2H, Ph), 7.23-7.16 (m, 1H, Ph), 4.21-4.12 (m, 0.5H, NCH), 3.97 (br d, *J* = 12.0 Hz, 0.5H, NCH), 3.60-3.25 (m, 1.5H, NCH), 2.86-2.52 (m, 2.5H, NCH), 2.31 (br s, 1H, NCH), 2.06-1.84 (m, 1H, NCH), 1.55-1.37 (m, 15H, CMe_3 + CH_2), 1.33-1.22 (m, 12H, C*Me*$_2$Ph + CH_2), 0.95-0.83 (m, 15H, CH_2 + Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.6 (C=O), 153.9 (C=O), 148.3 (*ipso*-Ph), 148.2 (*ipso*-Ph), 128.0 (Ph), 126.3 (Ph), 79.3 (*C*Me$_3$), 79.0 (*C*Me$_3$), 60.0 (*C*Me$_2$Ph), 50.2 (NCH_2), 46.9 (NCH_2), 45.9 (NCH_2), 45.6 (NCH_2), 43.0 (NCH), 29.2 (CH_2), 28.4 (C*Me*$_3$), 27.9 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 25.7 (CH_2), 22.1 (C*Me*$_2$Ph), 20.7 (C*Me*$_2$Ph), 13.7 (Me), 11.1 (CH_2), 10.4 (CH_2); MS (ESI) *m/z* 595 $(M + H)^+$; HRMS *m/z* calcd for $C_{30}H_{54}N_2O_2Sn$ $(M + H)^+$ 595.3285, found 595.3261 (+3.6 ppm error).

Lab Book Reference: JDF7_607

***tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 264**

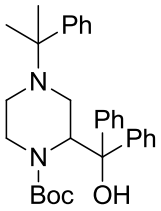


264

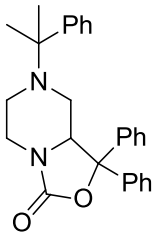
Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and *tert*-butyl isocyanate (64 mg, 74 µL, 0.65 mmol, 1.3 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **264** (55 mg, 27%) as a white solid, mp 61-64 °C; R_F (8:2 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2933, 1651 (C=O), 1524, 1488, 1430, 1371, 1345, 1283, 1152, 1102, 951, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2H, Ph), 7.31-7.24 (m, 2H, Ph), 7.23-7.17 (m, 1H, Ph), 5.88 (br s, 1H, NH), 4.47 (br s, 1H, NCH), 3.86 (br s, 1H, NCH), 3.59 (d, *J* = 11.5 Hz, 1H, NCH), 2.92 (br s, 1H, NCH), 2.49 (br s, 1H, NCH), 2.30 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.09 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.45 (s, 9H, CMe_3), 1.41 (s, 9H, CMe_3), 1.35 (s, 3H, C*Me*$_2$Ph), 1.33 (s, 3H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 169.4 (C=O, CONH), 155.1 (C=O, Boc), 148.5 (*ipso*-Ph), 128.1 (Ph), 126.5 (Ph), 126.1 (Ph), 80.6 (O*C*Me$_3$), 59.7 (*C*Me$_2$Ph), 57.3 (br, NCH), 51.8 (NCH_2), 51.2 (N*C*Me$_3$), 46.5 (NCH_2), 42.1 (br, NCH_2), 28.9 (OC*Me*$_3$), 28.4 (OC*Me*$_3$), 27.8 (NC*Me*$_3$), 20.3 (C*Me*$_2$Ph); MS (ESI) *m/z* 404 $(M + H)^+$; HRMS *m/z* calcd for $C_{23}H_{37}N_3O_3$ $(M + H)^+$ 404.2908, found 404.2914 (+2.2 ppm error).

Lab Book Reference: JDF7_643

***tert*-Butyl 2-(hydroxydiphenylmethyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 266 and 1,1-diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 267**



266



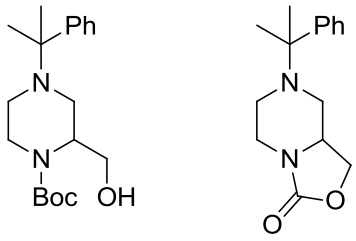
267

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **266** (55 mg, 23%) as a white solid, mp 54-56 °C; R_F (7:3 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2961, 2934, 1655 (C=O), 1427, 1395, 1345, 1326, 1284, 1232, 1151, 1096, 1001, 957, 690, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 8.25 (s, 0.5H, OH), 8.10 (s, 0.5H, OH), 7.70 (d, *J* = 7.5 Hz, 2H, Ph), 7.62 (t, *J* = 7.5 Hz, 2H, Ph), 7.46 (d, *J* = 7.5 Hz, 1H, Ph), 7.42-7.07 (m, 10H, Ph), 5.16 (d, *J* = 3.0 Hz, 0.5H, NCH), 4.84 (d, *J* = 3.0 Hz, 0.5H, NCH), 4.09 (dd, *J* = 13.5, 3.0 Hz, 0.5H, NCH), 3.82-3.62 (m, 1.5H, NCH), 3.27-3.16 (m, 1H, NCH), 2.69 (d, *J* = 11.0 Hz, 0.5H, NCH), 2.61 (d, *J* = 11.0 Hz, 0.5H, NCH), 2.46 (dd, *J* = 11.5, 4.0 Hz, 0.5H, NCH), 2.41 (dd, *J* = 11.5, 4.0 Hz, 0.5H, NCH), 2.25-2.09 (m, 1H, NCH), 1.32 (s, 1.5H, C*Me*$_2$Ph), 1.29 (s, 1.5H, C*Me*$_2$Ph), 1.24 (s, 1.5H, C*Me*$_2$Ph), 1.22 (s, 4.5H, CMe_3), 1.16 (s, 1.5H, C*Me*$_2$Ph), 1.15 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.5 (C=O), 154.2 (C=O), 147.1 (*ipso*-Ph), 146.5 (*ipso*-Ph), 145.7 (*ipso*-Ph), 145.5 (*ipso*-Ph), 145.0 (*ipso*-Ph), 144.7 (*ipso*-Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 127.6 (Ph), 127.5 (Ph), 127.3 (Ph), 126.9 (Ph), 126.9 (Ph), 126.8 (Ph), 126.7 (Ph), 126.5 (Ph), 126.4 (Ph), 126.4 (Ph), 126.2 (Ph), 126.2 (Ph), 126.0 (Ph), 126.0 (Ph), 83.9 (Ph_2COH), 83.8 (Ph_2COH), 79.6 (CMe_3), 60.3 (CMe_2Ph), 60.3 (CMe_2Ph), 55.6 (NCH), 54.0 (NCH), 48.5 (NCH_2), 47.5 (NCH_2), 46.8 (NCH_2), 46.7 (NCH_2), 42.2 (NCH_2), 41.2 (NCH_2), 28.1 (C*Me*$_3$), 27.9 (C*Me*$_3$), 26.4 (C*Me*$_2$Ph), 26.3 (C*Me*$_2$Ph), 19.7 (C*Me*$_2$Ph), 19.6 (C*Me*$_2$Ph); MS (ESI) *m/z* 487 (M +

H)$^+$; HRMS *m/z* calcd for $C_{30}H_{38}N_2O_3$ (M + H)$^+$ 487.2955, found 487.2944 (+2.4 ppm error) and oxazolidinone **267** (152 mg, 74%) as a white solid, mp 122-124 °C; R_F (7:3 petrol-EtOAc) 0.1; IR ($CHCl_3$) 2963, 2931, 1723 (C=O), 1470, 1426, 1390, 1342, 1282, 1241, 1159, 1100, 1059, 1016, 971, 895, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (m, 4H, Ph), 7.39–7.19 (m, 11H, Ph), 4.42 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.83–3.72 (m, 1H, NCH), 3.04 (td, *J* = 12.0, 4.0 Hz, 1H, NCH), 2.69–2.63 (m, 1H, NCH), 2.56 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, NCH), 2.09 (td, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.55 (t, *J* = 11.0 Hz, 1H, NCH), 1.24 (s, 3H, C*Me*$_2$Ph), 1.18 (s, 3H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.2 (C=O), 148.3 (*ipso*-Ph), 142.5 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 127.8 (Ph), 126.5 (Ph), 125.9 (Ph), 125.8 (Ph), 125.7 (Ph), 88.3 (Ph$_2$*C*O), 62.4 (NCH), 60.2 (*C*Me$_2$Ph), 49.3 (NCH$_2$), 45.3 (NCH$_2$), 42.5 (NCH$_2$), 25.0 (C*Me*$_2$Ph), 23.3 (C*Me*$_2$Ph); MS (ESI) *m/z* 413 (M + H)$^+$; HRMS *m/z* calcd for $C_{27}H_{28}N_2O_2$ (M + H)$^+$ 413.2224, found 413.2216 (+2.6 ppm error).

Lab Book Reference: JDF7_606

tert-Butyl 2-(hydroxymethyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 268 and 7-(2-Phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 269



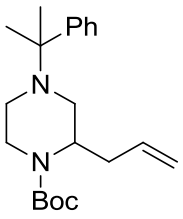
268 **269**

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.50 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and a suspension of paraformaldehyde (30 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **268** (96 mg, 57%) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2972, 2933, 1655 (C=O), 1392, 1370, 1345, 1290, 1196, 1152, 1100, 995, 895, 767, 747, 728, 692, 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 2H, Ph), 7.32 (t, *J* =

7.5 Hz, 2H, Ph), 7.25-7.20 (m, 1H, Ph), 4.19-3.57 (m, 5H, NCH + $CH_2O\mathit{H}$ + $C\mathit{H}_2OH$), 3.26 (br s, 1H, NCH), 2.94 (d, *J* = 11.0 Hz, 1H, NCH), 2.72 (br s, 1H, NCH), 2.41 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.19 (td, *J* = 11.5, 3.0 Hz, 1H, NCH), 1.44 (s, 9H, CMe_3), 1.38 (s, 6H, $C\mathit{Me}_2Ph$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (C=O), 147.4 (*ipso*-Ph), 128.3 (Ph), 126.7 (Ph), 125.9 (Ph), 79.8 ($\mathit{C}Me_3$), 65.4 (CH_2OH), 59.9 ($\mathit{C}Me_2Ph$), 52.0 (NCH), 52.0 (NCH_2), 46.2 (NCH_2), 42.1 (NCH_2), 28.5 ($C\mathit{Me}_3$), 24.2 ($C\mathit{Me}_2Ph$), 22.7 ($C\mathit{Me}_2Ph$); MS (ESI) *m/z* 335 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{30}N_2O_3$ $(M + H)^+$ 335.2329, found 335.2325 (+1.2 ppm error) and oxazolidinone **269** (34 mg, 26%) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.1; IR ($CHCl_3$) 2973, 1720 (C=O), 1496, 1545, 1404, 1194, 1045, 914, 771, 725, 659, 617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 2H, Ph), 7.35-7.29 (m, 2H, Ph), 7.26-7.20 (m, 1H, Ph), 4.32 (t, *J* = 8.0 Hz, 1H, $C\mathit{H}_AH_BO$), 3.88-3.72 (m, 3H, $CH_A\mathit{H}_BO$ + NCH), 3.05 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 2.85-2.74 (m, 2H, NCH), 2.21 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 2.04 (t, *J* = 11.0 Hz, 1H, NCH), 1.34 (s, 6H, $C\mathit{Me}_2Ph$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.0 (C=O), 148.3 (*ipso*-Ph), 128.2 (Ph), 126.5 (Ph), 125.9 (Ph), 65.5 (CH_2O), 60.2 ($\mathit{C}Me_2Ph$), 54.0 (NCH), 51.3 (NCH_2), 45.4 (NCH_2), 42.0 (NCH_2), 25.2 ($C\mathit{Me}_2Ph$), 23.1 ($C\mathit{Me}_2Ph$); MS (ESI) *m/z* 261 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{20}N_2O_2$ $(M + H)^+$ 261.1598, found 261.1587 (+3.9 ppm error).

Lab Book Reference: JDF7_641

***tert*-Butyl 2-allyl-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 270**



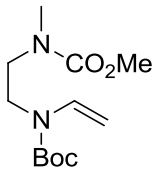
270

Using general procedure E, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h, CuCN.2LiCl (0.25 mmol, 0.5 eq.) in THF (1 mL) and allyl bromide (121 mg, 87 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column

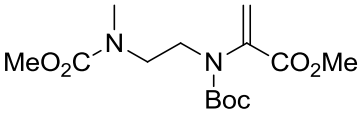
chromatography on silica with 8:2 petrol-Et_2O as eluent gave *N*-Boc piperazine **270** (138 mg, 80%) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2972, 2930, 2776, 1658 (C=O), 1397, 1344, 1305, 1197, 1153, 1092, 972, 950, 907, 761, 732, 691, 658 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.48 (m, 2H, Ph), 7.34-7.28 (m, 2H, Ph), 7.24-7.18 (m, 1H, Ph), 5.73-5.63 (m, 1H, C*H*=CH_2), 5.09-5.02 (m, 1H, CH=CH_AH_B), 4.99-4.94 (m, 1H, CH=CH_AH_B), 4.01 (br s, 1H, NCH), 3.80 (br s, 1H, NCH), 2.98 (t, *J* = 11.5 Hz, 1H, NCH), 2.67 (br s, 2H, NCH or CH_2), 2.57- 2.37 (m, 2H, NCH or CH_2), 2.26 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.21-2.08 (m, 1H, NCH), 1.43 (s, 9H, CMe_3), 1.33 (s, 3H, C*Me*$_2$Ph), 1.30 (s, 3H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.8 (C=O), 148.9 (*ipso*-Ph), 125.7 (CH=*C*H_2), 128.0 (Ph), 126.3 (Ph), 126.0 (Ph), 116.8 (*C*H=CH_2), 79.3 (*C*Me_3), 59.4 (*C*Me_2Ph), 52.0 (br, NCH), 48.0 (NCH_2), 46.4 (NCH_2), 39.6 (br, NCH_2), 34.5 (CH_2), 28.4 (*C*Me_3), 24.5 (C*Me*$_2$Ph), 23.2 (C*Me*$_2$Ph); MS (ESI) *m/z* 345 $(M + H)^+$; HRMS *m/z* calcd for $C_{21}H_{33}N_2O_2$ $(M + H)^+$ 345.2537, found 345.2526 (+3.1 ppm error).

Lab Book Reference: JDF7_666

2-Methylbutan-2-yl *N*-ethenyl-*N*-(2-[(methoxycarbonyl)(methyl)amino]ethyl)carbamate 271 and Methyl 2-(*tert*-butoxycarbonyl(2-(methoxycarbonyl(methyl)amino)ethyl)amino)acrylate 272



271



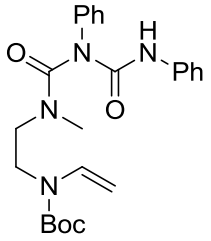
272

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-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) and methyl chloroformate (189 mg, 155 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3-1:1 petrol-EtOAc as eluent gave vinyl carbamate **271** (88 mg, 34%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2983, 1697 (C=O), 1630 (C=O), 1486, 1423, 1393, 1368, 1233, 1216, 1155, 575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) *δ* 7.11 (dd, *J* =15.0, 10.0 Hz, 0.5H, C*H*=CH_2), 6.95 (dd, *J* =

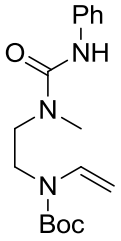
15.0, 10.0 Hz, 0.5H, C*H*=CH_2), 4.48 (m, 0.5H, CH=CH_AH_B), 4.46-4.18 (m, 1.5H, CH=CH_AH_B + CH=CH_2), 3.69 (s, 3H, OMe), 3.69-3.57 (m, 2H, NCH_2), 3.39-3.35 (m, 2H, NCH_2), 2.93 (s, 1.5H, NMe), 2.91 (s, 1.5H, NMe), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 156.6 (C=O), 152.9 (C=O), 152.5 (C=O), 132.9 (*C*H=CH_2), 132.6 (*C*H=CH_2), 91.1 (CH=*C*H_2), 90.6 (CH=*C*H_2), 81.4 (*C*Me_3), 81.2 (*C*Me_3), 52.6 (OMe), 52.5 (OMe), 45.9 (NCH_2), 45.6 (NCH_2), 41.2 (NCH_2), 40.4 (NCH_2), 35.5 (NMe), 28.1 (C*Me*$_3$); MS (ESI) *m/z* 281 [(M + Na)$^+$ 100], 159 [(M – Boc)$^+$, 40]; HRMS *m/z* calcd for $C_{12}H_{22}N_2O_4$ (M + Na)$^+$ 281.1476, found 281.1472 (–1.0 ppm error); and vinyl carbamate **272** (35mg, 11%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3023, 1734 (C=O, CO_2Me), 1699 (C=O, Boc), 1486, 1439, 1395, 1369, 1236, 1161, 765; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.92 (br s, 1H, C=CH_AH_B), 5.56 (br s, 0.5H, C=CH_AH_B), 5.40 (br s, 0.5H, C=CH_AH_B), 3.78 (s, 1.5H, OMe), 3.77 (s, 1.5H, OMe), 3.67 (s, 3H, OMe), 3.62-3.55 (m, 2H, NCH_2), 3.48-3.45 (m, 2H, NCH_2), 3.95 (s, 1.5H, NMe), 3.94 (s, 1.5H, NMe), 1.41 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 166.2 (C=O), 157.0 (C=O), 156.7 (C=O), 153.7 (C=O), 153.6 (C=O), 140.5 (*C*=CH_2), 140.0 (*C*=CH_2), 117.7 (C=*C*H_2), 81.4 (*C*Me_3), 81.2 (*C*Me_3), 52.6 (OMe), 52.5 (OMe), 52.3 (OMe), 52.2 (OMe), 47.9 (NCH_2), 47.1 (NCH_2), 35.2 (NMe), 34.8 (NMe), 28.0 (C*Me*$_3$); MS (ESI) *m/z* 339 [(M + Na)$^+$ 100], 217 [(M – Boc)$^+$, 20]; HRMS *m/z* calcd for $C_{14}H_{24}N_2O_6$ (M + Na)$^+$ 339.1527, found 339.1526 (+0.2 ppm error).

Lab Book Reference: JDF2_186

***tert*-Butyl 2-(1-methyl-3-phenyl-3-(phenylcarbamoyl)ureido)ethyl(vinyl)carbamate 275 and *tert*-Butyl 2-(1-methyl-3-phenylureido)ethyl(vinyl)carbamate 274 and *tert*-Butyl 4-methyl-2-(phenylcarbamoyl)piperazine-1-carboxylate 273**



275



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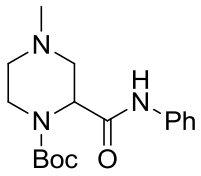


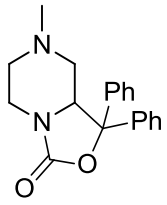
273

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-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) and phenyl isocyanate (238 mg, 218 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-1:1 petrol-EtOAc and then EtOAc as eluent gave vinyl carbamate **275** (127 mg, 29%) as a colourless gum, R_F (3:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3346 (NH), 3006, 1701 (C=O, Boc), 1629 (C=O, urea), 1597, 1533, 1498, 1444, 1381, 1368, 1315, 1278, 1247, 1215, 1154, 1056, 908, 856, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 8.63 (br s, 0.7H, NH), 8.55 (br s, 0.3H, NH), 7.54-7.27 (m, 9H, Ph), 7.07-6.92 (m, 2H, Ph + C*H*=CH_2), 4.44 (d, J = 15.5 Hz, 1H, CH=CH_AH_B), 4.25 (d, J = 9.0 Hz, 1H, CH=CH_AH_B), 3.85 (br s, 1.3H, NCH_2), 3.68 (br s, 0.7H, NCH_2), 3.42 (t, J = 6.5 Hz, 2H, NCH_2), 2.79 (s, 3H, NMe), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.1 (C=O), 152.8 (C=O), 152.5 (C=O), 138.4 (*ipso*-Ph), 137.8 (*ipso*-Ph), 132.5 (*C*H=CH_2), 129.1 (Ph), 128.7 (Ph), 127.7 (Ph), 126.8 (Ph), 123.3 (Ph), 119.7 (Ph), 91.4 (CH=*C*H_2), 81.9 (*C*Me_3), 46.8 (NCH_2), 40.0 (NCH_2), 36.9 (NMe), 28.1 (C*Me*$_3$); MS (ESI) *m/z* 339 [(M – Boc)$^+$]; HRMS *m/z* calcd for $C_{14}H_{23}N_4O_2$ 339.1816, found 339.1809 (+1.6 ppm error), vinyl carbamate **274** (77 mg, 24%) as a pale yellow oil, R_F (3:1 petrol-EtOAc) 0.1; IR ($CHCl_3$) 3010, 1704 (C=O, Boc), 1629 (C=O, urea), 1500, 1421, 1368, 1245, 1154, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.39 (m, 3H, Ph + NH), 7.28 (t, J = 7.0 Hz, 2H, Ph), 7.03-7.00 (m, 2H, Ph + C*H*=CH_2), 4.47 (d, J = 16.0 Hz, 1H, CH=CH_AH_B), 4.47 (br d, J = 8.0 Hz, 1H, CH=CH_AH_B), 3.72 (t, J = 6.5 Hz, 2H, NCH_2), 3.46 (br s, 2H, NCH_2), 3.06 (s, 3H, NMe), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.2 (C=O), 148.8 (C=O), 133.7 (*ipso*-Ph), 132.8 (*C*H=CH_2), 129.4 (Ph), 128.8 (Ph), 128.5 (Ph), 91.4 (CH=*C*H_2), 82.3 (*C*Me_3), 46.1 (NCH_2), 40.9 (NCH_2),

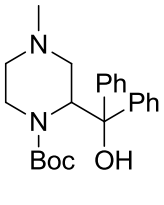
35.5 (NMe), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 342 [(M + Na)$^+$ 100], 320 [(M + H)$^+$, 20], 220 [(M – Boc)$^+$, 80]; HRMS *m/z* calcd for $C_{17}H_{25}N_3O_3$ (M + H)$^+$ 320.1974 , found 320.1958 (+0.6 ppm error) and *N*-Boc piperazine **273** (111 mg, 35%) as a white solid, mp 135-137 °C; R_F (EtOAc) 0.3; IR ($CHCl_3$) 3008, 2981, 2948, 2804, 1686 (C=O), 1599, 1524, 1498, 1442, 1411, 1368, 1296, 1168, 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br s, 1H, NH), 7.54-7.51 (m, 2H, Ph), 7.31 (t, *J* = 8.0 Hz, 2H, Ph), 7.09 (t, *J* = 7.0 Hz, 1H, Ph), 4.76 (br s, 1H, NCH), 4.11 (br s, 1H, NCH), 3.39 (br d, *J* = 11.5 Hz, 1H, NCH), 3.17 (td, J = 13.0, 2.0 Hz, 1H, NCH), 2.77 (br d, *J* = 11.5 Hz, 1H, NCH), 2.33 (s, 3H, NMe), 2.15 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.07-2.01 (m, 1H, NCH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.1 (NHC=O), 155.3 (NC=O) 137.6 (*ipso*-Ph), 128.8 (Ph), 124.1 (Ph), 119.7 (Ph), 81.4 (*C*Me$_3$), 54.5 (NCH_2), 54.2 (NCH_2), 46.0 (NMe), 28.2 (C*Me*$_3$); MS (ESI) *m/z* 320 [(M + H)$^+$, 20], 264 [(M – CMe$_3$)$^+$, 30]; HRMS *m/z* calcd for $C_{17}H_{25}N_3O_3$ (M + H)$^+$ 320.1974, found 320.1981 (+2.4 ppm error).

Lab Book Reference: JDF2_187

7-Methyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one 276 and *tert*-Butyl 2-(hydroxydiphenylmethyl)-4-methylpiperazine-1-carboxylate 277



276



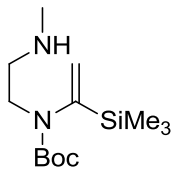
277

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-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in THF (1 mL) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2-95:5 CH_2Cl_2-MeOH as eluent gave oxazolidinone **276** (263 mg, 83%) as a white solid, mp 96-98 °C; R_F (19:1 CH_2Cl_2-MeOH) 0.4; IR ($CHCl_3$) 2948, 2804, 1751 (C=O), 1450, 1409, 1360, 1301, 1255, 1138, 1032, 988, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H, Ph), 7.37-7.23 (m, 8H, Ph), 4.50 (dd, *J* = 11.0,

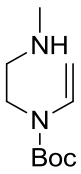
3.5 Hz, 1H, NCH), 3.83 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.12 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.68-2.64 (m, 1H, NCH), 2.43 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.18 (s, 3H, NMe), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.43 (t, *J* = 11.0 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (C=O), 142.2 (*ipso*-Ph), 138.6 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 125.8 (Ph), 125.6 (Ph), 85.1 (Ph_2CO), 60.9 (NCH), 56.9 (NCH_2), 53.2 (NCH_2), 46.3 (NMe), 41.5 (NCH_2); MS (ESI) *m/z* 309 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{20}N_2O_2$ $(M + H)^+$ 309.1598, found 309.1599 (+0.1 ppm error) and *N*-Boc piperazine **277** (45 mg, 12%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.5; IR ($CHCl_3$) 3680 (OH), 3019, 2980, 2855, 2807, 1681 (C=O), 1461, 1417, 1367, 1350, 1304, 1287, 1215, 1169, 1146, 1027, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.70-7.07 (m, 10H, Ph), 5.23 (br d, *J* = 4.0 Hz, 0.5H, NCH), 4.90 (br d, *J* = 4.0 Hz, 0.5H, NCH), 4.17-4.11 (m, 0.5H, NCH), 3.86-3.72 (m, 1.5H, NCH), 2.97-2.92 (m, 1H, NCH), 2.87-2.84 (m, 0.5H, NCH), 2.78-2.76 (m, 0.5H, NCH), 2.28 (dd, *J* = 12.0, 4.0 Hz, 0.5H, NCH), 2.24 (dd, *J* = 12.0, 4.0 Hz, 0.5H, NCH), 2.17 (s, 1.5H, NMe), 2.14 (s, 1.5H, NMe), 2.10-1.98 (m, 1H, NCH), 1.25 (s, 4.5H, CMe_3), 1.21 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.6 (C=O), 154.2 (C=O), 147.7 (*ipso*-Ph), 147.2 (*ipso*-Ph), 145.0 (*ipso*-Ph), 144.7 (*ipso*-Ph), 128.3 (Ph), 128.1 (Ph), 127.5 (Ph), 127.3 (Ph), 126.7 (Ph), 126.6 (Ph), 126.5 (Ph) 126.3 (Ph), 126.1 (Ph), 126.0 (Ph), 83.5 (Ph_2COH), 83.4 (Ph_2COH), 79.8 (CMe_3), 79.7 (CMe_3), 56.6 (NCH_2), 55.8 (NCH_2), 55.2 (NCH), 54.4 (NCH_2), 54.3 (NCH_2), 53.5 (NCH), 45.8 (NMe), 45.7 (NMe), 41.4 (NCH_2), 40.3 (NCH_2), 28.2 (CMe_3), 28.0 (CMe_3); MS (ESI) *m/z* 383 $(M + H)^+$; HRMS *m/z* calcd for $C_{23}H_{30}N_2O_3$ $(M + H)^+$ 383.2329, found 383.2317 (+3.6 ppm error).

Lab Book Reference: JDF1_28

***tert*-Butyl 2-(methylamino)ethyl(1-(trimethylsilyl)vinyl)carbamate 279 and *tert*-Butyl 2-(methylamino)ethyl(vinyl)carbamate 278**



279



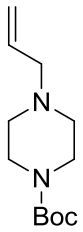
278

s-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.4 mmol, 2.4 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) and TMEDA (278 mg, 360 µL, 2.4 mmol, 2.4 eq.) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was warmed to –10 °C and stirred for 1 h. The solution was cooled to –78 °C then Me_3SiCl (361 mg, 305 µL, 2.4 mmol, 2.4 eq.) was added dropwise. The reaction mixture was warmed to –60 °C, stirred for 1 h then allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-MeOH as eluent gave silane **279** (86 mg, 32%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; IR ($CHCl_3$) 2972, 1656 (C=O), 1432, 1372, 1346, 1228, 1197, 1136, 831, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (br s, 1H, C=CH_AH$_B$), 5.13 (br s, 1H, C=CH$_A$$H_B$), 3.59 (t, J = 7.0 Hz, 2H, NCH_2), 2.79 (t, J = 7.0 Hz, 2H, NCH_2), 2.53 (br s, 1H, NH), 2.49 (s, 3H, Me), 1.47 (s, 9H, CMe_3), 0.15 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.4 (C=O or C=CH_2), 153.3 (C=O or C=CH_2), 112.7 (br, C=CH_2), 80.6 (CMe$_3$), 49.5 (NCH_2), 46.7 (NCH_2), 35.6 (NMe), 28.5 (CMe_3), 0.5 ($SiMe_3$); MS (ESI) *m/z* 273 [$(M + H)^+$, 100], 217 [$(M – CMe_3)^+$, 40], 173 [(M – Boc), 20]; HRMS *m/z* calcd for $C_{17}H_{24}N_2O_2$ $(M + H)^+$ 273.1993, found 273.2000 (–1.9 ppm error) and vinyl carbamate **278** (75 mg, 37%) as a pale oil, R_F (9:1 CH_2Cl_2-MeOH) 0.1; IR ($CHCl_3$) 3513 (NH), 2978, 1698 (C=O), 1629 (C=C), 1456, 1368, 1152, 862, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (br s, 1H, CH=CH_2), 4.35 (d, J = 16.0 Hz, 1H, CH=CH_AH$_B$), 4.21 (br s, 1H, CH=CH$_A$$H_B$), 3.65 (br s, 2H, NCH_2), 2.79 (t, J = 7.0 Hz, 2H, NCH_2), 2.47 (s, 3H, NMe), 2.11 (br s, 1H, NH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9 (C=O), 132.9 (CH=CH_2), 90.8 (CH=CH_2), 81.3 (CMe$_3$), 48.2 (NCH_2), 41.9 (NCH_2), 36.0 (NMe), 28.2 (CMe_3); MS (ESI) *m/z* 201 [(M

+ H)$^+$, 100], 145 [(M – CMe_3)$^+$, 100], 101 [(M – Boc)$^+$, 50]; HRMS *m/z* calcd for $C_{10}H_{20}N_2O_2$ (M + H)$^+$ 201.1598, found 201.1595 (+2.0 ppm error).

Lab Book Reference: JDF5_414

tert-Butyl 4-allylpiperazine-1-carboxylate 239

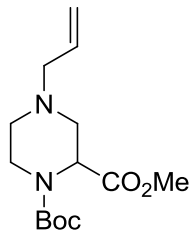


239

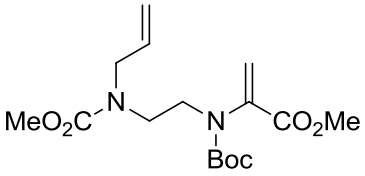
Allyl bromide (3.57 g, 2.56 mL, 29.5 mmol, 1.1 eq.) was added dropwise to a stirred suspension of *N*-Boc piperazine **257** (5.0 g, 26.8 mmol, 1.0 eq.) and K_2CO_3 (2.98 g, 53.7 mmol, 2.0 eq.) in acetone (60 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solids were removed by filtration and washed with acetone (100 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1 petrol-acetone as eluent gave *N*-Boc-*N′*-allyl piperazine **239** (5.15 g, 85%) as a pale yellow oil, R_F (3:1 petrol-acetone) 0.3; IR ($CHCl_3$) 2815, 2368, 1685 (C=O), 1457, 1427, 1366, 1287, 1248, 1169, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.79 (m, 1H, C*H*=CH_2), 5.21-5.15 (m, 2H, CH=C*H*$_2$), 3.43 (br s, 4H, NCH_2), 3.00-2.98 (m, 2H, NCH_2), 2.38 (br s, 4H, NCH_2), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 134.6 (*C*H=CH_2), 118.2 (CH=*C*H_2), 79.5 (*C*Me_3), 61.7 (NCH_2), 52.8 (NCH_2), 43.9 (NCH_2), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 227 [(M + H)$^+$, 100], 171 [(M – CMe_3)$^+$, 40], 127 [(M – Boc)$^+$, 20] ; HRMS *m/z* cal*c*d for $C_{12}H_{22}N_2O_2$ (M + H)$^+$ 227.1754, found 227.1758 (–1.1 ppm error).

Lab Book Reference: JDF1_74

1-*tert*-Butyl 2-methyl 4-allylpiperazine-1,2-dicarboxylate 280 and Methyl 2-((2-(allyl(methoxycarbonyl)amino)ethyl)(*tert*-butoxycarbonyl)amino)acrylate 281



280



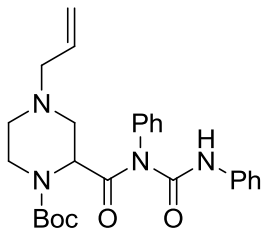
281

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-*N′*-allyl piperazine **239** (226 mg, 1.0 mmol, 1.0 eq.) and methyl chloroformate (190 mg, 154 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **280** (70 mg, 25%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 3019, 2981, 2954, 1743 (C=O, CO_2Me), 1692 (C=O, Boc), 1476, 1456, 1436, 1408, 1368, 1328, 1302, 1222, 1211, 1168, 1118, 1047, 785, 738, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.77 (dddd, J = 16.5, 10.0, 6.5, 6.0 Hz, 1H, C*H*=CH_2), 5.20-5.18 (m, 0.5H, CH=CH_AH_B), 5.16-5.13 (m, 1.5H, CH=CH_AH_B + CH=CH_AH_B), 4.73 (br s, 0.5H, NCH), 4.55 (br s, 0.5H, NCH), 3.86 (br d, J = 14.0 Hz, 0.5H, NCH), 3.77-3.71 (m, 0.5H, NCH), 3.74 (s, 1.5H, OMe), 3.71 (s, 1.5H, OMe), 3.37 (br t, J = 13.0 Hz, 1H, NCH), 3.24 (td, J = 13.0, 3.5 Hz, 0.5H, NCH), 3.14 (td, J = 13.0, 3.5 Hz, 0.5H, NCH), 3.04 (d, J = 12.0 Hz, 0.5H, NCH), 3.03 (d, J = 12.0 Hz, 0.5H, NCH), 2.90 (d, J = 13.0 Hz, 0.5H, NCH), 2.89 (d, J = 13.0 Hz, 0.5H, NCH), 2.81 (d, J = 10.0 Hz, 0.5H, NCH), 2.73 (d, J = 10.0 Hz, 0.5H, NCH), 2.13-2.10 (m, 1H, NCH), 2.02 (td, J = 12.0, 3.5 Hz, 1H, NCH), 1.47 (s, 4.5H, CMe_3), 1.43 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.5 (C=O, CO_2Me), 171.1 (C=O, CO_2Me), 155.7 (C=O, Boc), 155.3 (C=O, Boc), 135.4 (*C*H=CH_2), 118.0 (CH=*C*H_2), 80.2 (*C*Me_3), 61.1 (NCH_2), 55.4 (NCH), 54.2 (NCH), 53.3 (NCH_2), 52.4 (NCH_2), 52.2 (OMe), 41.9 (NCH_2), 41.0 (NCH_2), 28.2 (C*Me*$_3$); MS (ESI) *m/z* 285 [$(M + H)^+$, 100], 229 [$(M - CMe_3)^+$, 30], 185 [$(M - Boc)^+$, 10]; HRMS *m/z* calcd for $C_{14}H_{24}N_2O_4$ $(M + H)^+$ 285.1809, found 285.1821 (–1.9 ppm error) and vinyl carbamate **281** (55 mg, 16%) as a pale yellow oil, R_F (1:1 petrol-EtOAc) 0.5; IR ($CHCl_3$) 3018, 2818, 1744 (C=O), 1688 (C=O), 1455, 1409, 1366, 1329, 1301, 1223, 1205, 1170, 1119, 1046, 788, 668 cm^{-1}; ^1H NMR (400

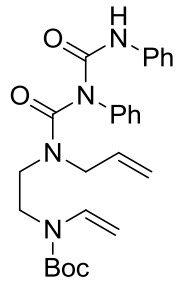
MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.90 (s, 1H, C=CH_AH$_B$), 5.81-5.73 (m, 1H, CH=CH$_2$), 5.56 (s, 0.5H, C=CH$_A$$H_B$), 5.40 (s, 0.5H, C=CH$_A$$H_B$), 5.19-5.13 (m, 2H, C=CH$_2$), 3.92 (d, J = 5.0 Hz, 1H, NCH), 3.88 (d, J = 5.0 Hz, 1H, NCH), 3.77 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.63-3.55 (m, 2H, NCH$_2$), 3.45-3.39 (m, 2H, NCH$_2$), 1.42 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 165.3 (C=O), 156.7 (C=O), 156.6 (C=O), 153.6 (C=O), 153.5 (C=O), 140.5 (*C*=CH$_2$), 140.2 (*C*=CH$_2$), 133.5 (*C*H=CH$_2$), 133.3 (*C*H=CH$_2$), 117.3 (C=*C*H$_2$ or CH=*C*H$_2$), 116.6 (C=*C*H$_2$ or CH=*C*H$_2$), 81.2 (*C*Me$_3$), 52.6 (OMe), 52.3 (OMe), 50.3 (NCH$_2$), 50.1 (NCH$_2$), 48.2 (NCH$_2$), 47.5 (NCH$_2$), 45.3 (NCH$_2$), 44.4 (NCH$_2$), 28.0 (CMe_3); MS (ESI) *m/z* 365 [(M + Na)$^+$, 60], 343 [(M + H)$^+$, 30], 243 [(M – Boc)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{26}N_2O_6$ (M + H)$^+$ 343.1864, found 343.1850 (+3.9 ppm error).

Lab Book Reference: JDF2_127

tert-Butyl 4-allyl-2-(phenyl(phenylcarbamoyl)carbamoyl)piperazine-1-carboxylate 282 and _tert_-Butyl 2-(1-allyl-3-phenyl-3-(phenylcarbamoyl)ureido)ethyl(vinyl)carbamate 283



282



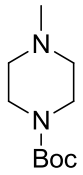
283

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-*N′*-allyl piperazine **239** (226 mg, 1.0 mmol, 1.0 eq.) and phenyl isocyanate (238 mg, 218 µL, 2.0 mmol, 2.0 eq.) worked up with 20% NaOH$_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **282** (192 mg, 41%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.4; IR ($CHCl_3$) 3684 (NH), 3015, 2814, 1718 (C=O), 1596, 1551, 1449, 1366, 1307, 1164, 1042, 991, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 11.35 (s, 1H, NH), 7.56-7.54 (m, 2H, Ph), 7.49-7.27 (m, 7H, Ph), 7.10-7.06 (m, 1H, Ph), 5.83 (dddd, J = 17.5, 10.0, 7.5, 5.5 Hz, 1H, CH=CH$_2$),

5.23 (br d, J = 10.0 Hz, 1H, CH=CH_AH$_B$), 5.17 (dd, J = 17.5, 1.5 Hz, 1H, CH=CH$_A$$H_B$), 4.68 (br s, 1H, NCH), 3.87 (br d, J = 12.0 Hz, 0.4H, NCH), 3.75-3.67 (m, 1.6H, NCH), 3.10 (dd, J = 13.5, 5.0 Hz, 1H, NCH), 2.99 (td, J = 12.0, 1.5 Hz, 1H, NCH), 2.88-2.79 (m, 1H, NCH), 2.73-2.68 (m, 1H, NCH), 2.00 (td, J = 12.0, 5.0 Hz, 1H, NCH), 1.76-1.68 (m, 1H, NCH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 176.1 (C=O), 175.7 (C=O), 156.2 (C=O), 155.2 (C=O), 152.9 (C=O), 152.0 (C=O), 137.8 (*ipso*-Ph), 136.8 (*ipso*-Ph), 134.6 (*C*H=CH$_2$), 129.9 (Ph), 129.4 (Ph), 129.1 (Ph), 128.9 (Ph), 124.0 (Ph), 120.2 (Ph), 118.5 (CH=*C*H$_2$), 80.5 (*C*Me$_3$), 61.2 (NCH$_2$), 55.6 (NCH), 54.5 (NCH), 53.0 (NCH$_2$), 52.8 (NCH$_2$), 52.1 (NCH$_2$), 42.6 (NCH$_2$), 41.6 (NCH$_2$), 25.4 (C*Me*$_3$); MS (ESI) *m/z* 465 (M + H)$^+$; HRMS *m/z* calcd for $C_{26}H_{32}N_4O_4$ (M + H)$^+$ 465.2496, found 465.2491 (+1.8 ppm error) and vinyl carbamate **283** (66 mg, 14%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 3685 (NH), 3347 (NH), 3032, 2402, 1682 (C=O), 1630 (C=O), 1600, 1537, 1502, 1444, 1368, 1311, 1245, 1166, 930, 851, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H, NH), 7.62-6.91 (m, 10H, Ph), 5.88 (ddt, J = 17.0, 10.0, 5.5 Hz, 1H, NC*H*=CH$_2$), 5.31-5.05 (m, 3H, C*H*=CH$_2$ + CH=C*H*$_2$), 4.42 (d, J = 16.0 Hz, 1H, CH=C*H*$_2$), 4.25 (d, J = 9.0 Hz, 1H, CH=C*H*$_2$), 4.04-3.87 (m, 2H, NCH$_2$), 3.76-3.66 (m, 2H, NCH$_2$), 3.49-3.32 (m, 2H, NCH$_2$), 1.52 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2 (C=O), 153.4 (C=O), 153.2 (C=O), 139.9 (*C*H=CH$_2$), 137.2 (*C*H=CH$_2$), 134.7 (*ipso*-Ph), 132.6 (*ipso*-Ph), 130.5 (Ph), 129.7 (Ph), 128.9 (Ph), 128.7 (Ph), 122.4 (Ph), 119.4 (Ph), 117.3 (CH=*C*H$_2$), 91.3 (CH=*C*H$_2$), 82.3 (*C*Me$_3$), 50.5 (NCH$_2$), 43.8 (NCH$_2$), 41.4 (NCH$_2$), 28.2 (C*Me*$_3$); MS (ESI) *m/z* 465 [(M + H)$^+$, 20], 346 [(M - CONHPh)$^+$, 100]; HRMS *m/z* calcd for $C_{26}H_{32}N_4O_4$ (M + H)$^+$ 465.2496, found 465.2539 (–9.8 ppm error).

Lab Book Reference: JDF2_128

***tert*-Butyl 4-methylpiperazine-1-carboxylate 151**

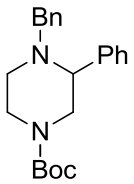


151

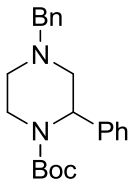
s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-methyl piperazine **151** (200 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred for 1 h at –78 °C. Then, the solution was warmed to 0 °C and stirred at 0 °C for 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-MeOH as eluent gave *N*-Boc piperazine **151** (176 mg, 88%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2.

Lab Book Reference: JDF2_115

***tert*-Butyl 4-benzyl-3-phenylpiperazine-1-carboxylate 295 and *tert*-butyl 4-benzyl-2-phenylpiperazine-1-carboxylate 295**



295



294

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to

rt and stirred at rt for 30 min. Then, bromobenzene (207 mg, 140 μL, 1.3 mmol, 1.3 eq.) was added, followed by the addition of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 eq.) and $^tBu_3PHBF_4$ (18 mg, 0.06 mmol, 0.06 eq.) in one portion. The reaction was stirred at rt for 16 h. Then, 35% $NH_4OH(aq)$ (0.2 mL) was added and the solution stirred at rt for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a 67:33 mixture of *N*-Boc piperazine **295** and *N*-Boc piperazine **294** (by ^1H NMR spectroscopy) (147 mg, 42%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 1.34H, Ph), 7.31-7.19 (m, 8.66H, Ph), 5.23 (br s, 0.33H, NCH), 4.10-3.89 (m, 1.67, NCH), 3.79 (d, *J* = 13.5 Hz, 0.67H, NCH), 3.57 (d, *J* = 13.0 Hz, 0.33H, CH_AH$_B$Ph), 3.45 (d, *J* = 13.0 Hz, 0.33H, CH$_A$$H_B$Ph), 3.30-3.27 (m, 1H, NCH), 3.03 (td, *J* = 12.5, 3.5 Hz, 0.33H, NCH), 3.02-2.76 (m, 3H, NCH), 2.41 (dd, *J* = 12.0, 4.0 Hz, 0.33H, NCH), 2.16 (td, *J* = 12.0, 3.5 Hz, 0.33H, NCH), 2.07 (td, *J* = 12.0, 3.0 Hz, 0.67H, NCH), 1.47 (s, 3H, CMe_3), 1.45 (s, 6H, CMe_3).

Lab Book Reference: JDF7_618

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (207 mg, 140 μL, 1.3 mmol, 1.3 eq.) was added, followed by the addition of $Pd(dba)_2$ (29 mg, 0.05 mmol, 0.05 eq.) and RuPhos (23 mg, 0.05 mmol, 0.05 eq.) in one portion. The reaction was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave a 60:40 mixture of *N*-

Boc piperazine **295** and *N*-Boc piperazine **294** (by ^{1}H NMR spectroscopy) (223 mg, 63%) as a colourless oil.

Lab Book Reference: JDF7_628

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (207 mg, 140 μL, 1.3 mmol, 1.3 eq.) was added, followed by the addition of PEPPSI-^{i}Pr (34 mg, 0.05 mmol, 0.05 eq.) in one portion. The reaction was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a 95:5 mixture (by ^{1}H NMR) of *N*-Boc piperazine **295** and *N*-Boc piperazine **294** (by ^{1}H NMR spectroscopy) (38%) as a colourless oil.

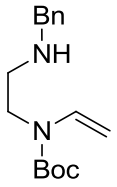
Lab Book Reference: JDF7_617

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in THF (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (104 mg, 70 μL, 0.65 mmol, 1.3 eq.) was added followed by the addition of PEPPSI-^{i}Pr (34 mg, 0.05 mmol, 0.05 eq.) in one portion. The reaction was heated and stirred at reflux for 16 h. Upon cooling, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with

9:1-7:3 petrol-EtOAc as eluent gave a 90:10 mixture (by ^{1}H NMR) of *N*-Boc piperazine **295** and *N*-Boc piperazine **294** (by ^{1}H NMR spectroscopy) (66 mg, 37%) as a colourless oil and *N*-Boc piperazine **117** (52 mg, 37%).

Lab Book Reference: JDF10_967

tert-Butyl (2-(benzylamino)ethyl)(vinyl)carbamate 299



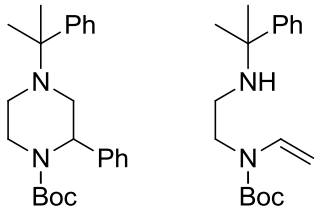
299

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in THF (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (104 mg, 70 μL, 0.65 mmol, 1.3 eq.) was added. This mixture was added to a stirred suspension of $Pd(dba)_2$ (14 mg, 0.025 mmol, 0.05 eq.) and DavePhos (10 mg, 0.025 mmol, 0.05 eq.) in THF (1 mL) at rt under Ar. The reaction was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 7:3-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **117** (67 mg, 49%) as a white solid and alkene **299** (64 mg, 46%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; IR (ATR) 2978, 2936, 2821, 1702 (C=O), 1625 (C=C), 1452, 1421, 1364, 1327, 1247, 1213, 1163, 1137, 1028, 977, 836, 769, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 4H, Ph), 7.29-7.21 (m, 1H, Ph), 7.04 (br s, 1H, C*H*=CH_2), 4.33 (d, *J* = 16.0 Hz, 1H, CH=CH_AH_B), 4.20 (br s, 1H, , CH=CH_AH_B), 3.82 (s, 2H, CH_2Ph), 3.65 (br s, 2H, NCH_2), 2.83 (t, *J* = 6.5 Hz, 2H, NCH_2), 1.47 (s, 9H, CMe_3) (NH not resolved); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 153.0 (C=O), 140.0 (*ipso*-Ph), 133.0 (*C*H=CH_2), 128.3 (Ph), 128.0 (Ph), 127.0 (Ph), 90.8 (CH=*C*H_2), 81.2 (*C*Me_3), 53.9 (*C*H_2Ph), 46.0 (NCH_2), 42.5 (NCH_2), 28.1 (C*Me*$_3$); MS (ESI) *m/z* 277 [$(M + H)^+$, 100], 221 [$(M – CMe_3)^+$, 20]; HRMS *m/z* calcd for $C_{16}H_{25}N_2O_2$ $(M + H)^+$ 277.1911, found 277.1910 (+0.5 ppm error).

Lab Book Reference: JDF10_963

tert-Butyl 2-phenyl-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 300 and _tert_-butyl (2-((2-phenylpropan-2-yl)amino)ethyl)(vinyl)carbamate 301



300 **301**

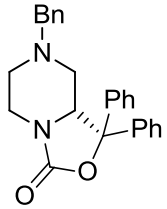
s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in THF (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (104 mg, 70 μL, 0.65 mmol, 1.3 eq.) was added, followed by the addition of $Pd(dba)_2$ (14 mg, 0.025 mmol, 0.05 eq.) and RuPhos (12 mg, 0.025 mmol, 0.05 eq.) in one portion. The reaction was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products. Purification by flash column chromatography on silica with 85:15 petrol-Et_2O then 4:1 petrol:EtOAc as eluent gave *N*-Boc piperazine **300** (23 mg, 12%) as a pale yellow oil, R_F (4:1 petrol-Et_2O) 0.3; IR (ATR) 2974, 1689 (C=O), 1494, 1448, 1412, 1390, 1364, 1295, 10251, 1230, 1164, 1113, 1029, 1012, 975, 956, 762, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.17 (m, 10H, Ph), 5.17 (br s, 1H, NCH), 3.90 (d, *J* = 13.0 Hz, 1H, NCH), 3.26 (d, *J* = 12.0 Hz, 1H, NCH), 3.07 (td, *J* = 12.5, 3.5 Hz, 1H, NCH), 2.71 (d, *J* = 8.5 Hz, 1H, NCH),

2.63 (dd, *J* = 12.0, 4.0 Hz, 1H, NCH), 2.29 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.43 (s, 9H, CMe_3), 1.35 (s, 3H, C*Me*$_2$Ph), 1.33 (s, 3H, C*Me*$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2 (C=O), 148.4 (*ipso*-Ph), 140.9 (*ipso*-Ph), 128.0 (Ph), 127.9 (Ph), 127.2 (Ph), 126.4 (Ph), 126.2 (Ph), 79.7 (*C*Me_3), 59.8 (*C*Me_2Ph), 54.2 (NCH), 49.2 (NCH_2), 46.4 (NCH_2), 41.0 (NCH_2), 28.4 (C*Me*$_3$), 24.0 (C*Me*$_2$Ph), 23.3 (C*Me*$_2$Ph) (Ph not resolved); MS (ESI) *m/z* 381 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{32}N_2O_2$ $(M + H)^+$ 381.2537, found 381.2533 (+0.8 ppm error), and alkene **301** (46 mg, 30%) as a pale yellow oil, R_F (4:1 petrol-Et_2O) 0.1; IR (ATR) 2974, 2930, 1703 (C=O), 1625 ($CH=CH_2$), 1454, 1421, 1358, 1327, 1249, 1215, 1155, 1129, 1029, 835, 763, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H, Ph), 7.34-7.28 (m, 2H, Ph), 7.23-7.17 (m, 1H, Ph), 7.14-6.80 (br m, 1H, C*H*=CH_2), 4.16 (br s, 2H, CH=C*H*$_2$), 3.53 (br s, 2H NCH_2), 2.51 (t, *J* = 7.0 Hz, 2H, NCH_2), 1.47-1.42 (br m, 15H, CMe_3 + C*Me*$_2$Ph) (NH not resolved); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.1 (C=O), 147.8 (*ipso*-Ph), 133.0 (*C*H=CH_2), 128.3 (Ph), 126.3 (Ph), 125.8 (Ph), 90.8 (CH=*C*H_2), 81.2 (*C*Me_3), 55.9 (*C*Me_2Ph), 43.6 (NCH_2), 40.5 (NCH_2), 29.7 (C*Me*$_2$Ph), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 305 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{28}N_2O_2$ $(M + H)^+$ 305.2224, found 305.2213 (+3.9 ppm error) and *N*-Boc piperazine **241** (80 mg, 53%).

Lab Book Reference: JDF11_1006

6.5 Experimental for Chapter Four

(*R*)-7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*)-183

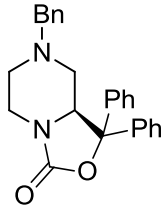


(*R*)-**183**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (457 mg, 448 µL, 1.95 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (*R*)-**183** (310 mg, 54%, 81:19 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +145.9 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**183** 14.4 min, (*R*)-**183** 18.9 min.

Lab Book Reference: JDF1_35

(*S*)-7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*)-183



(*S*)-**183**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography

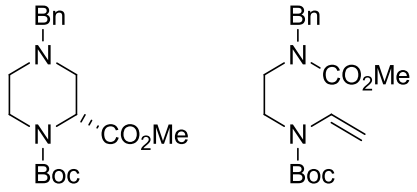
on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (*S*)-**183** (137 mg, 36%, 75:25 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –114.9 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**183** 14.4 min, (*R*)-**183** 18.9 min.

Lab Book Reference: JDF1_61

Using general procedure C, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (606 mg, 1.95 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (415 mg, 1.5 mmol, 1.0 eq.) in Et_2O (10 mL) for 1 h and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (*S*)-**183** (345 mg, 60%, 86:14 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –157.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**183** 14.4 min, (*R*)-**183** 18.9 min.

Lab Book Reference: JDF1_49

(*R*)-1-*tert*-butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate (*R*)-208 and *tert*-Butyl *N*-[2-[benzyl(methoxycarbonyl)amino]ethyl]-*N*-ethenylcarbamate 314



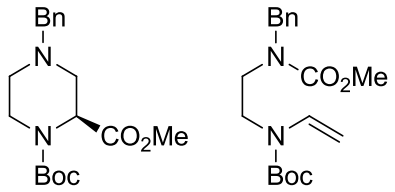
(*R*)-**208** **314**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (457 mg, 448 µL, 1.95 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 90 min and methyl chloroformate (189 mg, 155 µL, 2.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**208** (236 mg, 71%,

88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +27.5 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**208** 5.4 min, (*S*)-**208** 6.3 min, and vinyl carbamate **314** (39 mg, 12%) as a colourless oil, R_F (8:2 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2973, 2934, 1672 (C=O), 1485, 1454, 1430, 1387, 1371, 1346, 1225, 1200, 1148, 769, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.34-7.19 (m, 5H, Ph), 7.10-6.94 (br m, 1H, C*H*=CH_2), 4.58-4.37 (br m, 2.5H, CH=CH_2 + NCH_2), 4.30-4.17 (m, 1.5H, NCH_2), 3.77 (s, 1.5H, OMe), 3.44 (br s, 1.5H, OMe), 3.68-3.59 (br m, 2H, NCH_2), 3.38 (br s, 1H, NCH_2), 3.30 (br s, 1H, NCH_2), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 157.6 (C=O), 157.3 (C=O), 156.0 (C=O), 155.8 (C=O), 137.4 (*ipso*-Ph), 128.6 (*C*H=CH_2), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 79.2 (*C*Me_3), 52.8 (CO_2*Me*), 50.9 (N*C*H_2Ph), 50.5 (N*C*H_2Ph), 46.4 (NCH_2), 45.7 (NCH_2), 39.0 (NCH_2), 28.3 (C*Me*$_3$) (CH=*C*H_2 not resolved), MS (ESI) *m/z* 357 $[(M + Na)^+$, 100], 335 $[(M + H)^+$, 10], 220 $[(M – Boc)^+$, 80], HRMS *m/z* calcd for $C_{18}H_{26}N_2O_4$ $(M + H)^+$ 335.1965, found 335.1972 (–2.6 ppm error).

Lab Book Reference: JDF5_451

(*S*)-1-*tert*-Butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate (*S*)-208 and *tert*-Butyl *N*-[2-[benzyl(methoxycarbonyl)amino]ethyl]-*N*-ethenylcarbamate 314



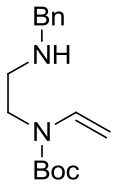
(*S*)-**208** **314**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**208** (295 mg, 88%, 85:15 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –28.7 (*c* 1.0 in

$CHCl_3$); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**208** 5.4 min, (*S*)-**208** 6.3 min, and vinyl carbamate **314** (28 mg, 8%) as a colourless oil.

Lab Book Reference: JDF5_469

tert-Butyl (2-(benzylamino)ethyl)(vinyl)carbamate 299

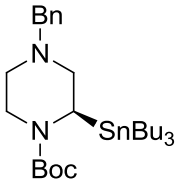


299

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and Me_3SiOTf (222 mg, 181 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2:MeOH as eluent gave alkene **299** (71 mg, 51%) as a colourless oil, R_F (97:3 CH_2Cl_2:MeOH) 0.1.

Lab Book Reference: JDF10_941

(*R*)-_tert_-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate (*R*)-181



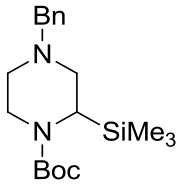
(*R*)-**181**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 10 min and Bu_3SnCl (650 mg, 542 µL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with

19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**181** (96 mg, 17%, 77:23 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –26.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**181** 7.2 min, (*R*)-**181** 7.8 min.

Lab Book Reference: JDF5_468

tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 175

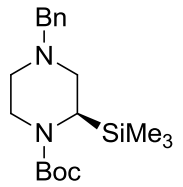


175

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and Me_3SiCl (217 mg, 253 µL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **175** (186 mg, 53%, 50:50 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**175** 3.0 min, (*S*)-**175** 3.4 min.

Lab Book Reference: JDF5_474

(*R*)-_tert_-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate (*R*)-175



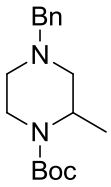
(*R*)-**175**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (404 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117**

(276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and Me_3SiCl (217 mg, 254 µL, 2.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**175** (37 mg, 9%, 52:48 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –0.1 (*c* 0.65 in $CHCl_3$); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**175** 3.1 min, (*S*)-**175** 3.4 min. The major enantiomer is assumed to be the expected (*R*) configuration.

Lab Book Reference: JDF3_231

tert-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate 176

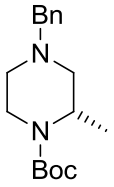


176

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-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.), TMEDA (232 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine **176** (190 mg, 65%) as a colourless oil.

Lab Book Reference: JDF3_250

(*S*)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (*S*)-176

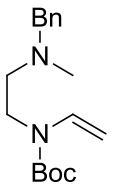


(*S*)-**176**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (404 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and methyl iodide (284 mg, 125 µL, 2.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**176** (395 mg, 45%, 55:45 er by CSP-HPLC) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.6; $[\alpha]_D$ +4.8 (*c* 1.0 in EtOH) (lit.,[150] $[\alpha]_D$ +56 (*c* 0.44 in EtOH) for (*S*)-**176** of >99:1 er); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**176** 9.6 min, (*S*)-**176** 10.2 min.

Lab Book Reference: JDF2_192

***tert*-Butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 315**



315

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (404 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 17:3-7:3 petrol-EtOAc as eluent gave vinyl carbamate **315** (140 mg, 51%) as colourless oil, R_F (4:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 3019, 2980, 2793, 2399, 1698 (C=O), 1627 (C=C), 1521, 1494, 1423, 1391, 1217, 1152, 1018, 928, 847, 761, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-

7.22 (m, 5H, Ph), 7.10-6.95 (br m, 1H, C*H*=CH_2), 4.23-4.10 (m, 2H, CH=CH_2), 3.68-3.51 (m, 2H, NCH_2), 3.55 (s, 2H, CH_2Ph), 2.53 (br s, 2H, NCH_2), 2.29 (s, 3H, NMe), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 153.1 (C=O), 139.0 (*ipso*-Ph), 132.8 (*C*H=CH_2), 128.9 (Ph), 128.2 (Ph), 127.0 (Ph), 90.5 (CH=*C*H_2), 81.1 (*C*Me_3), 62.7 (N*C*H_2Ph), 62.5 (N*C*H_2Ph), 53.3 (NCH_2), 53.1 (NCH_2), 42.7 (NMe), 42.5 (NMe), 41.4 (NCH_2), 40.9 (NCH_2), 28.2 (C*Me*$_3$); MS (ESI) *m/z* 291 [$(M + H)^+$, 100], 235 [$(M - CMe_3)^+$, 20], 191 [$(M - Boc)^+$, 10]; HRMS *m/z* calcd for $C_{17}H_{26}N_2O_2$ $(M + H)^+$ 291.2067, found 291.2072 (–1.0 ppm error).

Lab Book Reference: JDF3_232

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 10 min and dimethyl sulfate (252 mg, 189 µL, 2.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave vinyl carbamate **315** (145 mg, 50%) as a colourless oil.

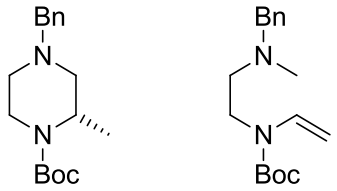
Lab Book Reference: JDF5_475

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate (+)-**26** (126 mg, 0.5 mmol, 1.3 eq.) in Et_2O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 10 min. Then, TMEDA (280 mg, 375 µL, 2.5 mmol, 5.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 30 min. Then, dimethyl sulfate (126 mg, 97 µL, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 8:2 petrol-EtOAc as eluent gave vinyl carbamate **315** (50 mg, 34%) as a colourless oil.

Lab Book Reference: JDF5_480

(*S*)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (*S*)-176 and *tert*-butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 315



(*S*)-**176** **315**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 90 min and methyl iodide (142 mg, 62 µL, 1.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**176** (43 mg, 33%, 61:39 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel IC (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**176** 12.3 min, (*S*)-**176** 14.7 min, and vinyl carbamate **315** (19 mg, 13%) as a colourless oil.

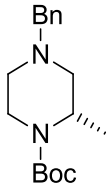
Lab Book Reference: JDF7_619

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 90 min and dimethyl sulfate (126 mg, 97 µL, 1.0 mmol, 2.0 eq.), worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**176** (16 mg, 11%, 58:42 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1})

(*R*)-**176** 6.8 min, (*S*)-**176** 7.3 min, and vinyl carbamate **315** (63 mg, 43%) as a colourless oil.

Lab Book Reference: JDF5_485

(*S*)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (*S*)-176

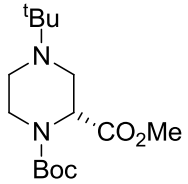


(*S*)-**176**

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (–)-sparteine (152 mg, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc-*N′*-benzyl piperazine **117** (138 mg, 0.5 mmol, 1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 90 min. Then, TMEDA (280 mg, 375 µL, 2.5 mmol, 5.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 30 min. Then, methyl iodide (142 mg, 62 µL, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and 20% $NaOH_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**176** (70 mg, 48%, 87:13 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel IC (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**176** 12.4 min, (*S*)-**176** 15.3 min.

Lab Book Reference: JDF7_620

(*R*)-1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate (*R*)-245

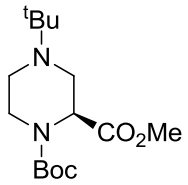


(*R*)-**245**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-*tert*-butyl piperazine **152** (121 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 6 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**245** (108 mg, 72%, 89:11 er by CSP-HPLC) as a pale yellow oil, $[\alpha]_D$ +22.2 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**245** 16.0 min, (*S*)-**245** 21.8 min.

Lab Book Reference: JDF2_153

***(S)*-1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate (*S*)-245**

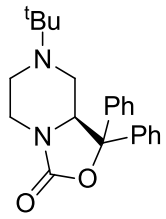


(*S*)-**245**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 10 min and methyl chloroformate (190 mg, 155 µL, 2.0 mmol, 2.0 eq.) worked up with 20% $NaOH_{(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**245** (270 mg, 90%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**245** 14.6 min, (*S*)-**245** 23.4 min.

Lab Book Reference: JDF5_470

(*S*)-7-*tert*-Butyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*)-246



(*S*)-**246**

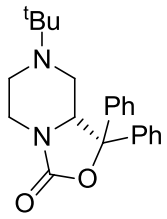
Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (403 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*S*)-**246** (125 mg, 36%, 85:15 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**246** 13.4 min, (*R*)-**246** 17.3 min.

Lab Book Reference: JDF4_398

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*S*)-**246** (265 mg, 76%, 86:14 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –179.3 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**246** 13.4 min, (*R*)-**246** 17.7 min.

Lab Book Reference: JDF4_400

(*R*)-7-*tert*-Butyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*)-246

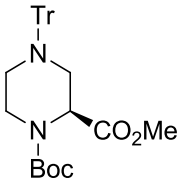


(*R*)-**246**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.), *N*-Boc-*N′*-*tert*-butyl piperazine **152** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 6 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*R*)-**246** (252 mg, 72%, 90:10 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +184.1 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**246** 13.4 min, (*R*)-**246** 16.5 min.

Lab Book Reference: JDF4_392

(*S*)-1-*tert*-Butyl 2-methyl 4-tritylpiperazine-1,2-dicarboxylate (*S*)-247



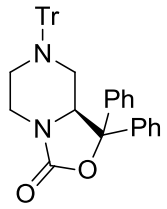
(*S*)-**247**

Using general procedure D, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**247** (196 mg, 81%, 81:19

er by CSP-HPLC) as a white solid, $[\alpha]_D$ –24.0 (*c* 1.0 in $CHCl_3$); CP-HPLC: Chiralcel AD (95:5 hexane:*i*-PrOH, 0.2 mL min^{-1}) (*R*)-**247** 38.4 min, (*S*)-**247** 50.4 min.

Lab Book Reference: JDF5_416

(*S*)-1,1-Diphenyl-7-trityltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*)-249

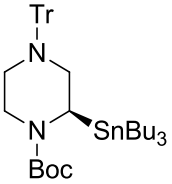


(*S*)-**249**

Using general procedure D, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**249** (215 mg, 80%, 73:27 by CSP-HPLC) as a white solid, $[\alpha]_D$ –121.8 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**249** 5.6 min, (*R*)-**249** 6.7 min.

Lab Book Reference: JDF6_504

(*R*)-*tert*-Butyl 2-(tributylstannyl)-4-tritylpiperazine-1-carboxylate (*R*)-251



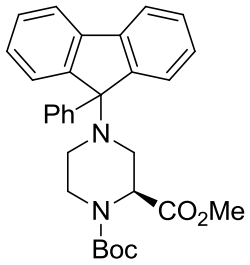
(*R*)-**251**

Using general procedure D, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-trityl piperazine **203** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine

surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**251** (265 mg, 74%, 82:18 er by CSP-HPLC) as a pale yellow oil, $[\alpha]_D$ –27.4 (*c* 1.1 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**251** 6.7 min, (*S*)-**251** 7.6 min.

Lab Book Reference: JDF6_505

(*S*)-1-*tert*-Butyl 2-methyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2-dicarboxylate (*S*)-255



(*S*)-**255**

Using general procedure D, *s*-BuLi (0.39 mL of a 1.3 M solution in hexanes, 0.50 mmol, 1.3 eq.), *N*-Boc piperazine **240** (165 mg, 0.39 mmol, 1.0 eq.), (+)-sparteine surrogate (+)-**26** (99 mg, 0.50 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (74 mg, 60 µL, 0.78 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**255** (129 mg, 68%, 84:16 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –100.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**255** 25.1 min, (*S*)-**255** 30.4 min.

Lab Book Reference: JDF5_417

Using general procedure D, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **240** (213 mg, 0.50 mmol, 1.0 eq.), (+)-sparteine surrogate

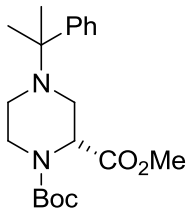
(+)-**26** (126 mg, 0.65 mmol, 1.3 eq.) in MTBE (10 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**255** (144 mg, 59%, 85:15 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**255** 25.1 min, (*S*)-**255** 30.4 min.

Lab Book Reference: JDF6_526

Using general procedure D, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **240** (213 mg, 0.50 mmol, 1.0 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.) in toluene (5 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**255** (98 mg, 40%, 81:19 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**255** 25.1 min, (*S*)-**255** 30.4 min.

Lab Book Reference: JDF6_526

(*R*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*R*)-259



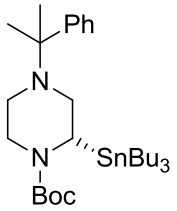
(*R*)-**259**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 6 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica

with 19:1-8:2 CH_2Cl_2-Et_2O as eluent gave *N*-Boc piperazine (*R*)-**259** (128 mg, 71%, 90:10 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +39.0 (*c* 0.85 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**259** 11.5 min, (*S*)-**259** 19.5 min.

Lab Book Reference: JDF7_603

(*S*)-*tert*-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannyl)piperazine-1-carboxylate (*S*)-263

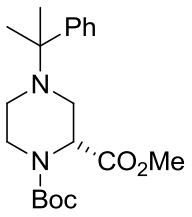


(*S*)-**263**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 6 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**263** (180 mg, 61%, 89:11 er by CSP-HPLC of a derivative (*R*)-**259**) as a yellow oil, $[\alpha]_D$ +32.6 (*c* 1.0 in $CHCl_3$).

Lab Book Reference: JDF7_626

(*R*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*R*)-259

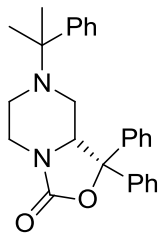


(*R*)-**259**

n-BuLi (35 µL of a 2.2 M solution in hexanes, 0.08 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannane (*S*)-**263** (35 mg, 0.06 mmol, 1.0 eq.) and TMEDA (9 mg, 12 µL, 0.08 mmol, 1.3 eq.) in Et_2O (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, methyl chloroformate (11 mg, 9 µL, 0.12 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 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 8:2 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*)-**259** (15 mg, 69%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**259** 11.2 min, (*S*)-**259** 18.7 min.

Lab Book Reference: JDF7_661

(*R*)-1,1-Diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*)-267

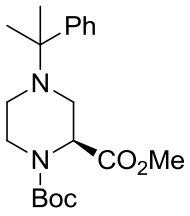


(*R*)-**267**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 μL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 6 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 petrol-EtOAc as eluent gave oxazolidinone (*R*)-**267** (110 mg, 53%, 91:9 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +144.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**267** 19.7 min, (*R*)-**267** 27.7 min.

Lab Book Reference: JDF7_625

(*S*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*S*)-259



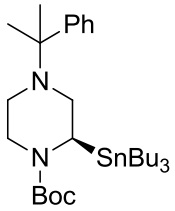
(*S*)-**259**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.5 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and methyl chloroformate (95 mg, 77 μL, 1.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica

with 19:1-8:2 CH_2Cl_2-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**259** (151 mg, 83%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –36.1 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**259** 11.5 min, (*S*)-**259** 19.3 min.

Lab Book Reference: JDF7_646

(*R*)-*tert*-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannyl)piperazine-1-carboxylate (*R*)-263

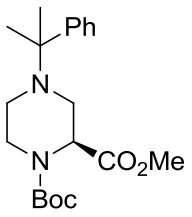


(*R*)-**263**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.5 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**263** (294 mg, 99%, 86:14 er by CSP-HPLC of a derivative (*S*)-**259**) as a yellow oil, $[\alpha]_D$ –32.8 (*c* 1.0 in $CHCl_3$);

Lab Book Reference: JDF7_648

(*S*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*S*)-259

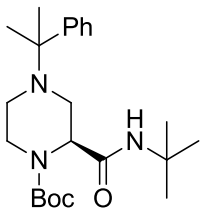


(*S*)-**259**

n-BuLi (35 µL of a 2.2 M solution in hexanes, 0.08 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannane (*R*)-**263** (35 mg, 0.06 mmol, 1.0 eq.) and TMEDA (9 mg, 12 µL, 0.08 mmol, 1.3 eq.) in Et_2O (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, methyl chloroformate (11 mg, 9 µL, 0.12 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 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 8:2 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**259** (15 mg, 69%, 86:14 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**259** 11.2 min, (*S*)-**259** 18.7 min.

Lab Book Reference: JDF7_660

(*S*)-*tert*-Butyl 2-(tert-butylcarbamoyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (*S*)-264

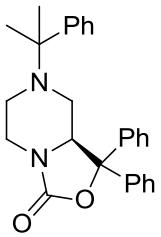


(*S*)-**264**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.5 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and *tert*-butyl isocyanate (64 mg, 74 µL, 0.65 mmol, 1.3 eq.) worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 17:3-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*)-**264** (108 mg, 54%, 87:13 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –33.2 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (98:2 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**264** 14.3 min, (*S*)-**264** 16.6 min.

Lab Book Reference: JDF7_651

(*S*)-1,1-Diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*)-267



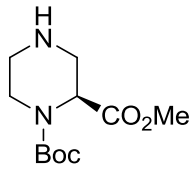
(*S*)-**267**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.5 mmol, 1.3 eq.), *N*-Boc-*N′*-cumyl piperazine **241** (152 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated

$NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave oxazolidinone (*S*)-**267** (150 mg, 73%, 87:13 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –106.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**267** 19.7 min, (*R*)-**267** 28.9 min.

Lab Book Reference: JDF7_647

(*S*)-1-*tert*-Butyl 2-methyl piperazine-1,2-dicarboxylate (*S*)-321



(*S*)-**321**

10% Pd/C (5 mg) was added to a stirred solution of *N*-Boc-piperazine (*S*)-**259** (20 mg, 0.055 mmol, 1.0 eq.) in MeOH (5 mL). Then, the reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 48 h. The mixture was filtered through Celite® and washed with MeOH (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine (*S*)-**321** (14 mg, quant.) as a pale yellow oil, $[\alpha]_D$ –45.9 (*c* 0.95 in $CHCl_3$); IR (ATR) 3352 (NH), 2975, 1743 (C=O, CO_2Me), 1692 (C=O), 1454, 1391, 1364, 1340, 1317, 1290, 1252, 1223, 1201, 1112, 1072, 1038, 975, 917, 862, 829, 776, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.73 (s, 0.5H, NCH), 4.55 (s, 0.5H, NCH), 3.87 (br d, *J* = 13.0 Hz, 0.5H, NCH), 3.72-3.82 (m, 0.5H, NCH), 3.77 (s, 3H, CO_2Me), 3.49-3.59 (m, 1H, NCH), 3.11-3.21 (m, 0.5H, NCH), 2.86-3.08 (m, 2.5H, NCH), 2.65-2.79 (m, 1H, NCH), 1.47 (s, 4.5H, CMe_3), 1.43 (s, 4.5H, CMe_3) (NH not resolved); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.6 (*C*O_2Me), 155.9 (NC=O), 155.5 (NC=O), 80.4 (*C*Me_3), 55.5 (NCH), 54.2 (NCH), 52.3 (CO_2*Me*), 47.3 (NCH_2), 47.1 (NCH_2), 45.3 (NCH_2), 42.7 (NCH_2), 41.5 (NCH_2), 28.4 (C*Me*$_3$); MS (ESI) *m/z* 267 [(M + Na)$^+$, 30], 245 [(M + H)$^+$, 50], 189 [(M – CMe_3)$^+$, 100], 145 [(M – Boc)$^+$, 80]; HRMS *m/z* calcd for $C_{11}H_{20}N_2O_4$ (M + H)$^+$ 245.1493, found 245.1496 (+1.7 ppm error).

Lab Book Reference: JDF7_674

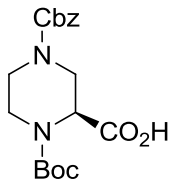
20% $Pd(OH)_2/C$ (5 mg) was added to a stirred solution of *N*-Boc-piperazine (*S*)-**259** (35 mg, 0.097 mmol, 1.0 eq.) and ammonium formate (30 mg, 0.48 mmol, 5.0 eq.) in EtOH (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 2 h. After cooling to rt, the mixture was filtered through Celite® and washed with EtOH (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine (*S*)-**321** (23 mg, 97%) as a colourless oil.

Lab Book Reference: JDF10_1053

10% Pd/C (5 mg) was added to a stirred solution of *N*-Boc-piperazine (*S*,*S*)-**330** (20 mg, 0.057 mmol, 1.0 eq.) in MeOH (5 mL). Then, the reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 48 h. The mixture was filtered through Celite® and washed with MeOH (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine (*S*)-**321** (14 mg, quant.) as a pale yellow oil.

Lab Book Reference: JDF7_675

(*S*)-4-(Benzyloxycarbonyl)-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (*S*)-322



(*S*)-**322**

Benzyl chloroformate (15 mg, 12 µL, 0.086 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc piperazine (*S*)-**321** (14 mg, 0.055 mmol, 1.0 eq.) and Et_3N (9 mg, 12 µL, 0.086 mmol, 1.5 eq.) in CH_2Cl_2 at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 x 5 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 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (16 mg, 74%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.3; $[\alpha]_D$ –3.4 (*c* 0.75 in $CHCl_3$); IR ($CHCl_3$) 2973, 1718 (C=O, CO_2Me), 1672 (C=O), 1492, 1409, 1346, 1302, 1203, 1193, 1094, 1025, 914, 776, 741, 721, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (45:55 mixture of rotamers) δ 7.28-7.40 (5H, m, Ph), 5.17 (br d, *J* = 12.0 Hz, 1H, C$H_A$$H_B$Ph), 5.08 (d, *J* = 12.0 Hz, 1H, C$H_A$$H_B$Ph), 4.76 (br s, 0.45H, NCH), 4.65 (br d, *J* = 13.5 Hz, 0.55H, NCH), 4.58 (br d, *J* = 12.0 Hz, 1H, NCH), 3.98-4.17 (m, 1H, NCH), 3.80-3.93 (m, 1H, NCH), 3.71 (br s, 1.35H, OMe), 3.59 (br s, 1.65H, OMe), 3.04-3.32 (m, 2H, NCH), 2.89 (br s, 1H, NCH), 1.47 (s, 5H, CMe_3), 1.43 (s, 4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 170.5 (*C*O_2Me), 170.3 (*C*O_2Me), 155.5 (NC=O), 155.0 (NC=O), 136.3 (*ipso*-Ph), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 80.9 (*C*Me_3), 67.4 (*C*H_2Ph), 54.8 (NCH), 53.4 (CO_2*Me*), 52.3 (CO_2*Me*), 44.7 (NCH_2), 43.2 (NCH_2), 42.9 (NCH_2), 40.0 (NCH_2), 28.2 (C*Me*$_3$); MS (ESI) *m/z* 401 [(M + Na)$^+$, 100], 323 [(M – Boc)$^+$, 30]; HRMS *m/z* calcd for $C_{19}H_{26}N_2O_6Na$ (M + Na)$^+$ 401.1683, found 401.1670 (+3.1 ppm error).

Lab Book Reference: JDF7_682

LiOH (3 mg, 0.13 mmol, 3.0 eq.) was added to a stirred solution of ester (16 mg, 0.042 mmol, 1.0 eq.) in 4:1:1 THF-MeOH-water (2 mL) at rt under air. The reaction was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. The residue was partitioned between 1M HCl (5 mL) and CH_2Cl_2 (5 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 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 66:33:1 CH_2Cl_2-EtOAc-AcOH as eluent gave carboxylic acid (*S*)-**322** (14 mg, 84%) as a pale yellow oil. R_F (66:33:1 CH_2Cl_2-EtOAc-AcOH); 0.2; $[\alpha]_D$ –14.9 (*c* 0.7 in $CHCl_3$) (lit.,[190] $[\alpha]_D$ –17.5 (*c* 1.02 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (45:55 mixture of rotamers) δ 7.27-7.40 (5H, m, Ph), 5.07-5.21 (m, 2H, CH_2Ph), 4.82 (br s, 0.45H, NCH), 4.63-4.72 (m, 1.55H, NCH), 4.60-4.74 (m, 2H, NCH), 3.09-3.27 (m, 2H, NCH), 2.93 (br s, 1H, NCH), 1.48 (s, 5H, CMe_3), 1.44 (s, 4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 187.6 (COOH), 155.8 (NC=O), 155.4 (NC=O),

155.1 (NC=O), 136.0 (*ipso*-Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 81.2 (*C*Me_3), 67.8 (NCH), 54.6 (*C*H_2Ph), 53.4 (*C*H_2Ph), 44.5 (NCH_2), 44.5 (NCH_2), 44.3 (NCH_2), 43.2 (NCH_2), 41.4 (NCH_2), 40.2 (NCH_2), 28.3 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[190]

Lab Book Reference: JDF7_693

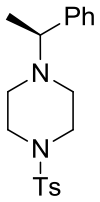
Benzyl chloroformate (15 mg, 12 µL, 0.086 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc piperazine (*S*)-**321** (14 mg, 0.057 mmol, 1.0 eq.) and Et_3N (9 mg, 12 µL, 0.086 mmol, 1.5 eq.) in CH_2Cl_2 at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 x 5 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 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (16 mg, 74%) as a colourless oil.

Lab Book Reference: JDF7_683

LiOH (3 mg, 0.13 mmol, 3.0 eq.) was added to a stirred solution of ester (16 mg, 0.042 mmol, 1.0 eq.) in 4:1:1 THF-MeOH-water (2 mL) at rt under air. The reaction was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. The residue was partitioned between 1M HCl (5 mL) and CH_2Cl_2 (5 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 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 66:33:1 CH_2Cl_2-EtOAc-AcOH as eluent gave carboxylic acid (*S*)-**322** (14 mg, 84%) as a pale yellow oil, R_F (66:33:1 CH_2Cl_2-EtOAc-AcOH); 0.2; $[\alpha]_D$ –14.3 (*c* 0.7 in $CHCl_3$) (lit.,[190] $[\alpha]_D$ –17.5 (*c* 1.02 in $CHCl_3$).

Lab Book Reference: JDF7_694

(*S*)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (*S*)-324

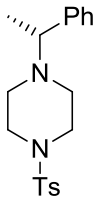


(*S*)-**324**

A mixture of *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide **323** (17.8 g, 60.0 mmol, 1.1 eq.), (*S*)-(−)-α-methylbenzylamine (6.6 g, 7.0 mL, 54.5 mmol, 1.0 eq., >99.5:0.5 er) and *i*-Pr_2NEt (15.5 g, 20.9 mL, 120 mmol, 2.2 eq.) was stirred and heated at 120 °C for 16 h. After being allowed to cool to rt, 7:3 H_2O-EtOH (200 mL) was added and the suspension was stirred for 16 h at rt. Then, the solids were removed by filtration and washed with 1:1 H_2O-EtOH (2 × 100 mL) and then cyclohexane (3 × 50 mL) to give *N*-tosyl piperazine (*S*)-**324** (17.9 g, 84%) as an-off white solid, mp 152-153 °C; $[\alpha]_D$ +48.7 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2978, 2818, 1598, 1492, 1452, 1348, 1304, 1166, 1136, 1093, 951, 908, 851, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.60 (m, 2H, Ar), 7.32-7.20 (m, 8H, Ar), 3.35 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.97 (br s, 4H, NCH), 2.58-2.53 (m, 2H, NCH), 2.47-2.43 (m, 2H, NCH), 2.43 (s, 3H, Ar*Me*), 1.31 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 143.6 (*ipso*-Ar), 143.2 (*ipso*-Ar), 132.4 (*ipso*-Ar), 129.6 (Ar), 128.3 (Ar), 127.9 (Ar), 127.4 (Ar), 127.1 (Ar), 64.4 (N*C*HPh), 49.5 (NCH_2), 46.3 (NCH_2), 21.5 (Me), 19.4 (Me); MS (ESI) *m/z* 345 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{24}N_2O_2S$ $(M + H)^+$ 345.1631, found 345.1628 (+0.0 ppm error).

Lab Book Reference: JDF5_422

(*R*)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (*R*)-324

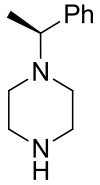


(*R*)-**324**

Using the above procedure, a mixture of *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide **323** (4.0 g, 13.3 mmol, 1.1 eq.), (*R*)-(−)-α-methylbenzylamine (1.47 g, 1.56 mL, 12.1 mmol, 1.0 eq., >98:2 er) and *i*-Pr_2NEt (3.4 g, 4.7 mL, 26.7 mmol, 2.2 eq.) gave *N*-tosyl piperazine (*R*)-**324** (3.5 g, 83%) as an off-white solid, $[\alpha]_D$ –46.3 (*c* 1.0 in $CHCl_3$).

Lab Book Reference: JDF6_533

(*S*)-1-(1-Phenylethyl)piperazine (*S*)-325



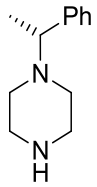
(*S*)-**325**

A suspension of to tosyl piperazine (*S*)-**324** (17.9 g, 52 mmol, 1.0 eq.) and 4-hydroxybenzoic acid (21.6 g, 156 mmol, 3.0 eq.) in HBr (33 wt. % in AcOH, 125 mL) was stirred for at rt for 3 d under air. Then, H_2O (150 mL) was added and the mixture was stirred for 2 h. The resulting white precipitate was removed by filtration and washed with H_2O (200 mL). The aqueous filtrate was extracted with toluene (3 × 100 mL). The aqueous layer was cooled to 0 °C and basified with solid KOH. Then, the basic solution was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give piperazine (*S*)-**325** (9.4 g, 95%) as a pale yellow oil, $[\alpha]_D$ –31.8 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2985, 2363, 1498, 1428, 1301, 1214, 1180, 1012, 913, 801, 692, 650, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.20 (m, 5H, Ph), 3.34 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.86 (t, *J* = 5.0

Hz, 4H, NCH), 2.40 (br s, 2H, NCH), 2.37-2.33 (m, 2H, NCH), 1.94 (br s, 1H, NH), 1.35 (d, J = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.8 (*ipso*-Ph), 128.1 (Ph), 127.6 (Ph), 126.8 (Ph), 65.3 (N*C*HPh), 51.8 (NCH_2), 46.3 (NCH_2), 19.5 (CH*Me*); MS (ESI) *m/z* 191 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{18}N_2$ $(M + H)^+$ 191.1543, found 191.1549 (–1.9 ppm error).

Lab Book Reference: JDF5_424

(*R*)-1-(1-Phenylethyl)piperazine (*R*)-325

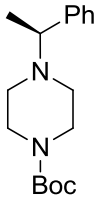


(*R*)-**325**

Using the above procedure, tosyl piperazine (*R*)-**324** (3.5 g, 10 mmol, 1.0 eq.) and 4-hydroxybenzoic acid (4.1 g, 30 mmol, 3.0 eq.) in HBr (33 wt. % in AcOH, 30 mL) gave piperazine (*R*)-**325** (1.5 g, 80%) as a pale yellow oil, $[\alpha]_D$ +32.6 (*c* 1.0 in $CHCl_3$).

Lab Book Reference: JDF6_537

(*S*)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (*S*)-308



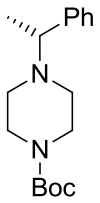
(*S*)-**308**

A solution of di-*tert*-butyl dicarbonate (14.0 g, 64.2 mmol, 1.3 eq.) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of piperazine (*S*)-**325** (9.4 g, 49.4 mmol, 1.0 eq.) in CH_2Cl_2 (100 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, saturated $NaHCO_{3(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 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 9:1-1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**308** (13.4 g, 93%) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.2; $[\alpha]_D$ –40.3 (*c* 1.0 in $CHCl_3$) (lit.,[183] $[\alpha]_D$ –32 (*c* 1.04 in $CHCl_3$) for (*S*)-**308** of >99:1 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H, Ph), 3.39 (t, *J* = 5.0 Hz, 4H, NCH_2), 3.37 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.44-2.41 (m, 2H, NCH), 2.35-2.31 (m, 2H, NCH), 1.43 (s, 9H, CMe_3), 1.36 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.7 (C=O), 143.6 (*ipso*-Ph), 128.2 (Ph), 127.6 (Ph), 127.0 (Ph), 79.4 (*C*Me_3) 64.7 (N*C*HPh), 50.2 (NCH_2); 44.0 (NCH_2), 28.4 (C*Me*$_3$), 19.6 (CH*Me*). Spectroscopic data consistent with those reported in the literature.[183]

Lab Book Reference: JDF5_426

(*R*)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (*R*)-308

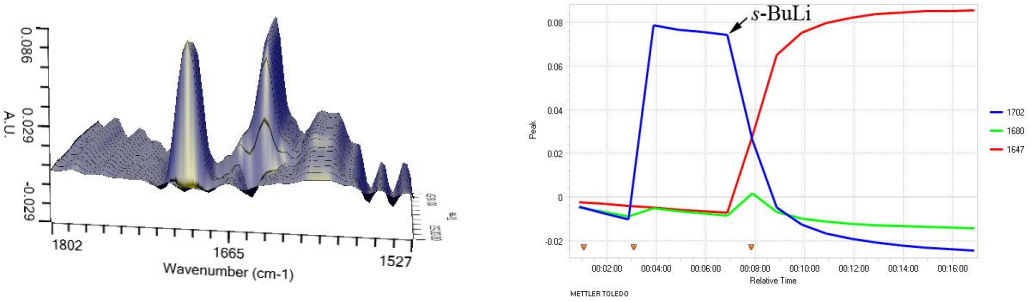


(R)-**308**

Using the above procedure, di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmol, 1.1 eq.) and piperazine (*R*)-**325** (1.5 g, 7.9 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) gave *N*-Boc piperazine (*R*)-**308** (2.2 g, 96%) as a pale yellow oil, $[\alpha]_D$ +43.5 (*c* 1.0 in $CHCl_3$) (lit.,[183] $[\alpha]_D$ –32 (*c* 1.04 in $CHCl_3$) for (*S*)-**308** of >99:1 er); Spectroscopic data consistent with those reported in the literature.[183]

Lab Book Reference: JDF6_538

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-308 (TMEDA)

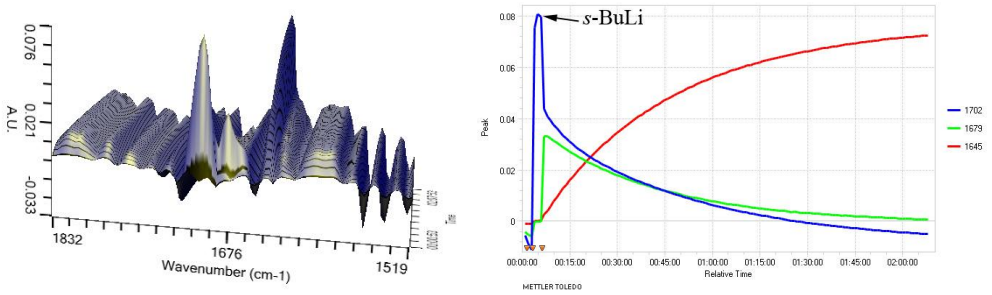


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, TMEDA (151 mg, 195 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). 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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 10 min.

For *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **326**. A new peak at 1647 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **327**. After a lithiation time of 7 min, complete lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** to give the lithiated intermediate **327** was observed.

Lab Book Reference: JDF4_363

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-308 ((–)-sparteine)

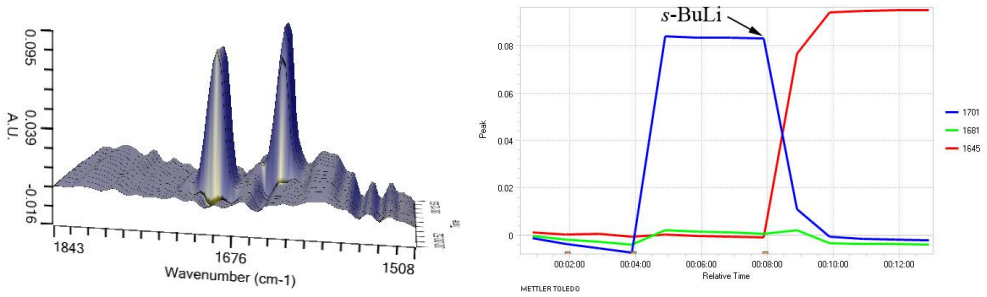


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 2 h.

For *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **326**. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **327**. After a lithiation time of 2 h, incomplete lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** to give the lithiated intermediate **327** and *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** was observed.

Lab Book Reference: JDF4_365

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-308 ((+)-sparteine surrogate (+)-26)

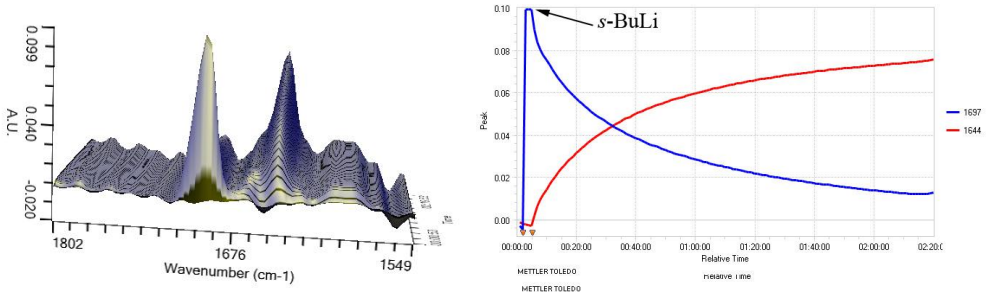


Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C a solution of diamine (+)-**26** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (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, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 5 min.

For *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308**, a peak at 1701 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **326**. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **327**. After a lithiation time of 2 min, complete lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** to give the lithiated intermediate **327** was observed.

Lab Book Reference: JDF5_430

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-308 (THF)

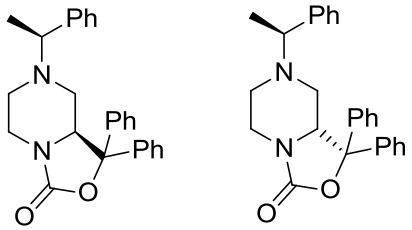


THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added. The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 130 min.

For *N*-Boc-*N′*-(*S*)-α-methylbenzyl piperazine (*S*)-**308**, 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 $\nu_{C=O}$ in the lithiated intermediate **328**. After a lithiation time of 130 min, complete lithiation of *N*-Boc-*N′*-methyl piperazine (*S*)-**308** to give the lithiated intermediate was observed **328**.

Lab Book Reference: JDF6_557

(*S*)-1,1-Diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*,*S*)-309 and (*R*)-1,1-diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*,*S*)-310



(*S*,*S*)-**309** (*R*,*S*)-**310**

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 piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) for 3 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in THF (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 60:40 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (207 mg, 52%) as a white solid, mp 139-140 °C; R_F (7:3 petrol-EtOAc) 0.2; $[\alpha]_D$ –244.9 (*c* 1.0 in $CHCl_3$) (lit.,[183] $[\alpha]_D$ +213 (*c* 0.108 in $CHCl_3$) for (*S*,*S*)-**309** of >99:1 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H, Ph), 7.40-7.22 (m, 11H, Ph), 7.18-7.16 (m, 2H, Ph), 4.51 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.74 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.34 (q, *J* = 7.0 Hz, 1H, C*H*Me), 3.04 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.72-2.60 (m, 2H, NCH), 1.86 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.46 (t, *J* = 11.0 Hz, 1H, NCH), 1.22 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.0 (C=O), 142.7 (*ipso*-Ph), 142.3 (*ipso*-Ph), 138.7 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.3 (Ph), 127.2 (Ph), 126.0 (Ph), 125.8 (Ph), 85.3 (Ph_2CO), 64.3 (CH), 61.4 (CH), 52.5 (NCH_2), 49.1 (NCH_2), 41.9 (NCH_2), 19.2 (CH*Me*) and *N*-Boc piperazine (*R*,*S*)-**310** (128 mg, 32%) as a white solid, mp 127-129 °C; R_F (7:3 petrol-EtOAc) 0.1; $[\alpha]_D$ +187.7 (*c* 1.0 in $CHCl_3$) (lit.,[183] $[\alpha]_D$ –132 (*c* 0.11 in $CHCl_3$) for (*R*,*S*)-**310** of >99:1 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H, Ph), 7.38-7.20 (m, 11H, Ph), 7.18-7.14 (m, 2H, Ph), 4.43 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.81 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.48 (q, *J* = 7.0 Hz, 1H, C*H*Me), 3.10 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.82-2.70 (m, 1H, NCH), 2.43 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.02 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.49 (t, *J* = 11.0 Hz, 1H, NCH), 1.26 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*

155.8 (C=O), 142.0 (*ipso*-Ph), 141.8 (*ipso*-Ph), 138.3 (*ipso*-Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 126.8 (Ph), 125.6 (Ph), 125.4 (Ph), 84.9 (Ph_2CO), 63.3 (CH), 61.2 (CH), 52.8 (NCH_2), 47.1 (NCH_2), 41.6 (NCH_2), 16.7 (CH*Me*); Spectroscopic data for (*S*,*S*)-**309** and (*R*,*S*)-**310** consistent with those reported in the literature.[183]

Lab Book Reference: JDF4_389

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 piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.), TMEDA (148 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 70:30 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (231 mg, 58%) as a white solid and *N*-Boc piperazine (*R*,*S*)-**310** (59 mg, 15%) as a white solid.

Lab Book Reference: JDF4_388

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 piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.), TMEDA (148 mg, 195 µL, 1.3 mmol, 1.3 eq.) in MTBE (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in MTBE (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 70:30 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (218 mg, 56%) as a white solid and *N*-Boc piperazine (*R*,*S*)-**310** (80 mg, 20%) as a white solid.

Lab Book Reference: JDF4_391

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine

(*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 90:10 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (122 mg, 31%) as a white solid, and *N*-Boc piperazine (*R*,*S*)-**310** (15 mg, 4%) as a white solid.

Lab Book Reference: JDF4_399

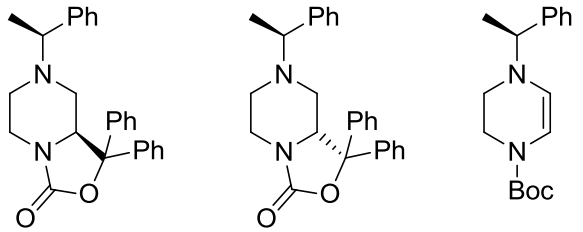
Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*S*,*S*)-**27** (404 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 91:9 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (126 mg, 32%) as a white solid, and *N*-Boc piperazine (*R*,*S*)-**310** (9 mg, 2%) as a white solid.

Lab Book Reference: JDF4_397

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), diamine (*R*,*R*)-**27** (404 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 30:70 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (24 mg, 6%) as a white solid, and *N*-Boc piperazine (*R*,*S*)-**310** (60 mg, 15%) as a white solid.

Lab Book Reference: JDF4_395

(*S*,*S*)-1,1-Diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*,*S*)-309, (*R*)-1,1-diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*S*,*S*)-310 and (*S*)-*tert*-butyl 4-(1-phenylethyl)-3,4-dihydropyrazine-1(2H)-carboxylate (*S*)-329

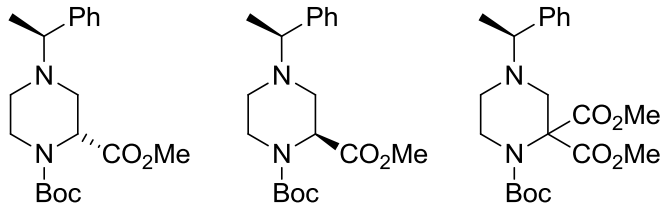


(*S*,*S*)-**309** (*R*,*S*)-**310** (*S*)-**329**

Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (305 mg, 299 µL, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 40:60 mixture of (*S*,*S*)-**309** and (*R*,*S*)-**310** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**309** (67 mg, 16%) as a white solid, *N*-Boc piperazine (*R*,*S*)-**310** (113 mg, 29%) as a white solid and alkene (*S*)-**329** as a clear oil (29 mg, 10%), R_F (8:2 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2971, 1664 (C=O), 1505, 1471, 1430, 1371, 1347, 1203, 1189, 1147, 914, 774, 722, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.41-7.21 (m, 5H, Ph), 6.00 (d, *J* = 6.5 Hz, 0.3H, C*H*=CH), 5.85 (d, *J* = 6.5 Hz, 0.7H, C*H*=CH), 5.64 (d, *J* = 6.5 Hz, 0.3H, CH=C*H*), 5.50 (d, *J* = 6.5 Hz, 0.7H, CH=C*H*), 4.11-4.00 (m, 1H, C*H*Me), 3.69-3.58 (m, 1H, NCH), 3.57-3.47 (m, 1H, NCH), 2.95 (t, *J* = 5.0 Hz, 1.4H, NCH), 2.91 (t, *J* = 5.0 Hz, 0.6H, NCH), 1.48 (s, 2.7H, CMe_3), 1.46 (s, 6.3H, CMe_3), 1.44 (s, 3H, C*H*Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 151.7 (C=O), 143.8 (*ipso*-Ph), 142.2 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph), 127.5 (Ph), 127.2 (Ph), 127.0 (Ph), 126.5 (Ph), 118.0 (*C*H=CH), 117.1 (*C*H=CH), 102.9 (CH=*C*H), 102.7 (CH=*C*H), 80.1 (*CMe*$_3$), 61.3 (N*C*HPh), 44.1 (NCH_2), 42.1 (NCH_2), 40.8 (NCH_2), 28.4 (C*Me*$_3$), 18.3 (CH*Me*); MS (ESI) *m/z* 289 [(M + H)$^+$, 100] 233 [(M – CMe_3)$^+$, 20]; HRMS *m/z* calcd for $C_{17}H_{24}N_2O_2$ (M + H)$^+$ 289.1906, found 289.1911 (+1.6 ppm error).

Lab Book Reference: JDF4_394

(*R*)-1-*tert*-Butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R*,*S*)-331, (*S*)-1-*tert*-butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S*,*S*)-330 and (*S*)-1-*tert*-butyl 2,2-dimethyl 4-(1-phenylethyl)piperazine-1,2,2-tricarboxylate (*S*)-332



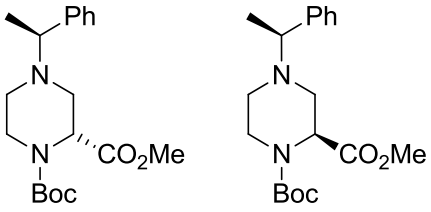
(*R*,*S*)-**331** (*S*,*S*)-**330** (*S*)-**332**

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 piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.), TMEDA (148 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl chloroformate (189 mg, 155 µL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 68:32 mixture of (*R*,*S*)-**330** and (*S*,*S*)-**331** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*S*)-**331** (27 mg, 8%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.2; $[\alpha]_D$ +23.4 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) 1717 (C=O, CO_2Me), 1660 (C=O, Boc), 1498, 1453, 1398, 1346, 1199, 1101, 999, 913, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.34-7.16 (m, 5H, Ph), 4.73 (s, 0.55H, NCH), 4.56 (s, 0.45H, NCH), 3.74 (s, 1.65H, CO_2Me), 3.72 (s, 1.35H, CO_2Me), 3.82-3.63 (m, 1H, C*H*Me), 3.52-3.36 (m, 2H, NCH), 3.18 (td, *J* = 12.5, 3.5 Hz, 0.55H, NCH), 3.07 (td, *J* = 12.5, 3.5 Hz, 0.45H, NCH), 2.69 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.62 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.23 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.06-1.94 (m, 1H, NCH), 1.45 (s, 5H, CMe_3), 1.42 (s, 4H, CMe_3), 1.31 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.6 (*C*O_2Me), 171.3 (*C*O_2Me), 155.9 (NC=O), 155.3 (NC=O), 143.6 (*ipso*-Ph), 143.4 (*ipso*-Ph), 128.5 (Ph), 127.4 (Ph), 126.9 (Ph), 80.1 (*C*Me_3), 63.5 (N*C*HPh), 63.3 (N*C*HPh), 55.7 (NCH), 54.6 (NCH), 52.0 (CO_2*Me*), 50.4 (NCH_2), 50.2 (NCH_2), 50.0 (NCH_2), 42.3 (NCH_2), 41.3 (NCH_2), 28.3 (C*Me*$_3$), 18.7 (CH*Me*), 18.3 (CH*Me*); MS (ESI) *m/z* 349 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{28}N_2O_4$ $(M + H)^+$ 349.2118, found 349.2118 (+0.6 ppm error), *N*-Boc piperazine (*S*,*S*)-**330** (65 mg, 19%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.15; $[\alpha]_D$ –45.7 (*c* 1.5 in $CHCl_3$); IR ($CHCl_3$) 1717 (C=O, CO_2Me), 1661 (C=O, Boc), 1431, 1346,

1282, 1197, 1145, 1102, 1051, 959, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.34-7.17 (m, 5H, Ph), 4.62 (s, 0.55H, NCH), 4.45 (s, 0.45H, NCH), 3.88 (br d, *J* = 12.5 Hz, 0.45H, NCH), 3.79 (br d, *J* = 12.5 Hz, 0.55H, NCH), 3.71 (s, 1.35H, CO_2Me), 3.69 (s, 1.65H, CO_2Me), 3.41-3.14 (m, 3H, C*H*Me + NCH), 3.00 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.94 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.10-1.98 (m, 2H, NCH), 1.46 (s, 5H, CMe_3), 1.40 (s, 4H, CMe_3), 1.31 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.2 (*C*O_2Me), 171.0 (*C*O_2Me), 155.8 (NC=O), 155.3 (NC=O), 143.4 (*ipso*-Ph), 143.2 (*ipso*-Ph), 128.1 (Ph), 127.4 (Ph), 127.1 (Ph), 80.2 (*C*Me_3), 80.1 (*C*Me_3), 64.1 (N*C*HPh), 55.6 (NCH), 54.4 (NCH), 51.8 (CO_2*Me*), 51.7 (NCH_2), 51.5 (NCH_2), 49.2 (NCH_2), 42.2 (NCH_2), 41.2 (NCH_2), 28.3 (C*Me*$_3$), 28.2 (C*Me*$_3$), 19.9 (CH*Me*), 19.7 (CH*Me*); MS (ESI) *m/z* 349 $(M + H)^+$; HRMS *m/z* calcd for $C_{19}H_{28}N_2O_4$ $(M + H)^+$ 349.2118, found 349.2116 (+1.2 ppm error) and *N*-Boc piperazine (*S*)-**332** (99 mg, 24%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.1; $[\alpha]_D$ –16.3 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 1744 (C=O, CO_2Me), 1662 (C=O, Boc), 1430, 1346, 1267, 1146, 1062, 973, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) (55:45 mixture of rotamers) δ 7.34-7.28 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 4.01-3.87 (m, 1H, C*H*Me), 3.85 (m, 3H, CO_2Me), 3.65 (br s, 1.65H, CO_2Me), 3.56 (s, 1.35H, CO_2Me), 3.52–3.33 (m, 2H, NCH), 3.12-2.83 (m, 1.45H, NCH), 2.69 (br s, 0.55H, NCH), 2.53-1.93 (m, 2H, NCH), 1.42 (s, 9H, CMe_3), 1.38 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.4 (*C*O_2Me), 153.4 (NC=O), 152.5 (NC=O), 147.3 (*ipso*-Ph), 143.3 (*ipso*-Ph), 128.4 (Ph), 127.8 (Ph), 127.2 (Ph), 80.4 (*C*Me_3), 64.3 (*C*HMe), 63.9 (*C*HMe), 58.9 (OMe), 55.7 (OMe), 50.2 (NCH_2), 48.4 (NCH_2), 48.3 (NCH_2), 43.9 (NCH_2), 28.2 (C*Me*$_3$), 20.1 (CH*Me*), 19.9 (CH*Me*); MS (ESI) *m/z* 407 $(M + H)^+$; HRMS *m/z* calcd for $C_{21}H_{20}N_2O_6$ $(M + H)^+$ 407.2177, found 407.2185 (–0.2 ppm error).

Lab Book Reference: JDF5_404

(*R*)-1-*tert*-Butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R*,*S*)-331, (*S*)-1-*tert*-butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S*,*S*)-330



(*R*,*S*)-**331** (*S*,*S*)-**330**

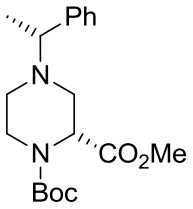
Using general procedure C, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (505 mg, 2.6 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (581 mg, 2.0 mmol, 1.0 eq.) in Et_2O (10 mL) for 10 min and methyl chloroformate (378 mg, 309 µL, 4.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 95:5 mixture of (*S*,*S*)-**330** and (*R*,*S*)-**331** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*S*)-**331** (31 mg, 4%) as a colourless oil and *N*-Boc piperazine (*S*,*S*)-**330** (623 mg, 90%, >99:1 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (98:2 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**330** 7.3 min, (*S*,*S*)-**330** 10.8 min,

Lab Book Reference: JDF8_708

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 3 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 37:63 mixture of (*S*,*S*)-**330** and (*R*,*S*)-**331** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*S*)-**331** (85 mg, 49%) as a colourless oil and *N*-Boc piperazine (*S*,*S*)-**330** (47 mg, 27%) as a colourless oil.

Lab Book Reference: JDF8_710

(*R*)-1-*tert*-Butyl 2-methyl 4-((*R*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R*,*R*)-330

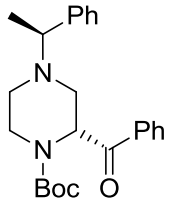


(*R*,*R*)-**330**

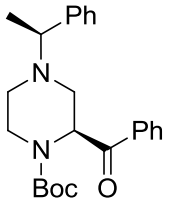
Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and methyl chloroformate (95 mg, 77 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a >95:5 mixture of (*R*,*R*)-**330** and (*S*,*R*)-**331** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*R*)-**330** (158 mg, 91%) as a colourless oil.

Lab Book Reference: JDF7_621

(*R*)-tert-butyl 2-benzoyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*S*)-334 and (*S*)-tert-butyl 2-benzoyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-333



(*R*,*S*)-**334**



(*S*,*S*)-**333**

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), TMEDA (74 mg, 97 µL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and *N*-methoxy-*N*-methylbenzamide (107 mg, 99 µL, 0.65 mmol, 1.3 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 29:71 mixture of (*R*,*S*)-**334** and (*S*,*S*)-**333** (by ^{1}H NMR

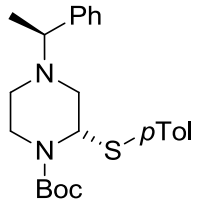
spectroscopy). Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2-Et_2O as eluent gave *N*-Boc piperazine (*R*,*S*)-**334** (34 mg, 17%) as a white solid, mp 104-105 °C; R_F (98:2 CH_2Cl_2-Et_2O) 0.2; $[\alpha]_D$ +1.9 (*c* 0.65 in $CHCl_3$); IR ($CHCl_3$) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1429, 1385, 1345, 1283, 1234, 1144, 1102, 1051, 931, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.83-7.69 (m, 2H, Ph), 7.56-7.46 (m, 1H, Ph), 7.46-7.37 (m, 2H, Ph), 7.22-7.07 (m, 5H, Ph), 5.48 (br s, 0.55H, NCH), 5.31 (br s, 0.45H, NCH), 3.78 (br d, *J* = 11.0 Hz, 0.45H, NCH), 3.69 (br d, *J* = 11.0 Hz, 0.55H, NCH), 3.50-3.23 (m, 3H, C*H*Me + NCH), 2.78-2.56 (m, 1H, NCH), 2.49-2.34 (m, 1H, NCH), 2.14-1.97 (m, 1H, NCH), 1.45 (s, 4.95H, CMe_3), 1.37 (s, 3.05H, CMe_3), 1.02 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 199.4 (COPh), 156.1 (NC=O), 143.4 (*ipso*-Ph), 136.6 (*ipso*-Ph), 136.5 (*ipso*-Ph), 132.3 (Ph), 128.6 (Ph), 128.6 (Ph), 128.5 (Ph), 128.5 (Ph), 127.8 (Ph), 127.7 (Ph), 127.5 (Ph), 127.2 (Ph), 126.8 (Ph), 80.1 (*C*Me_3), 64.5 (*C*HMe), 59.0 (NCH), 58.0 (NCH), 52.9 (NCH_2), 50.4 (NCH_2), 42.5 (NCH_2), 41.7 (NCH_2), 28.3 (C*Me*$_3$), 28.3 (C*Me*$_3$), 18.4 (CH*Me*), 18.3 (CH*Me*); MS (ESI) *m/z* 395 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{30}N_2O_3$ $(M + H)^+$ 395.2329, found 395.2312 (+4.3 ppm error), and *N*-Boc piperazine (*S*,*S*)-**333** (123 mg, 62%) as a white solid, mp 127-129 °C; R_F (98:2 CH_2Cl_2-Et_2O) 0.1; $[\alpha]_D$ –2.6 (*c* 0.8 in $CHCl_3$); IR ($CHCl_3$) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1430, 1385, 1346, 1281, 1234, 1150, 1102, 1051, 931, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.75-7.59 (m, 2H, Ph), 7.55-7.43 (m, 1H, Ph), 7.41-7.31 (m, 2H, Ph), 7.06-6.78 (m, 5H, Ph), 5.39 (br s, 0.55H, NCH), 5.21 (br s, 0.45H, NCH), 3.91 (br d, *J* = 12.0 Hz, 0.45H, NCH), 3.82 (br d, *J* = 12.0 Hz, 0.55H, NCH), 3.62-3.43 (m, 1H, C*H*Me), 3.24-3.02 (m, 2.45H, NCH), 2.98 (br d, *J* = 10.0 Hz, 0.55H), 2.22 (dd, *J* = 12.0, 4.5 Hz, 1H, NCH), 2.04 (br s, 1H, NCH), 1.47 (s, 4.95H, CMe_3), 1.36 (s, 3.05H, CMe_3), 1.17 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 200.0 (COPh), 156.2 (NC=O), 155.6 (NC=O), 143.2 (*ipso*-Ph), 143.1 (*ipso*-Ph), 136.1 (*ipso*-Ph), 136.1 (*ipso*-Ph), 132.6 (Ph), 128.6 (Ph), 128.5 (Ph), 128.0 (Ph), 127.7 (Ph), 127.0 (Ph), 126.7 (Ph), 80.2 (*C*Me_3), 64.5 (*C*HMe), 58.9 (NCH), 57.9 (NCH), 52.3 (NCH_2), 52.3 (NCH_2), 49.7 (NCH_2), 42.6 (NCH_2), 41.8 (NCH_2), 28.5 (C*Me*$_3$), 28.3 (C*Me*$_3$), 20.2 (CH*Me*); 20.1 (CH*Me*); MS (ESI) *m/z* 395 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{30}N_2O_3$ $(M + H)^+$ 395.2329, found 395.2311 (+4.3 ppm error).

Lab Book Reference: JDF8_703

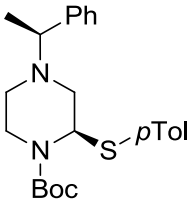
Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and *N*-methoxy-*N*-methylbenzamide (107 mg, 99 µL, 0.65 mmol, 1.3 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 7:93 mixture of (*R*,*S*)-**334** and (*S*,*S*)-**333** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2-Et_2O as eluent gave *N*-Boc piperazine (*R*,*S*)-**334** (12 mg, 6%) as a white solid and *N*-Boc piperazine (*S*,*S*)-**333** (170 mg, 86%) as a white solid.

Lab Book Reference: JDF8_723

(*S*)-*tert*-Butyl 4-((*S*)-1-phenylethyl)-2-(*p*-tolylthio)piperazine-1-carboxylate (*S*,*S*)-336 and (*R*)-*tert*-butyl 4-((*S*)-1-phenylethyl)-2-(*p*-tolylthio)piperazine-1-carboxylate (*R*,*S*)-335



(*S*,*S*)-**336**



(*R*,*S*)-**335**

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), TMEDA (74 mg, 97 µL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and *p*-tolyl disulfide (246 mg, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 31:69 mixture of (*S*,*S*)-**336** and (*R*,*S*)-**335** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica (prewashed with 99:1 CH_2Cl_2-Et_3N) with CH_2Cl_2 as eluent gave *N*-Boc piperazine (*S*,*S*)-**336** (55 mg, 27%) as a pale yellow oil, R_F (CH_2Cl_2) 0.2; $[\alpha]_D$ –46.5 (*c* 0.4 in $CHCl_3$); IR ($CHCl_3$) 2931, 2881, 1661 (C=O), 1469, 1429, 1387, 1347, 1283, 1283, 1253, 1146, 1101, 1001, 930, 846, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:45 mixture of rotamers) δ 7.44-7.30 (m, 6H, Ar), 7.29-7.23 (m, 1H, Ar), 7.08 (br d, *J* = 7.0 Hz, 2H, Ar), 5.76 (br s, 0.35H, NCH), 5.56 (br s, 0.65H, NCH), 3.86 (br d, *J* = 12.0 Hz, 0.65H, NCH), 3.69 (br s, 0.35H, NCH), 3.60-

3.38 (m, 2H, NCH + C*H*Me), 3.27 (br d, *J* = 10.5 Hz, 1H, NCH), 2.77 (br s, 1H, NCH), 2.41 (br d, *J* = 9.5 Hz, 1H, NCH), 2.32 (s, 3H, Ar*Me*), 2.00 (br s, 1H, NCH), 1.36 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.29 (br s, 3.2H, CMe_3), 1.10 (br s, 5.8H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 153.4 (C=O), 143.4 (*ipso*-Ph), 138.0 (*ipso*-Ph), 135.1 (Ph), 134.2 (Ph), 131.0 (*ipso*-Ph), 129.8 (Ph), 129.6 (Ph), 128.5 (Ph), 128.3 (Ph), 127.6 (Ph), 127.0 (Ph), 79.9 (*C*Me_3), 65.0 (NCH), 63.8 (*C*HMe), 54.8 (NCH_2), 50.5 (NCH_2), 40.0 (NCH_2), 38.5 (NCH_2), 28.0 (C*Me*$_3$), 27.7 (C*Me*$_3$), 21.1 (ArMe), 19.0 (CH*Me*); MS (ESI) *m/z* 413 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{32}N_2O_2S$ $(M + H)^+$ 413.2257, found 413.2268 (–3.0 ppm error) and *N*-Boc piperazine (*R*,*S*)-**335** (130 mg, 67%) as a pale yellow oil, R_F (CH_2Cl_2) 0.1; $[\alpha]_D$ +37.9 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2934, 2776, 1662 (C=O), 1469, 1429, 1388, 1346, 1287, 1196, 1149, 1101, 1047, 998, 921, 844, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:45 mixture of rotamers) δ 7.34 (br d, *J* = 4.0 Hz, 6H, Ar), 7.29-7.22 (m, 1H, Ar), 7.06 (br d, *J* = 7.0 Hz, 2H, Ar), 5.67 (br s, 0.35H, NCH), 5.46 (br s, 0.65H, NCH), 3.98 (br d, *J* = 11.5 Hz, 0.65H, NCH), 3.80 (br s, 0.35H, NCH), 3.62 (br t, *J* = 11.5 Hz, 1H, NCH), 3.43 (br s, 1H, C*H*Me), 3.15-2.95 (m, 2H, NCH), 2.30 (s, 3H, Ar*Me*), 2.32-2.22 (m, 1H, NCH), 2.08 (br t, *J* = 10.0 Hz, 1H, NCH) 1.40 (br d, *J* = 6.5 Hz, 3H, CH*Me*), 1.29 (br s, 3.2H, CMe_3), 1.08 (br s, 5.8H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 153.3 (C=O), 142.8 (*ipso*-Ph), 137.9 (*ipso*-Ph), 137.7 (*ipso*-Ph), 135.1 (Ph), 134.3 (Ph), 130.7 (*ipso*-Ph), 130.2 (*ipso*-Ph), 129.6 (Ph), 128.3 (Ph), 127.6 (Ph), 127.0 (Ph), 79.9 (*C*Me_3), 64.6 (NCH), 64.3 (*C*HMe), 55.4 (NCH_2), 54.5 (NCH_2), 50.0 (NCH_2), 39.8 (NCH_2), 38.4 (NCH_2), 28.1 (C*Me*$_3$), 27.6 (C*Me*$_3$), 21.0 (ArMe), 19.8 (CH*Me*); MS (ESI) *m/z* 413 $(M + H)^+$; HRMS *m/z* calcd for $C_{24}H_{32}N_2O_2S$ $(M + H)^+$ 413.2257, found 413.2247 (+2.5 ppm error).

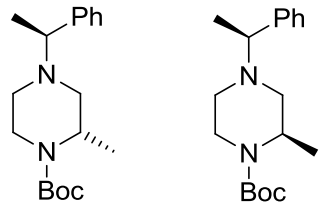
Lab Book Reference: JDF8_711

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and *p*-tolyl disulfide (246 mg, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 5:95 mixture of (*S*,*S*)-**336** and (*R*,*S*)-**335** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica (prewashed with

99:1 CH_2Cl_2-Et_3N) with CH_2Cl_2 as eluent gave *N*-Boc piperazine (*S*,*S*)-**336** (8 mg, 4%) as a pale yellow oil, and *N*-Boc piperazine (*R*,*S*)-**335** (178 mg, 86%) as a pale yellow oil.

Lab Book Reference: JDF8_723

(*S*)-*tert*-Butyl 2-methyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-338 and (*R*)-*tert*-butyl 2-methyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*S*)-337



(*S*,*S*)-**338** (*R*,*S*)-**337**

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 piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.), TMEDA (148 mg, 195 µL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and methyl iodide (284 mg, 125 µL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 37:63 mixture of (*S*,*S*)-**338** and (*R*,*S*)-**337** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 17:3-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**338** (104 mg, 35%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.2; $[\alpha]_D$ +24.2 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2961, 2889, 2769, 1654 (C=O), 1430, 1394, 1346, 1301, 1258, 1212, 1196, 1147, 1112, 1068, 1015, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H, Ph), 7.25-7.21 (m, 1H, Ph), 4.20 (br s, 1H, NCH), 3.70 (br d, *J* = 13.0 Hz, 1H, NCH), 3.34 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.00 (td, *J* = 13.0, 3.5 Hz, 1H, NCH), 2.77 (dt, *J* = 11.0, 2.0 Hz, 1H, NCH), 2.64-2.60 (m, 1H, NCH), 2.16 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 1.89 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 1.44 (s, 9H, CMe_3), 1.31 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.26 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.7 (C=O), 144.4 (*ipso*-Ph), 128.8 (Ph), 127.5 (Ph), 126.8 (Ph), 79.2 (*C*Me_3), 64.0 (N*C*HPh), 53.9 (NCH_2), 51.1 (NCH_2), 47.2 (NCH), 39.3 (NCH_2), 28.4 (C*Me*$_3$), 19.2 (CH*Me*), 16.0 (CH*Me*); MS (ESI) *m/z* 305 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{28}N_2O_2$ $(M + H)^+$ 305.2224, found 305.2238 (–3.4

ppm error) and *N*-Boc piperazine (*R*,*S*)-**337** (189 mg, 62%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.1; $[\alpha]_D$ –92.8 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2933, 2770, 1645 (C=O), 1430, 1394, 1346, 1297, 1268, 1196, 1149, 1114, 1067, 1014, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H, Ph), 4.07 (br s, 1H, NCH), 3.83 (br d, *J* = 13.0 Hz, 1H, NCH), 3.29 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.12 (td, *J* = 13.0, 3.5 Hz, 1H, NCH), 3.01-2.96 (m, 1H, NCH), 2.50 (dt, *J* = 11.0, 2.0 Hz, 1H, NCH), 2.02-1.94 (m, 2H, NCH), 1.43 (s, 9H, CMe_3), 1.33 (d, *J* = 6.5 Hz, CH*Me*), 1.17 (d, *J* = 6.5 Hz, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.7 (C=O), 144.4 (*ipso*-Ph), 128.2 (Ph), 127.3 (Ph), 126.8 (Ph), 79.2 (*C*Me_3), 64.5 (N*C*HPh), 55.6 (NCH_2), 49.9 (NCH_2), 47.1 (NCH), 39.4 (NCH_2), 28.4 (C*Me*$_3$), 20.0 (CH*Me*), 15.6 (CH*Me*); MS (ESI) *m/z* 305 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{28}N_2O_2$ $(M + H)^+$ 305.2224, found 305.2223 (+0.6 ppm error).

Lab Book Reference: JDF5_413

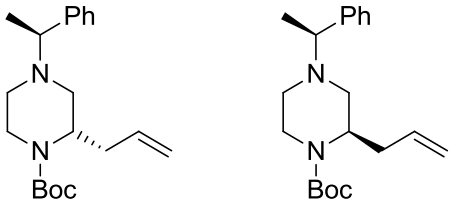
Using general procedure C, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (290 mg, 1.0 mmol, 1.0 eq.), in Et_2O (7 mL) for 1 h and methyl iodide (284 mg, 125 µL, 2.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 24:76 mixture of (*S*,*S*)-**338** and (*R*,*S*)-**337** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**338** (46 mg, 15%) as a colourless oil, and *N*-Boc piperazine (*R*,*S*)-**337** (161 mg, 53%) as a colourless oil

Lab Book Reference: JDF5_420

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), TMEDA (74 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 28:72 mixture of (*S*,*S*)-**338** and (*R*,*S*)-**337** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 17:3-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**338** (33 mg, 23%) as a colourless oil, and *N*-Boc piperazine (*R*,*S*)-**337** (104 mg, 72%) as a colourless oil.

Lab Book Reference: JDF10_976

(*S*)-*tert*-Butyl 2-allyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-340 and (*R*)-*tert*-butyl 2-allyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*S*)-339



(*S*,*S*)-**340** (*R*,*S*)-**339**

Using general procedure E, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), TMEDA (76 mg, 97 µL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) for 1 h, CuCN.2LiCl (0.25 mmol, 0.5 eq.) in THF (1 mL) and allyl bromide (121 mg, 87 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 32:68 mixture of (*S*,*S*)-**340** and (*R*,*S*)-**339** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**340** (37 mg, 23%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; $[\alpha]_D$ +7.6 (*c* 1.4 in $CHCl_3$); IR ($CHCl_3$) 2960, 2770, 2323, 2304, 1654 (C=O), 1430, 1397, 1346, 1304, 1282, 1233, 1152, 1092, 1050, 929, 904, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H, Ph), 7.27-7.21 (m, 1H, Ph), 5.74 (td, *J* = 17.0, 7.5 Hz, 1H, C*H*=CH_2), 5.09-5.02 (m, 1H, CH=CH_AH$_B$), 5.02-4.98 (m, 1H, CH=CH$_A$$H_B$), 4.08 (s, 1H, NCH), 3.74 (s, 1H, NCH), 3.34 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.04-2.85 (m, 2H, NCH), 2.70-2.40 (m, 3H, NCH + CH_2), 2.08 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 1.91 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.43 (s, 9H, CMe_3), 1.29 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 154.8 (C=O), 144.4 (*ipso*-Ph), 135.6 (CH=*C*H_2), 128.2 (Ph), 127.4 (Ph), 126.8 (Ph), 117.0 (*C*H=CH_2), 79.3 (*C*Me_3), 64.0 (*C*HMe), 51.0 (NCH_2), 50.9 (NCH_2), 39.7 (br, NCH_2), 34.3 (CH_2), 28.3 (C*Me*$_3$), 19.0 (CH*Me*); MS (ESI) *m/z* 331 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{30}N_2O_2$ $(M + H)^+$ 331.2380, found 331.2371 (+2.5 ppm error), and (*R*,*S*)-**339** (93 mg, 56%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.1; $[\alpha]_D$ –47.3 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2931, 2323, 2304, 1653 (C=O), 1430, 1390, 1345, 1300, 1282, 1233, 1148, 1092, 1050, 935, 904, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H, Ph), 7.26-7.20 (m, 1H, Ph), 5.63 (td, *J* = 17.0, 7.5 Hz, 1H, C*H*=CH_2), 5.01

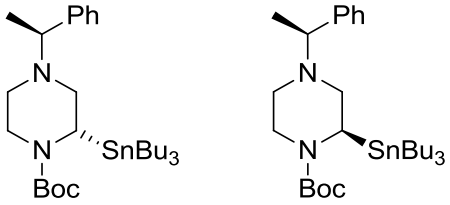
(dd, *J* = 17.0, 1.5 Hz, 1H, CH=C*H*$_A$H$_B$), 4.95-4.90 (m, 1H, CH=CH$_A$*H*$_B$), 3.90 (br s, 2H, NCH), 3.30 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.07 (br t, *J* = 12.5 Hz, 1H, NCH), 2.98 (br d, *J* = 8.0 Hz, 1H, NCH), 2.61 (d, *J* = 11.0 Hz, 1H, NCH), 2.53-2.31 (m, 2H, CH_2), 1.99 (td, *J* = 11.5, 6.0 Hz, 1H, NCH), 1.93 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 1.43 (s, 9H, CMe_3), 1.33 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8 (C=O), 144.0 (*ipso*-Ph), 135.5 (CH=*C*H$_2$), 128.2 (Ph), 127.5 (Ph), 126.9 (Ph), 117.0 (*C*H=CH$_2$), 79.3 (*C*Me$_3$), 64.5 (*C*HMe), 52.8 (NCH_2), 49.8 (NCH_2), 39.3 (br, NCH_2), 34.4 (CH_2), 28.4 (C*Me*$_3$), 19.8 (CH*Me*); MS (ESI) *m/z* 331 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{30}N_2O_2$ $(M + H)^+$ 331.2380, found 331.2372 (+2.5 ppm error).

Lab Book Reference: JDF7_699

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate (+)-**26** (194 mg, 0.65 mmol, 1.3 eq.) in Et_2O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then a solution of CuCN.2LiCl (0.25 mmol, 0.5 eq.) in THF (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then, allyl bromide (121 mg, 87 µL, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained a 5:95 mixture of (*S*,*S*)-**340** and (*R*,*S*)-**339** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*S*,*S*)-**340** (8 mg, 5%) as a colourless oil and (*R*,*S*)-**339** (130 mg, 79%) as a colourless oil.

Lab Book Reference: JDF8_706

(*S*)-*tert*-Butyl 4-((*S*)-1-phenylethyl)-2-(tributylstannyl)piperazine-1-carboxylate (*S*,*S*)-342 and (*R*)-*tert*-butyl 4-((*S*)-1-phenylethyl)-2-(tributylstannyl)piperazine-1-carboxylate (*R*,*S*)-341

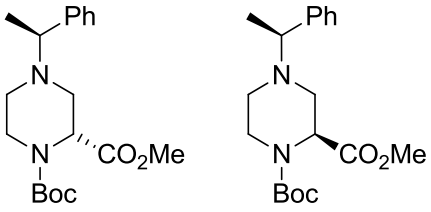


(*S*,*S*)-**342** (*R*,*S*)-**341**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and Bu_3SnCl (325 mg, 271 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 7:93 mixture of (*S*,*S*)-**342** and (*R*,*S*)-**341** (by derivatisation to (*R*,*S*)-**331** and (*S*,*S*)-**330**). Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a mixture of diastereomeric *N*-Boc piperazine (*S*,*S*)-**342** and (*R*,*S*)-**341** (272 mg, 94%) as a pale yellow oil, R_F (19:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.19-7.35 (m, 5H, Ph), 3.97-4.16 (m, 1H, C*H*Me), 3.60 (br s, 0.5H, NCH), 3.45 (br s, 0.5H, NCH), 3.21-3.38 (m, 1.5H, NCH), 2.94 (br d, *J* = 9.5 Hz, 0.5H, NCH), 2.65-2.77 (m, 0.5H, NCH), 2.56-2.68 (m, 1H, NCH), 2.39-2.46 (m, 1H, NCH), 2.18-2.32 (m, 1H, NCH), 1.93-2.04 (m, 0.5H, NCH), 1.32-1.7 (m, 18H, CH_2 + CH*Me* + C*Me*$_3$), 1.21-1.34 (m, 6H, CH_2), 0.79-0.97 (m, 15H, CH_2 + Me).

Lab Book Reference: JDF8_725

(*R*)-1-*tert*-Butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R*,*S*)-331, (*S*)-1-*tert*-butyl 2-methyl 4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S*,*S*)-330

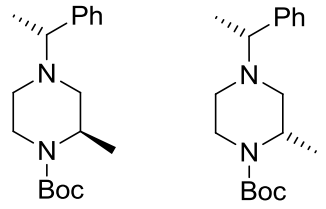


(*R*,*S*)-**331** (*S*,*S*)-**330**

n-BuLi (51 µL of a 2.2 M solution in hexanes, 0.11 mmol, 1.3 eq.) was added dropwise to a stirred solution of diastereomeric stannanes (*S*,*S*)-**342** and (*R*,*S*)-**341** (50 mg, 0.09 mmol, 1.0 eq.) and TMEDA (13 mg, 17 µL, 0.11 mmol, 1.3 eq.) in Et_2O (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, methyl chloroformate (16 mg, 13 µL, 0.17 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure gave the crude product which contained a 7:93 mixture of (*R*,*S*)-**331** and (*S*,*S*)-**330** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a mixture of diastereomeric *N*-Boc piperazines (*R*,*S*)-**331** and (*S*,*S*)-**330** (19 mg, 64%).

Lab Book Reference: JDF8_727

(*R*)-*tert*-Butyl 2-methyl-4-((*R*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*R*)-338 and (*S*)-*tert*-butyl 2-methyl-4-((*R*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*R*)-337



(*R*,*R*)-**338** (*S*,*R*)-**337**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-**308** (145 mg, 0.5 mmol, 1.0 eq.), in Et_2O (5 mL) for 3 h and methyl iodide (142 mg, 62 µL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product which contained a 45:55 mixture of (*R*,*R*)-**338** and (*S*,*R*)-**337** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-1:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*R*)-**338** (41 mg, 27%) as a colourless oil, $[\alpha]_D$ –7.8 (*c* 1.6 in $CHCl_3$) and *N*-Boc piperazine (*S*,*R*)-**337** (48 mg, 32%) as a colourless oil, $[\alpha]_D$ +80.2 (*c* 1.0 in $CHCl_3$).

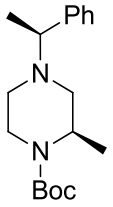
Lab Book Reference: JDF6_577

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (–)-sparteine (152 mg, 149 µL, 0.65 mmol, 1.3 eq.) in Et_2O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc piperazine (*R*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 3 h. Then, TMEDA (240 mg, 375 µL, 2.5 mmol, 5.0 eq.) was added dropwise, and the resulting solution was stirred at –78 °C for 30 min. Then, methyl iodide (142 mg, 62 µL, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and saturated $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude products in which contained a 10:90 mixture of

(*R*,*R*)-**338** and (*S*,*R*)-**337** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*R*)-**338** (5 mg, 3%) as a colourless oil and *N*-Boc piperazine (*S*,*R*)-**337** (106 mg, 70%) as a colourless oil.

Lab Book Reference: JDF6_578

(*R*)-*tert*-butyl 2-methyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*S*)-337

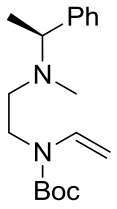


(*R*,*S*)-**337**

n-BuLi (51 µL of a 2.2 M solution in hexanes, 0.11 mmol, 1.3 eq.) was added dropwise to a stirred solution of diastereomeric stannanes (*S*,*S*)-**342** and (*R*,*S*)-**341** (50 mg, 0.09 mmol, 1.0 eq.) and TMEDA (13 mg, 17 µL, 0.11 mmol, 1.3 eq.) in Et_2O (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, methyl iodide (25 mg, 11 µL, 0.17 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure gave the crude product which contained a 7:93 mixture of (*S*,*S*)-**338** and (*R*,*S*)-**337** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*,*S*)-**337** (18 mg, 69%).

Lab Book Reference: JDF8_732

(S)-*tert*-Butyl (2-(methyl(1-phenylethyl)amino)ethyl)(vinyl)carbamate (*S*)-343

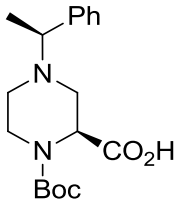


(*S*)-**343**

Using general procedure C, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (+)-**26** (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**308** (145 mg, 0.5 mmol, 1.0 eq.) in Et_2O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113 μL, 1.0 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et_2O as eluent gave alkene (*S*)-**343** (71 mg, 46%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.2; $[\alpha]_D$ –21.0 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) 2973, 2930, 2851, 2779, 1707 (C=O), 1623 (C=C), 1453, 1419, 1360, 1324, 1247, 1205, 1150, 1060, 863, 832, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 4H, Ph), 7.25-7.18 (m, 1H, Ph), 7.08-6.82 (br m, 1H, C*H*=CH_2), 4.17-3.92 (m, 2H, CH=C*H*$_2$), 3.70-3.36 (m, 3H, NCH + C*H*Me), 2.59-2.53 (m, 1H, NCH), 2.46-2.32 (m, 1H, NCH), 2.30 (br s, 3H, NMe), 1.45 (br s, 9H, CMe_3), 1.35 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 153.2 (C=O), 152.4 (C=O), 143.9 (*ipso*-Ph), 132.7 (*C*H=CH_2), 128.2 (Ph), 127.5 (Ph), 126.8 (Ph), 90.3 (CH=*C*H_2), 81.0 (*C*Me_3), 63.9 (*C*HMe), 63.7 (CHMe), 50.4 (NCH_2), 49.9 (NCH_2), 41.5 (NCH_2), 41.0 (NCH_2), 28.1 (C*Me*$_3$), 18.6 (CH*Me*), 18.4 (CH*Me*); MS (ESI) *m/z* 305 (M + H)$^+$; HRMS *m/z* calcd for $C_{18}H_{28}N_2O_2$ (M + H)$^+$ 305.2224, found 305.2224 (+0.3 ppm error).

Lab Book Reference: JDF10_977

(*S*)-1-(*tert*-Butoxycarbonyl)-4-((*S*)-1-phenylethyl)piperazine-2-carboxylic acid (*S*,*S*)-344

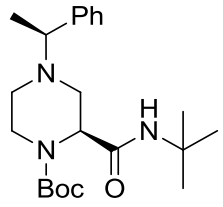


(*S*,*S*)-**344**

Lithium hydroxide (4 mg, 0.17 mmol, 3.0 eq.) was added to a stirred solution of methyl ester (*S*,*S*)-**330** (20 mg, 0.06 mmol, 1.0 eq.) in THF/MeOH/water (4:1:1, 3 mL) under air. The resulting solution was stirred at room temperature for 48 h. The volatiles were removed under reduced pressure. Then, water (5 mL) was added and the pH was adjusted to pH 4-5 with 1M $HCl_{(aq)}$. The aqueous was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *N*-Boc piperazine (*S*,*S*)-**344** (18 mg, 94%) as a white solid, mp 72-74 °C; $[\alpha]_D$ –70.8 (*c* 0.75 in $CHCl_3$); IR ($CHCl_3$) 2934, 1666 (C=O), 1433, 1371, 1346, 1280, 1148, 1102, 1048, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 8.08 (br s, 1H, COOH), 7.29-7.40 (m, 5H, Ph), 4.75 (br s, 0.45H, NCH), 4.60 (br s, 0.55H, NCH), 4.12 (q, *J* = 7.0 Hz, 1H, C*H*Me), 3.97 (br d, *J* = 14.0 Hz, 0.55H, NCH), 3.85 (br d, *J* = 14.0 Hz, 0.45H, NCH), 3.76 (t, *J* = 11.0 Hz, 1H, NCH), 3.41-3.64 (m, 1H, NCH), 3.29 (br d, *J* = 10.5 Hz, 0.55H, NCH), 3.21 (br d, *J* = 10.5 Hz, 0.45H, NCH), 2.47 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.18-2.38 (m, 1H, NCH), 1.56-1.69 (m, 3H, CH*Me*), 1.41 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 172.7 (COOH), 155.1 (NC=O), 154.9 (NC=O), 136.9 (*ipso*-Ph), 128.8 (Ph), 128.7 (Ph), 80.4 (*C*Me$_3$), 64.8 (*C*HMe), 64.7 (*C*HMe), 54.7 (NCH), 53.5 (NCH), 49.3 (NCH_2), 40.5 (NCH_2), 39.1 (NCH_2), 28.3 (C*Me*$_3$), 16.9 (CH*Me*), 16.8 (CH*Me*); MS (ESI) *m/z* 335 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{26}N_2O_4$ $(M + H)^+$ 335.1965, found 335.1961 (+0.9 ppm error).

Lab Book Reference: JDF8_719

(*S*)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S*,*S*)-345

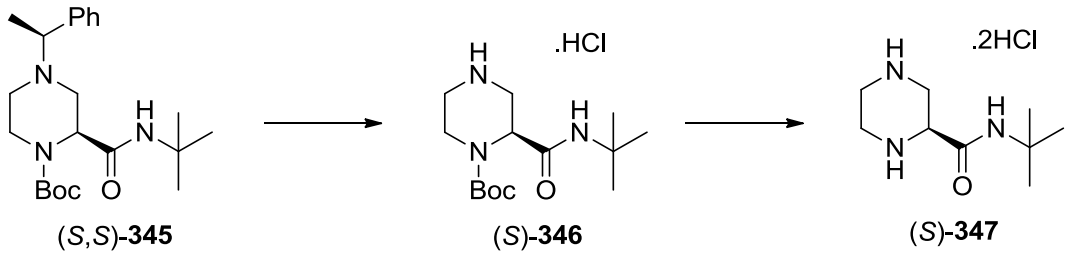


(*S*,*S*)-**345**

HATU (36 mg, 0.094 mmol, 1.5 eq.) was added in one portion to a stirred solution of acid (*S*,*S*)-**344** (21 mg, 0.063 mmol, 1.0 eq.), *tert*-butylamine (7 mg, 10 µL, 0.094 mmol, 1.5 eq.) and DIPEA (16 mg, 22 µL, 0.126 mmol, 2.0 eq.) in DMF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Saturated $NaHCO_{3(aq)}$ (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*,*S*)-**345** (24 mg, 98%) as a white solid, mp 91-93 °C; R_F (7:3 petrol-EtOAc) 0.3; $[\alpha]_D$ –61.1 (*c* 0.8 in $CHCl_3$); IR ($CHCl_3$) 2974, 2932, 1653 (C=O), 1490, 1431, 1394, 1346, 1194, 1148, 1101, 1015, 914, 769, 731, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H, Ph), 6.18 (br s, 1H, NH), 4.37 (br s, 1H, NCH), 3.94 (br s, 1H, NCH), 3.45 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.20 (br d, *J* = 11.5 Hz, 1H, NCH), 3.09 (br s, 1H, NCH), 2.89 (br d, *J* = 9.5 Hz, 1H, NCH), 1.94-2.12 (m, 2H, NCH), 1.44 (s, 9H, CMe_3), 1.36 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 168.9 (Me_3CNC=O), 155.0 (OC=O), 142.4 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 127.2 (Ph), 80.5 (O*C*Me_3), 64.1 (*C*HMe), 56.4 (NCH), 51.0 (N*C*Me_3), 50.7 (NCH_2), 49.2 (NCH_2), 41.4 (NCH_2), 28.7 (C*Me*$_3$), 28.3 (C*Me*$_3$), 18.2 (CH*Me*); MS (ESI) *m/z* 390 $(M + H)^+$; HRMS *m/z* calcd for $C_{22}H_{35}N_3O_3$ $(M + H)^+$ 390.2739, found 390.2751 (+3.5 ppm error).

Lab Book Reference: JDF8_762

(*S*)-*N*-*tert*-Butylpiperazine-2-carboxamide dihydrochloride (*S*)-347



(*S*,*S*)-**345** (*S*)-**346** (*S*)-**347**

1-Chloroethylchloroformate (27 mg, 20 µL, 0.189 mmol, 3.0 eq.) was added to a stirred solution of *N*-Boc piperazine (*S*,*S*)-**345** (25 mg, 0.063 mmol, 1.0 eq.) in 1,2-dichloroethane (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. After cooling to rt, the solvent was evaporated under reduced pressure. The intermediate bis-carbamate was purified by flash column chromatography on silica with 4:1 to 7:3 petrol-EtOAc as eluent, R_F (7:3 petrol-EtOAc) 0.2. A solution of bis-carbamate in MeOH (3 mL) was stirred and heated at reflux for 2 h. After cooling to rt, the solvent was evaporated under reduced pressure to give the *N*-Boc piperazine hydrochloride (*S*)-**346** as a white gum (17 mg, 84%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (br s, 1H, NH_2^+), 7.99 (br s, 1H, NH_2^+), 6.36 (br, s, 1H, CONH), 4.69 (br s, 1H, NCH), 4.07 (br s, 1H, NCH), 3.83 (br s, 1H, NCH), 3.60 (br d, *J* = 11.0 Hz, 1H, NCH), 3.30 (t, *J* = 13.0 Hz, 1H, NCH), 3.10 (br s, 2H, NCH), 1.48 (s, 9H, CMe_3), 1.31 (s, 9H, CMe_3). The crude product was used in the next step without further purification (≥90% purity by ^{1}H NMR spectroscopy).

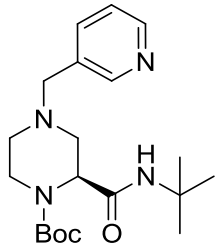
Lab Book Reference: JDF8_765

HCl (2.0 M solution in Et_2O, 1 mL) was added to a stirred solution of *N*-Boc piperazine hydrochloride (*S*)-**346** (17 mg, 0.053 mmol, 1.0eq.) in Et_2O (1 mL) at rt under air. The resulting suspension was stirred for 2 h. The resulting solids were removed by filtration and dried under reduced pressure to give piperazine dihydrochloride (*S*)-**347** (10 mg, 98%) as a white solid, mp 244-248 °C (decomp.); $[\alpha]_D$ +4.5 (*c* 0.7 in MeOH); IR (ATR) 3460, 3376, 3255, 2978, 2930, 2689, 1697 (C=O), 1681, 1646, 1449, 1366, 1296, 1290, 1254, 1223, 1075, 1067, 1053, 960, 931 cm^{-1}; ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.37 (dd, *J* = 12.0, 3.5 Hz, 1H, NCH), 3.90 (dd, *J* = 13.5, 3.0 Hz, 1H, NCH), 3.64-3.74 (m, 2H, NCH), 3.55 (td, *J* =13.5, 3.0 Hz, 1H, NCH), 3.25-3.41 (m, 2H, NCH), 1.38 (s, 9H,

CMe_3); ^{13}C NMR (100.6 MHz, MeOD-d_4) δ 164.0 (C=O), 55.2 (NCH), 53.2 (CMe_3), 44.3 (NCH_2), 41.1 (NCH_2), 40.7 (NCH_2), 28.7 (CMe_3); MS (ESI) *m/z* 186 $(M + H)^+$; HRMS *m/z* calcd for $C_9H_{20}N_3O$ $(M + H)^+$ 186.0601, found 186.1610 (–4.4 ppm error).

Lab Book Reference: JDF8_769

(*S*)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-(pyridin-3-ylmethyl)piperazine-1-carboxylate (*S*)-348

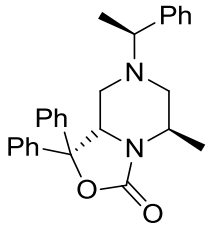


(*S*)-**348**

3-(Chloromethyl)pyridine hydrochloride (13mg, 0.077 mmol, 2.5 eq.) was added to a stirred solution of *N*-Boc piperazine hydrochloride (*S*)-**346** (10 mg, 0.031 mmol, 1.0 eq.) and Et_3N (16 mg, 22 µL, 0.155 mmol, 5.0 eq.) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 20% $NaOH_{(aq)}$ (3 mL) was added and the layers were separated. The aqueous was extracted with CH_2Cl_2 (3 × 5 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 19:1 CH_2Cl_2:MeOH as eluent gave *N*-Boc piperazine (*S*)-**348** (8 mg, 69%) as a pale yellow oil, $[\alpha]_D$ –35.5 (*c* 0.3 in $CHCl_3$); IR ($CHCl_3$) 2924, 2883, 1652 (C=O), 1487, 1432, 1372, 1346, 1283, 1145, 1102, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H, Ar), 7.70 (br s, 1H, Ar), 7.25-7.32 (m, 2H, Ar), 5.91 (br s, 1H, NH), 4.49 (br s, 1H, NCH), 3.98 (br s, 1H, NCH), 3.57 (d, *J* = 13.5 Hz, 1H, CH_AH_BAr), 3.49 (d, *J* = 13.5 Hz, 1H, CH_AH_BAr), 3.41 (dt, *J* = 11.5, 1.5 Hz, 1H, NCH), 3.05 (s, 1H, NCH), 2.71 (d, *J* = 10.5 Hz, 1H, NCH), 2.12-2.21 (m, 1H, NCH), 2.07 (td, *J* = 11.5, 2.5 Hz, 1H, NCH), 1.47 (s, 9H, CMe_3), 1.36 (s, 9H, CMe_3); MS (ESI) *m/z* 377 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{32}N_4O_3$ $(M + H)^+$ 377.2547, found 377.2535 (+2.6 ppm error).

Lab Book Reference: JDF8_776

(5*R*,8a*S*)-5-Methyl-1,1-diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*,*S*,*S*)-349

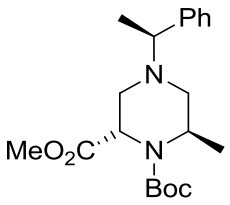


(*R*,*S*,*S*)-**349**

Using general procedure B, *s*-BuLi (0.16 mL of a 1.3 M solution in hexanes, 0.21 mmol, 1.3 eq.), *N*-Boc piperazine (*R*,*S*)-**337** (50 mg, 0.16 mmol, 1.0 eq.), TMEDA (25 mg, 32 µL, 0.21 mmol, 1.3 eq.) in Et_2O (3 mL), with a solution of benzophenone (60 mg, 0.33 mmol, 2.0 eq.) in Et_2O (0.5 mL), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et_2O as eluent gave oxazolidinone (*R*,*S*,*S*)-**349** (33 mg, 49%) as a white solid, mp 116-119 °C; R_F (8:2 petrol-Et_2O) 0.2; $[\alpha]_D$ –177.1 (*c* 1.6 in $CHCl_3$); IR ($CHCl_3$) 2983, 2963, 1718 (C=O), 1469, 1428, 1397, 1298, 1216, 1184, 1054, 1017, 986, 691, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.46 (m, 2H, Ph), 7.42-7.17 (m, 13H, Ph), 4.67 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 4.06-3.98 (m, 1H, NCH), 3.28 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.70 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, NCH), 2.51 (br d, *J* = 11.5 Hz, 1H, NCH), 1.99 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 1.42 (t, *J* = 11.0 Hz, 1H, NCH), 1.31 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.20 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 155.6 (C=O), 143.3 (*ipso*-Ph), 142.3 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.2 (Ph), 127.0 (Ph), 126.1 (Ph), 125.9 (Ph), 85.3 (*C*Me_3), 64.1 (*C*HMe), 58.0 (NCH), 54.3 (NCH_2), 52.8 (NCH_2), 46.4 (NCH), 19.5 (CH*Me*), 16.3 (CH*Me*); MS (ESI) *m/z* 413 $(M + H)^+$; HRMS *m/z* calcd for $C_{27}H_{28}N_2O_2$ $(M + H)^+$ 413.2224, found 413.2216 (+1.7 ppm error).

Lab Book Reference: JDF8_740

(2*S*,6*R*)-1-*tert*-Butyl 2-methyl 6-methyl-4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S*,*R*,*S*)-351

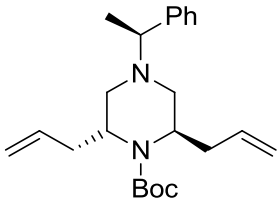


(*S*,*R*,*S*)-**351**

Using general procedure B, *s*-BuLi (0.16 mL of a 1.3 M solution in hexanes, 0.21 mmol, 1.3 eq.), *N*-Boc piperazine (*R*,*S*)-**337** (50 mg, 0.16 mmol, 1.0 eq.), TMEDA (25 mg, 32 µL, 0.21 mmol, 1.3 eq.) in Et_2O (3 mL) for 1 h and a methyl chloroformate (31 mg, 25 µL 0.33 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-7:3 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*R*,*S*)-**351** (46 mg, 77%) as pale yellow oil, R_F (8:2 petrol-Et_2O) 0.2; $[\alpha]_D$ –45.2 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) 2932, 2777, 1716 (C=O, ester), 1665 (C=O, Boc), 1468, 1431, 1347, 1298, 1235, 1151, 1068, 1011, 895, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, Ph), 4.20 (dd, *J* = 7.5, 4.0 Hz, 1H, NCH), 3.99-3.88 (m, 1H, NCH), 3.72 (s, 3H, CO_2Me), 3.32 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.86 (br s, 1H, NCH), 2.45 (br s, 2H, NCH), 2.31 (br s, 1H, NCH), 1.42 (s, 9H, CMe_3), 1.32 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.26-1.20 (m, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 172.1 (*C*O_2Me), 155.6 (NC=O), 143.5 (*ipso*-Ph), 128.2 (Ph), 127.4 (Ph), 127.0 (Ph), 80.6 (*C*Me_3), 64.1 (*C*HMe), 56.1 (br, NCH_2), 52.2 (NCH_2), 52.0 (CO_2*Me*), 49.0 (NCH), 28.1 (C*Me*$_3$), 19.7 (CH*Me*), 17.9 (CH*Me*) (NCH not resolved); MS (ESI) *m/z* 363 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{30}N_2O_4$ $(M + H)^+$ 363.2278, found 363.2272 (+1.2 ppm error).

Lab Book Reference: JDF8_749

(2*R*,6*R*)-*tert*-Butyl 2,6-diallyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R*,*R*,*S*)-353

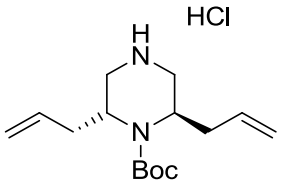


(*R*,*R*,*S*)-**353**

Using general procedure E, *s*-BuLi (0.15 mL of a 1.3 M solution in hexanes, 0.20 mmol, 1.3 eq.), *N*-Boc piperazine (*R*,*S*)-**339** (50 mg, 0.15 mmol, 1.0 eq.), TMEDA (23 mg, 29 µL, 0.20 mmol, 1.3 eq.) in Et_2O (3 mL) for 1 h, CuCN.2LiCl (0.076 mmol, 0.5 eq.) in THF (0.5 mL) and allyl bromide (37 mg, 26 µL, 0.3 mmol, 2.0 eq.), worked up with saturated $NaHCO_{3(aq)}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave *N*-Boc piperazine (*R*,*R*,*S*)-**353** (32 mg, 57%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; $[\alpha]_D$ –35.9 (*c* 1.5 in $CHCl_3$); IR ($CHCl_3$) 2972, 2932, 2886, 2774, 1665 (C=O), 1430, 1370, 1346, 1301, 1196, 1151, 980, 906, 840, 747, 692, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H, Ph), 7.25-7.20 (m, 1H, Ph), 5.75-5.62 (m, 2H, C*H*=CH_2), 5.05-4.94 (m, 4H, CH=C*H*$_2$), 3.74-3.68 (m, 2H, NCH), 3.34 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.66-2.42 (m, 6H, CH_2 + NCH), 2.36 (br d, *J* = 6.0 Hz, 1H, CH_2 or NCH), 2.33 (br d, *J* = 6.0 Hz, 1H, CH_2 or NCH), 1.44 (s, 9H, CMe_3), 1.34 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 156.0 (C=O), 144.0 (*ipso*-Ph), 135.6 (C*H*=CH_2), 128.2 (Ph), 127.5 (Ph), 126.9 (Ph), 116.9 (CH=*C*H_2), 79.6 (*C*Me_3), 64.4 (*C*HMe), 53.1 (NCH), 52.5 (NCH_2), 36.7 (CH_2), 28.4 (C*Me*$_3$), 19.9 (CH*Me*); MS (ESI) *m/z* 371 $(M + H)^+$; HRMS *m/z* calcd for $C_{23}H_{34}N_2O_2$ $(M + H)^+$ 371.2693, found 371.2689 (+0.7 ppm error).

Lab Book Reference: JDF8_743

(2*R*,6*R*)-*tert*-Butyl 2,6-diallylpiperazine-1-carboxylate hydrochloride (*R*,*R*)-354

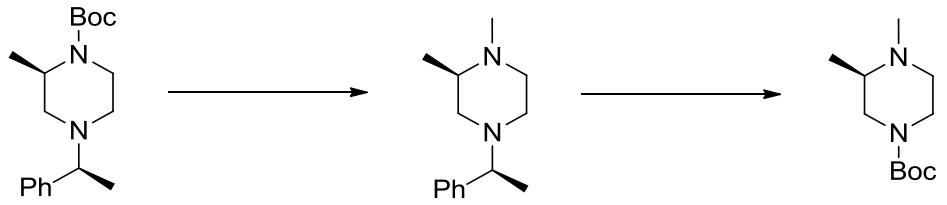


(*R*,*R*)-**354**

1-Chloroethylchloroformate (36 mg, 27 µL, 0.25 mmol, 3.0 eq.) was added to a stirred solution of *N*-Boc piperazine (*R*,*R*,*S*)-**353** (31 mg, 0.08 mmol, 1.0 eq.) in 1,2-dichloroethane (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. After cooling to rt, the solvent was evaporated under reduced pressure. The intermediate bis-carbamate was purified by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent, R_F (9:1 petrol-EtOAc) 0.2. A solution of bis-carbamate in MeOH (3 mL) was stirred and heated at reflux for 2 h. After cooling to rt, the solvent was evaporated under reduced pressure to give the *N*-Boc piperazine hydrochloride (*R*,*R*)-**354** as a hydroscopic solid (14 mg, 55%), $[\alpha]_D$ –34.9 (*c* 0.7 in $CHCl_3$); IR ($CHCl_3$) 2933, 2666 (NH_2^+), 1664 (C=O), 1564, 1438, 1366, 1347, 1313, 1240, 1196, 1150, 1103, 1047, 894, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 2H, NH_2^+), 5.84-5.72 (m, 2H, C*H*=CH_2), 5.41 (d, *J* = 17.0 Hz, 2H, CH=C$H_A$$CH_B$), 5.17 (d, *J* = 10.0 Hz, 2H, CH=CH_ACH_B), 4.01-3.90 (m, 2H, NCH), 3.45-3.23 (m, 4H, NCH), 2.59-2.48 (m, 2H, CH_2), 2.48-2.38 (m, 2H, CH_2), 1.47 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 153.8 (C=O), 133.0 (C*H*=CH_2), 120.0 (CH=*C*H_2), 81.1 (*C*Me_3), 48.9 (NCH), 40.7 (NCH_2), 37.8 (CH_2), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 267 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{26}N_2O_2$ $(M + H)^+$ 267.2067, found 267.2055 (+4.3 ppm error).

Lab Book Reference: JDF8_777

(*R*)-*tert*-Butyl 3,4-dimethylpiperazine-1-carboxylate (*R*)-356



(*R,S*)-**337** (*R,S*)-**355** (*R*)-**356**

A solution of *N*-Boc piperazine (*R,S*)-**337** (244 mg, 0.80 mmol, 1.0 eq.) in THF (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (122 mg, 3.2 mmol, 4.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at reflux for 16 h. After cooling to 0 °C, the mixture was diluted with Et_2O (10 mL). Water (122 µL), 20% $NaOH_{(aq)}$ (244 µL) and water (122 µL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure to give the crude amine (*R,S*)-**355** (153 mg, 88%) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.33 (m, 4H, Ph), 7.19-7.25 (m, 1H, Ph), 3.33 (q, *J* = 6.5 Hz, 1H, C*H*Me), 2.92 (br d, *J* = 11.0 Hz, 1H, NCH), 2.67-2.77 (m, 1H, NCH), 2.58-2.67 (m, 1H, NCH), 2.28 (s, 3H, NMe), 2.09-2.28 (m, 3H, NCH), 1.91 (m, 1H, NCH), 1.36 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.08 (d, *J* = 6.5 Hz, 3H, CH*Me*). The crude product was used in the next step without further purification (≥90% purity by ^{1}H NMR spectroscopy).

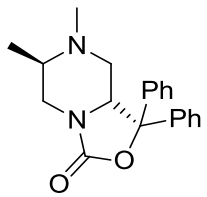
Lab Book Reference: JDF9_810

10% Pd/C (20 mg) was added to a stirred solution of *N*-Boc-*N′*-cumyl piperazine (*R,S*)-**355** (153 mg, 0.70 mmol, 1.0 eq.) in MeOH (10 mL) and conc. HCl (5 drops). Then, the reaction flask evacuated under reduced pressure and back filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 16 h. The mixture was filtered through Celite® and washed with MeOH (20 mL). The filtrate was evaporated under reduced pressure to give crude secondary amine hydrochloride. A solution of di-*tert*-butyl dicarbonate (183 mg, 0.84 mmol, 1.2 eq.) in CH_2Cl_2 (20mL) was added dropwise a stirred solution of

secondary amine hydrochloride (max. 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) and Et_3N (354 g, 488 mL, 3.5 mmol, 5.0 eq.) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 20% $NaOH_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 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 19:1 CH_2Cl_2-MeOH as eluent gave *N*-Boc piperazine (*R*)-**356** (130 mg, 87%) as a pale yellow oil, R_F (19:1 CH_2Cl_2-MeOH) 0.1; $[\alpha]_D$ –0.3 (*c* 0.9 in $CHCl_3$); IR ($CHCl_3$) 2934, 2889, 2809, 2755, 1659 (C=O), 1435, 1406, 1370, 1345, 1319, 1270, 1252, 1227, 1135, 1093, 1070, 1049, 1024, 964, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66-3.97 (m, 2H, NCH), 3.00 (br t, *J* = 11.0, 1H, NCH), 2.71 (br d, *J* = 11.5 Hz, 1H, NCH), 2.59 (br s, 1H, NCH), 2.27 (s, 3H, NMe), 2.15 (td, *J* = 11.5, 3.0 Hz, 1H, NCH), 1.96-2.07 (m, 1H, NCH), 1.42 (s, 9H, CMe_3), 1.04 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 154.5 (C=O), 79.6 (*C*Me_3), 57.5 (NCH), 54.9 (NCH_2), 50.2 (NCH_2), 49.2 (NCH_2), 44.0 (NCH_2), 43.2 (NCH_2), 42.4 (NMe), 28.2 (C*Me*$_3$), 16.3 (CH*Me*); MS (ESI) *m/z* 215 [$(M + H)^+$, 100], 159 [$(M – CMe_3)^+$, 20]; HRMS *m/z* calcd for $C_{11}H_{22}N_2O_2$ $(M + H)^+$ 215.1754, found 215.1746 (+3.9 ppm error).

Lab Book Reference: JDF9_812

(6*R*,8*R*)-6,7-Dimethyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*,*R*)-347



(*R*,*R*)-**357**

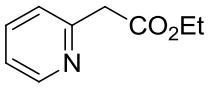
Using general procedure B, *s*-BuLi (0.14 mL of a 1.3 M solution in hexanes, 0.18 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-**356** (30 mg, 0.14 mmol, 1.0 eq.), TMEDA (21 mg, 27 µL, 0.18 mmol, 1.3 eq.) in Et_2O (3 mL) for 1 h and a solution of benzophenone (51 mg, 0.28 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $NaHCO_{3(aq)}$ (10

mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave oxazolidinone (*R*,*R*)-**357** (24 mg, 53%) as white solid, mp 184-187 °C; R_F (EtOAc) 0.2; $[\alpha]_D$ +151.4 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) 2972, 2885, 2813, 1724 (C=O), 1471, 1427, 1322, 1196, 1069, 996, 949, 915, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.55 (m, 2H, Ph), 7.26-7.42 (m, 8H, Ph), 4.63 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH), 3.76 (dd, *J* = 13.0 Hz, 3.5, 1H, NCH), 2.79 (dd, *J* = 13.0, 11.5 Hz, 1H, NCH), 2.46 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.21 (s, 3H, NMe) 1.99-2.11 (m, 1H, NCH), 1.70 (t, *J* = 11.5 Hz, 1H, NCH), 1.08 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 155.9 (C=O), 142.2 (*ipso*-Ph), 138.5 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 125.9 (Ph), 125.7 (Ph), 85.2 (Ph_2CO), 60.8 (NCH), 57.6 (NCH_2), 56.9 (NCH), 47.8 (NCH_2), 42.7 (NMe), 16.5 (CH*Me*); MS (ESI) *m/z* 323 $(M + H)^+$; HRMS *m/z* calcd for $C_{20}H_{23}N_2O_2$ $(M + H)^+$ 323.1754, found 323.1741 (+3.7 ppm error).

Lab Book Reference: JDF9_817

6.6 Experimental for Chapter Five

Ethyl 2-(pyridin-2-yl)acetate 364

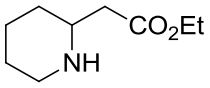


364

n-BuLi (2.5 M solution in hexanes, 84.0 mL, 0.21 mol, 2.05 eq.) was added dropwise to a stirred solution of diisopropylamine (22.3 g, 30.8 mL, 0.22 mol, 2.10 eq.) in THF (100 mL) at –78 °C under Ar. The resulting solution was warmed to 0 °C and stirred at 0 °C for 1 h. Then, the solution was transferred *via* cannula to a stirred solution of 2-picoline **402** (9.3 g, 9.9 mL, 0.10 mol, 1.0 eq.) and diethyl carbonate (35.4 g, 36.3 mL, 0.30 mol, 3.0 eq.) in THF (100 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. Saturated $NH_4Cl_{(aq)}$ (50 mL) and water (200 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave ester **364** (14.7 g, 89%) as a bright yellow oil, bp 110-120 °C/2.3 mmHg (lit.,[274] bp 110 °C/3 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (m, 1H, *o*-Ar), 7.64 (td, *J* = 7.5, 2.0 Hz, 1H, *p*-Ar), 7.28 (d, *J* = 7.5 Hz, 1H, *m*-Ar), 7.17 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, *m*-Ar), 4.16 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 3.82 (s, 2H, ArCH_2), 1.24 (t, *J* = 7.0 Hz, 3H, CH$_2$*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 170.6 (C=O), 154.4 (*ipso*-Ar), 149.4 (Ar), 136.6 (Ar), 123.8 (Ar), 122.0 (Ar), 61.0 (*C*H$_2$Me), 43.9 (Ar*C*H$_2$), 14.1 (CH$_2$*Me*). Spectroscopic data consistent with those reported in the literature.[275]

Lab Book Reference: JDF9_855

Ethyl 2-(piperidin-2-yl)acetate 365

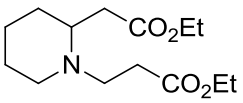


365

$PtO_2 \cdot H_2O$ (223 mg, 0.91 mmol, 0.006 eq.) was added to a stirred solution of pyridine **364** (25.0 g, 151 mmol, 1.0 eq.) in EtOH (250 mL) and 6M $HCl_{(aq)}$ (45 mL). The reaction flask evacuated under reduced pressure and back filled with N_2 three times. After a final evacuation, H_2 was charged at 2 atm and the reaction mixture was stirred vigorously at rt for 24 h. The mixture was filtered through Celite® and washed with EtOH (300 mL) and the filtrate was evaporated under reduced pressure. Then, the residue was dissolved in 2M $NH_4OH_{(aq)}$ (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the piperidine **365** (23.2 g, 90%) as a clear oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 2.96-3.05 (m, 1H, NCH), 2.87 (dddd, *J* = 10.5, 7.5, 5.5, 2.5 Hz, 1H, NCH), 2.58-2.68 (m, 1H, NCH), 2.33-2.37 (m, 1H, C*H*$_A$H$_B$CO$_2$Et), 2.27-2.32 (m, 1H, CH$_A$*H*$_B$CO$_2$Et), 2.04 (br s, 1H, NH), 1.68-1.78 (m, 1H, CH_2), 1.49-1.62 (m, 2H, CH_2), 1.26-1.44 (m, 2H, CH_2), 1.22 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.05-1.18 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 172.4 (C=O), 60.3 (*C*H$_2$Me), 53.3 (NCH), 46.8 (NCH_2), 41.7 (CH_2), 32.6 (CH_2), 26.0 (CH_2), 24.6 (CH_2), 14.2 (CH_2*Me*). Spectroscopic data consistent with those reported in the literature.[276]

Lab Book Reference: JDF10_927

Ethyl 3-(2-(2-ethoxy-2-oxoethyl)piperidin-1-yl)propanoate 366



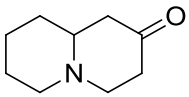
366

Ethyl acrylate (36.8 g, 40.1 mL, 0.37 mol, 3.0 eq.) was added dropwise to a stirred solution of piperidine **365** (21.0 g, 123 mmol, 1.0 eq.) and Et_3N (74.5 g, 103 mL, 0.74 mol, 6.0 eq.) in EtOH (400 mL) at rt under Ar. The resulting solution was stirred at rt

for 4 d. The mixture was concentrated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave di-ester **366** (31.3 g, 94%) as a clear oil, bp 155-165 °C/1.0 mmHg (lit.,[213] bp 175-180 °C/1.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 4.11 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 2.96–2.82 (m, 2H, NCH), 2.77–2.59 (m, 3H, NCH), 2.45 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CO$_2$Et), 2.39–2.23 (m, 2H, C*H*$_2$CO$_2$Et), 1.73–1.30 (m, 6H, CH_2), 1.24 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.24 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 172.6 (C=O), 60.4 (*C*H$_2$Me), 60.3 (*C*H$_2$Me), 56.3 (NCH), 50.2 (NCH_2), 49.4 (NCH_2), 35.7 (CH_2), 31.9 (CH_2), 30.7 (CH_2), 25.2 (CH_2), 22.0 (CH_2), 14.2 (Me), 14.2 (Me). Spectroscopic data consistent with those reported in the literature.[213]

Lab Book Reference: JDF10_902

Hexahydro-1H-quinolizin-2(6H)-one 361



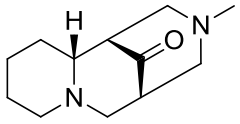
361

LHMDS (118 mL of a 1 M solution in THF, 118 mmol, 2.0 eq.) was added dropwise to a stirred solution of di-ester **366** (16.0 g, 58.9 mmol, 1.0 eq.) in THF (60 mL) at –78 °C under N_2. After stirring for 2 h at –78 °C, water (40 mL) was added and the solution was warmed to room temperature. 12 M $HCl_{(aq)}$ (30 mL) was added and the mixture was extracted with MTBE (3 × 100 mL). Then, saturated $K_2CO_{3(aq)}$ was added to the aqueous layer until pH 10 was obtained. The aqueous layer was extracted with MTBE (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude *β*-keto ester as a yellow oil. Then, 6 M HCl (300 mL) was added and the resulting solution was stirred and heated at reflux for 16 h. After cooling to room temperature, the solution was carefully neutralised with solid potassium carbonate until gas evolution stopped and the solution was saturated. The solid was removed by filtration and washed with MTBE (100 mL). Then, the layers were separated and the aqueous was extracted with MTBE (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude amino ketone **361** (7.15 g, 79%) as a pale yellow oil which was

sufficiently pure by ^{1}H NMR spectroscopy, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11–3.03 (m, 1H, NCH), 3.00–2.92 (m, 1H, NCH), 2.73–2.60 (m, 1H, NCH), 2.39–2.22 (m, 4H, NCH + CH_2CO), 2.12–1.98 (m, 2H, CH_2CO), 1.80–1.56 (m, 4H, CH_2), 1.41-1.15 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.4 (C=O), 61.8 (NCH), 55.4 (NCH_2), 55.3 (NCH_2), 48.1 (*C*H_2CO), 41.3 (*C*H_2CO), 33.6 (CH_2), 25.5 (CH_2), 23.2 (CH_2). Spectroscopic data consistent with those reported in the literature.[277]

Lab Book Reference: JDF9_895

3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocin-12-one 362



362

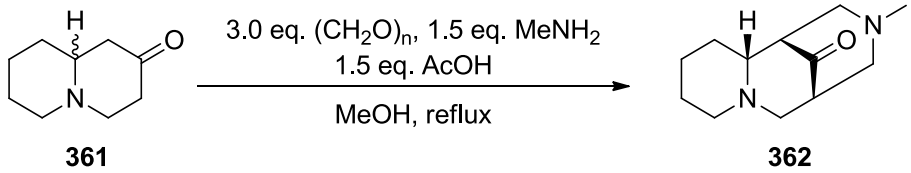
Methylamine (8.8 mL of a 8.0 M solution in EtOH, 46.6 mmol, 1.5 eq.) was added to a stirred solution of amino ketone **361** (7.10 g, 46.6 mmol, 1.0 eq.), paraformaldehyde (4.20 g, 140 mmol, 3.0 eq.) and acetic acid (2.80 g, 2.67 mL, 46.6 mmol, 1.0 eq.) in MeOH (100 mL) at room temperature under N_2. The resulting solution was stirred and heated at reflux for 24 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and 50% $KOH_{(aq)}$ (50 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diazatricyclic ketone **362** (3.27 g, 34%) as a colourless oil, bp 160-170 °C/1.0 mmHg (lit.,[213] bp 140-150 °C/0.8 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH or CHCO), 3.09–2.95 (m, 3H, NCH or CHCO), 2.94–2.86 (m, 1H, NCH or CHCO), 2.79 (ddd, *J* = 11.0, 8.5, 1.5 Hz, 1H, NCH or CHCO), 2.59–2.52 (m, 1H, NCH or CHCO), 2.40 (dd, *J* = 11.5, 3.0 Hz, 1H, NCH or CHCO), 2.36–2.29 (m, 1H, NCH or CHCO), 2.25 (s, 3H, NMe), 2.12 (dt, *J* = 11.0, 2.0 Hz, 1H, NCH or CHCO), 1.97–1.86 (m, 1H, NCH or CHCO), 1.81–1.70 (m, 1H, CH_2), 1.69–1.52 (m, 3H, CH_2), 1.41–1.32 (m, 1H, CH_2), 1.29–1.12 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.7 (C=O), 66.8 (NCH), 62.5 (NCH_2), 60.5 (NCH_2), 56.4 (NCH_2), 55.0 (NCH_2), 52.2 (NMe), 47.5 (CH), 45.4

(CH), 29.9 (CH_2), 25.5 (CH_2), 23.4 (CH_2). Spectroscopic data consistent with those reported in the literature.[213]

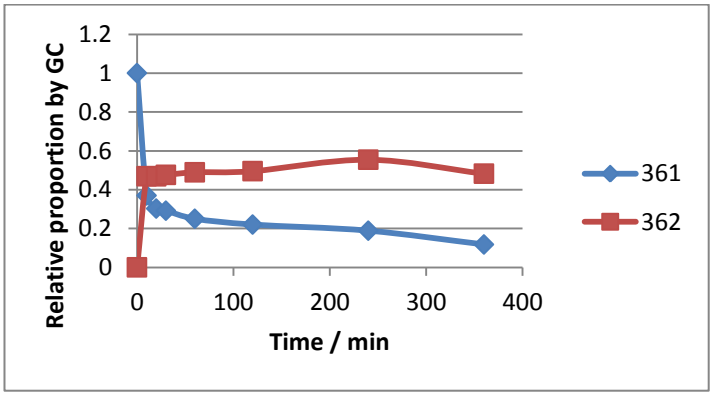
Lab Book Reference: JDF9_896

Methylamine (6.5 mL of a 8.0 M solution in EtOH, 52.2 mmol, 1.0 eq.) was added to a stirred solution of amino ketone **361** (7.95 g, 52.2 mmol, 1.0 eq.), paraformaldehyde (3.14 g, 105 mmol, 2.0 eq.) and acetic acid (3.13 g, 2.99 mL, 52.2 mmol, 1.0 eq.) in MeOH (80 mL) at room temperature under N_2. The resulting solution was stirred and heated at reflux for 24 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and 50% $KOH_{(aq)}$ (50 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diazatricyclic ketone **362** (4.07 g, 37%) as a colourless oil.

Lab Book Reference: JDF10_931



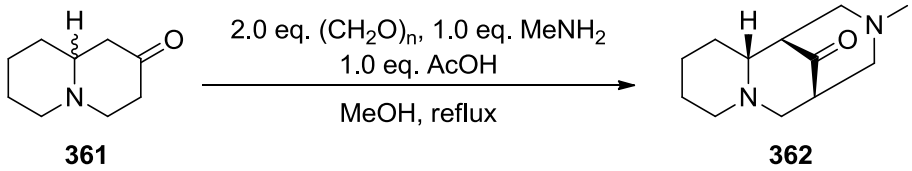
361 **362**



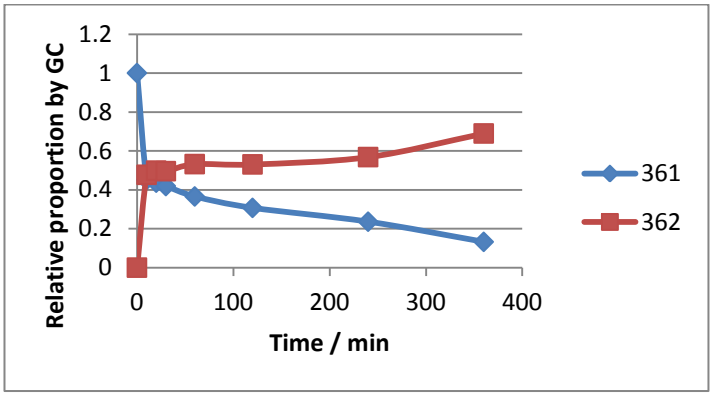
Methylamine (188 µL of a 8.0 M solution in EtOH, 1.5 mmol, 1.5 eq.) was added to a stirred solution of amino ketone **361** (152 mg, 1.0 mmol, 1.0 eq.), paraformaldehyde (90 mg, 3.0 mmol, 3.0 eq.) and acetic acid (90 mg, 86 µL, 1.5 mmol, 1.5 eq.) in MeOH (30

mL) at room temperature under N_2. The reaction mixture was quickly transferred to a pre-heated aluminium heating block and stirred and heated to reflux. After 10 min (from the beginning heating) a small sample (100 µL) was removed, diluted with MeOH (1 mL) and analysed by GC to determine the conversion of bicyclic ketone **361** to bispidone **362**. Samples were periodically taken over 24 h and analysed by GC.

Lab Book Reference: JDF10_923



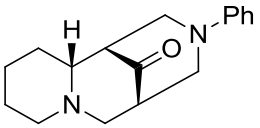
361 **362**



Methylamine (152 µL of a 8.0 M solution in EtOH, 1.0 mmol, 1.0 eq.) was added to a stirred solution of amino ketone **361** (152 mg, 1.0 mmol, 1.0 eq.), paraformaldehyde (60 mg, 2.0 mmol, 2.0 eq.) and acetic acid (60 mg, 57 µL, 1.0 mmol, 1.0 eq.) in MeOH (30 mL) at room temperature under N_2. The reaction mixture was quickly transferred to a pre-heated aluminium heating block and stirred and heated to reflux. After 10 min (from the beginning heating) a small sample (100 µL) was removed, diluted with MeOH (1 mL) and analysed by GC to determine the conversion of bicyclic ketone **361** to bispidone **362**. Samples were periodically taken over 24 h and analysed by GC.

Lab Book Reference: JDF10_922

Attempted synthesis of 3-Phenyldecahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocin-12-one 404

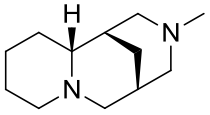


404

dl-Proline (6 mg, 0.05 mmol, 0.1 eq.) was added to a stirred solution of bicyclic ketone **361** (77 mg, 0.5 mmol, 1.0 eq.), aniline (70 mg, 68 µL, 1.5 eq.) and paraformaldehyde (45 mg, 1.5 mmol, 3.0 eq.) in DMSO (2 mL) and water (100 µL) at rt under air. The resulting mixture was stirred at rt for 48 h. Then, 20% $NaOH_{(aq.)}$ (5 mL) and Et_2O (5 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude mixture which contained a complex mixture of products (by ^1H NMR spectroscopy and mass spectrometry).

Lab Book Reference: JDF10_932

3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine 26



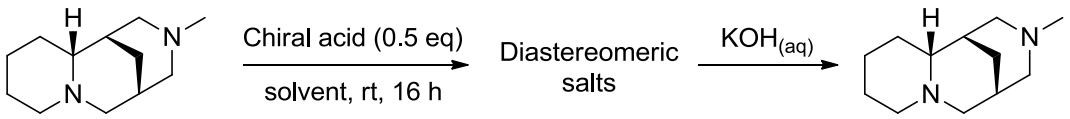
26

Hydrazine monohydrate (4.89 g, 4.74 mL, 97.7 mmol, 5.0 eq.) was added to a stirred solution of diazatricyclic ketone **362** (4.07 g, 19.5 mmol, 1.0 eq.) and KOH (11.0 g, 195 mmol, 10 eq.) in diethylene glycol (60 mL) at rt under N_2. The resulting solution was stirred and heated at 160 °C for 16 h. After cooling to 60 °C, H_2O (50 mL) and 1M $HCl_{(aq)}$ (50 mL) were added. The aqueous layer was extracted with MTBE (3 × 50 mL). Then, the pH of the aqueous layer was adjusted to pH 12 with 50% $KOH_{(aq)}$. The aqueous was extracted with MTBE (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine **26** (2.56 g, 68%) as a

colourless oil, bp 170-180 °C/2.0 mmHg (lit.,[213] bp 150-160 °C/0.8 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00-2.95 (m, 2H, NCH), 2.89 (m, 2H, NCH), 2.22 (ddd, J = 11.0, 3.5, 1.5 Hz, 1H, NCH), 2.14-2.11 (m, 1H, NCH), 2.13 (s, 3H, NMe), 1.94 (dd, J = 11.5, 3.0 Hz, 1H, NCH), 1.87 (br d, J = 11.0 Hz, 1H, NCH), 1.77-1.46 (m, 9H, NCH + CH), 1.32-1.20 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.4 (NCH), 60.4 (NCH_2), 60.3 (NCH_2), 57.6 (NCH_2), 56.3 (NCH_2), 47.2 (NMe), 35.0 (CH), 33.8 (CH_2), 30.4 (CH), 25.5 (CH_2), 24.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[213]

Lab Book Reference: JDF10_932

Resolution of 3-methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine 26



26 (+)-**26** / (–)-**26**

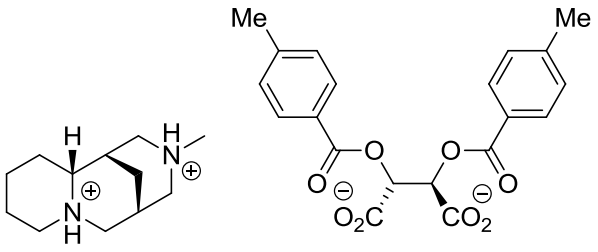
Using general procedure F, the results shown in Tables 5.2 and 5.3 were obtained

Entry	Resolving agent	Solvent	Yield / %	er [(–)/(+)][a]
1	(+)-**367**	MeCN	–	–
2	(+)-**367**	Acetone	–	–
3	(+)-**367**	IPA	–	–
4	(+)-**367**	MTBE	43	50:50
5	(–)-**368**	MeCN	–	–
6	(–)-**368**	Acetone	20	27:73
7	(–)-**368**	IPA	–	–
8	(–)-**368**	MTBE	26	36:64
9	(–)-**369**	MeCN	12	98:2
10	(–)-**369**	Acetone	32	72:28
11	(–)-**369**	IPA	–	–
12	(–)-**369**	MTBE	49	55:45
13	(*S*)-**370**	MeCN	–	–
14	(*S*)-**370**	Acetone	–	–
15	(*S*)-**370**	IPA	–	–

16	(*S*)-**370**	MTBE	–	–
17	(–)-**369**	MeOAc	33	77:23
18	(–)-**369**	EtOAc	40	80:20
19	(–)-**369**	^{n}PrOAc	35	77:23
20	(–)-**369**	^{i}PrOAc	33	69:31
21	(–)-**369**	BuOAc	38	66:34
22	(–)-**369**	MEK	–	–
23	(–)-**369**	MIBK	–	–
24	(–)-**369**	Et_2O	25	63:27
25	(–)-**369**	THF	31	81:19
26	(–)-**369**	2-Me THF	25	67:33
27	(–)-**369**	CPME	28	74:26
28	(–)-**369**	Toluene	40	57:42
29	(–)-**369**	Cyclohexane	–	–
30	(–)-**369**	BuCN	–	–
31	(–)-**369**	PhCN	–	–
32	(–)-**369**	8:2 MeCN / acetone	23	97:3
33	(–)-**369**	1:1 MeCN / acetone	23	90:10
34	(–)-**369**	19:1 MeCN / H_2O	–	–
35	(–)-**369**	9:1 MeCN / H_2O	–	–
36	(–)-**369**	8:2 MeCN / H_2O	–	–

[a] Enantiomeric ratio of the free base determined by CSP-GC

(1*S*,5*R*,11a*R*)-3-Methyldodecahydro-1,5-methanopyrido[1,2-a][1,5]diazocine-3,7-diium (2*R*,3*R*)-2,3-bis((4-methylbenzoyl)oxy)succinate (–)-26.(–)-369



(–)-**26**.(–)-**369**

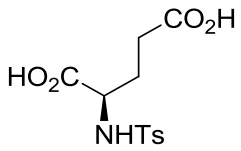
A solution of (−)-*O*,*O*′-di-*p*-toluoyl-L-tartaric acid (–)-**369** (193 mg, 0.5 mmol, 0.5 eq.) in 4:1 MeCN/acetone (0.3 mL) was added to a stirred solution of **26** (194 mg, 1.0 mmol, 1.0 eq.) in 4:1 MeCN/acetone (0.3 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solid was collected by filtration, washed with cold 4:1 MeCN-acetone (2 mL) and dried under reduced pressure to give salt (–)-**26**.(–)-**369** (154 mg, 27%) as a white solid, mp 155-156 °C (decomposition); ^{1}H NMR (400 MHz, MeOD) δ 8.02 (d, *J* = 8.0 Hz, 4H, Ar), 7.29 (d, *J* = 8.0 Hz, 4H, Ar), 5.87 (s, 2H, C*H*CO_2H), 3.39 (br d, *J* = 12.0 Hz, 1H, NCH), 3.29-3.21 (m, 2H, NCH), 3.20-3.12 (m, 1H, NCH), 2.95-2.82 (m, 2H, NCH), 2.69 (dt, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.62-2.55 (m, 1H, NCH), 2.46 (s, 3H, NMe), 2.49-2.38 (m, 1H, NCH), 2.41 (s, 6H, Ar*Me*), 2.17-2.10 (m, 1H, CH), 1.91-1.83 (m, 4H, CH + CH_2), 1.84- 1.64 (m, 4H, CH_2), 1.58-1.44 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, MeOD) *δ* 171.9 (C=O), 169.5 (C=O), 145.3 (*ipso*-Ar), 131.1 (Ar), 130.0 (Ar), 128.6 (*ipso*-Ar), 75.2 (*C*HCO_2H), 67.7 (NCH), 61.1 (NCH_2), 61.0 (NCH_2), 57.2 (NCH_2), 56.9 (NCH_2), 45.5 (NMe), 34.2 (CH), 32.2 (CH_2), 30.2 (CH_2), 29.9 (CH), 25.5 (CH_2), 24.2 (CH_2), 21.7 (Ar*Me*). Then, a portion of salt (–)-**26**.(–)-**369** (20 mg, 0.034 mmol) was dissolved in 20% $KOH_{(aq)}$ (2 mL) and MTBE (2 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 2 mL). The combined organics were dried ($MgSO_4$), and evaporated under reduced pressure to give the resolved surrogate (–)-**26** (95:5 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**26** 23.1 min, (–)-**26** 23.2 min.

Lab Book Reference: JDF10_937

A solution of (−)-*O*,*O*′-di-*p*-toluoyl-L-tartaric acid (–)-**369** (1.93 g, 5.0 mmol, 0.5 eq.) in 4:1 MeCN/acetone (2 mL) was added to a stirred solution of **26** (1.94 g, 10 mmol, 1.0 eq.) in 4:1 MeCN/acetone (4 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solid was collected by filtration, washed with cold 4:1 MeCN-acetone (5 mL) and dried under reduced pressure to give salt (–)-**26**.(–)-**369** (1.92 g, 33%) as a white solid. Then, a portion of the salt (20 mg, 0.034 mmol) was dissolved in 20% $KOH_{(aq)}$ (2 mL) and MTBE (2 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 2 mL). The combined organics were dried ($MgSO_4$), and evaporated under reduced pressure to give the resolved surrogate (–)-**26** (93:7 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**26** 23.0 min, (–)-**26** 23.3 min.

Lab Book Reference: JDF10_938

(*R*)-2-(4-Methylphenylsulfonamido)pentanedioic acid (*R*)-407



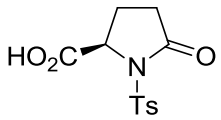
(*R*)-**407**

p-Toluenesulfonyl chloride (22.9 g, 120 mmol, 1.2 eq.) was added portionwise over 30 min to a stirred solution of D-glutamic acid (14.7 g, 100 mmol, 1.0 eq.) in 2M $NaOH_{(aq)}$ (200 mL) at 70 °C under air. The resulting solution was heated at 70 °C for 1 h. 2M $NaOH_{(aq)}$ was added dropwise to keep the pH > 9. Upon cooling to 0 °C the pH was adjusted to pH 1 with 12M $HCl_{(aq)}$. The aqueous mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *N*-tosyl glutamic acid (*R*)-**407** as a white solid (13.9 g, 46%) which was sufficiently pure by ^{1}H NMR spectroscopy, mp 114-116 °C (lit.,[249] 122-125°C); $[\alpha]_D$ –20.3 (*c* 1.0 in EtOAc) (lit.,[278] $[\alpha]_D$ +22 (*c* 1.0 in EtOAc) for (*S*)-**407**); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (br s, 2H, COOH), 8.07 (d, *J* = 9.0 Hz, 1H, NH), 7.64 (d, *J* = 9.0 Hz, 2H, Ar), 7.34 (d, *J* = 8.0 Hz, 2H, Ar), 3.74 (td, *J* = 9.0, 5.0 Hz, 1H, NCH), 2.36 (s, 3H, Ar*Me*), 2.19 (t, *J* = 7.5 Hz, 2H, CH_2COOH), 1.77-1.88 (m, 1H, CH_2), 1.58-1.7 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.5 (NC=O), 172.6 (C=O), 142.5 (*ipso*-Ar), 138.3 (*ipso*-Ar), 129.4 (Ar), 126.5 (Ar), 54.7 (NCH),

29.5 (CH_2), 27.4 (CH_2), 21.0 (Ar*Me*); Spectroscopic data consistent with those reported in the literature.[249]

Lab Book Reference: JDF9_816

(*R*)-5-Oxo-1-tosylpyrrolidine-2-carboxylic acid (*R*)-406

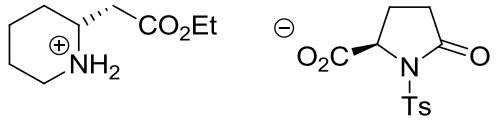


(*R*)-**406**

N,*N*′-Dicyclohexylcarbodiimide (3.41 g, 16.5 mmol, 1.25 eq.) was added to a solution of *N*-tosyl glutamic acid (*R*)-**407** (3.98 g, 13.2 mmol, 1.0 eq.) in MeCN (100 mL) at 0 °C under Ar. The resulting solution was heated to 60 °C and stirred at 60 °C for 16 h. Upon cooling to 0 °C the mixture was filtered through Celite® and washed with cold MeCN (20 mL). Then, the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc (30 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 × 30 mL). The combined aqueous layers were acidified with 12M $HCl_{(aq)}$ and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude *N*-tosyl pyrrolidinone (*R*)-**406** as a white solid (3.22 g, 86%) which was sufficiently pure by ^{1}H NMR spectroscopy, mp 126-127 °C (lit.,[279] 128-129°C); $[\alpha]_D$ +25.4 (*c* 1.1 in EtOAc) (lit.,[279] $[\alpha]_D$ –27.5 (*c* 1.5 in EtOAc) for (*S*)-**406**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br s, 1H, COOH), 7.97 (d, *J* = 8.5 Hz, 2H, Ar), 7.34 (d, *J* = 8.5 Hz, 2H, Ar), 4.91 (dd, *J* = 9.0, 2.5 Hz, 1H, NCH), 2.64–2.40 (m, 3H, CH_2), 2.44 (s, 3H, Ar*Me*), 2.28–2.12 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 175.5 (NC=O), 172.9 (COOH), 145.6 (*ipso*-Ar), 134.5 (*ipso*-Ar), 129.4 (Ar), 129.0 (Ar), 59.1 (NCH), 30.3 (CH_2), 23.1 (CH_2), 21.7 (Me). Spectroscopic data consistent with those reported in the literature.[279]

Lab Book Reference: JDF9_881

(*R*)-2-(2-Ethoxy-2-oxoethyl)piperidin-1-ium (*R*)-5-oxo-1-tosylpyrrolidine-2-carboxylate (*R*)-365.(*R*)-406

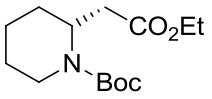


(*R*)-**365**. (*R*)-**406**

N-tosyl pyrrolidinone (*R*)-**406** (1.0 g, 3.5 mmol, 0.5 eq.) was added to a stirred solution of piperidine **365** (1.21 g, 7.0 mmol, 1.0 eq.) in IPA (52 mL) at rt. The resulting solution was stirred at rt for 30 min. Then, the mixture was cooled in a fridge for 3 h. The white solid was collected by filtration, washed with cold IPA (10 mL) and dried under reduced pressure to give salt (*R*)-**365**.(*R*)-**406** as a crystalline white solid (1.64 g, 36%, 93:7 er by CSP-HPLC of a derivative (*R*)-**374**). Salt (*R*)-**365**.(*R*)-**406** (1.1 g, 2.42 mmol) was added to IPA (88 mL) and the resulting suspension was heated to 80 °C. The resulting solution was stirred at 80 °C for 30 min. Upon cooling to rt white crystals formed. Then, the mixture was cooled in a fridge for 3 h. The salt was collected by filtration and washed with cold IPA (10 mL) and dried under reduced pressure to give the salt (*R*)-**365**.(*R*)-**406** as a crystalline white solid (890 mg, 81% (29% from **365**), >99:1 er by CSP-HPLC of a derivative (*R*)-**374**).

Lab Book Reference: JDF9_888

(*R*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (*R*)-374



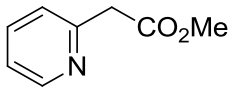
(*R*)-**374**

A solution of di-*tert*-butyl dicarbonate (423 mg, 1.93 mmol, 1.2 eq.) in CH_2Cl_2 (5 mL) was added dropwise a stirred solution of salt (*R*)-**365**.(*R*)-**406** (712 mg, 1.61 mmol, 1.0 eq.) and Et_3N (489 mg, 674 µL, 3.0 eq.) in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1M $HCl_{(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 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 9:1-4:1 petrol-EtOAc as eluent gave *N*-Boc piperidine (*R*)-**374** (363 g, 85%, >99:1 er) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; $[\alpha]_D$ +7.5 (*c* 1.0 in $CHCl_3$) (lit.,[225] $[\alpha]_D$ +7.4 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 1H, NCH), 4.10 (q, *J* = 7.0 Hz, 2H, CH_2Me), 3.97 (br d, *J* = 12.0 Hz, 1H, NCH), 2.76 (br t, *J* = 12.0 Hz, 1H, NCH), 2.51-2.6 (m, 1H, CH_AH$_B$CO$_2$Et), 2.45-2.55 (m, 1H, CH$_A$$H_BCO_2$Et), 1.3-1.7 (m, 6H, CH_2), 1.43 (s, 9H, CMe_3), 1.23 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.4 (*C*O$_2$Et), 154.7 (NC=O), 79.4 (*C*Me$_3$), 60.4 (*C*H$_2$Me), 47.8 (NCH), 39.2 (NCH$_2$), 35.3 (CH_2), 28.4 (C*Me*$_3$), 28.1 (CH_2), 25.2 (CH_2), 18.8 (CH_2), 14.1 (CH_2*Me*); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 16.7 min, (*S*)-**374** 18.1 min. Spectroscopic data consistent with those reported in the literature.[276]

Lab Book Reference: JDF9_877

Methyl 2-(pyridin-2-yl)acetate 410



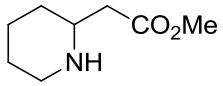
410

n-BuLi (2.5 M solution in hexanes, 20.0 mL, 50 mmol, 2.0 eq.) was added dropwise to a stirred solution of diisopropylamine (5.57 g, 7.71 mL, 55 mmol, 2.2 eq.) in THF (20 mL) at –78 °C under Ar. The resulting solution was warmed to 0 °C and stirred at 0 °C for 30 min. Then, the solution was transferred *via* cannula to a stirred solution of 2-picoline **402** (2.33 g, 2.47 mL, 25 mmol, 1.0 eq.) and dimethylcarbonate (6.76 g, 6.32 mL, 75 mmol, 3.0 eq.) in THF (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and stirred at rt for 30 min. Saturated $NH_4Cl_{(aq)}$ (10 mL) and water (20 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave ester **410** (2.86 g, 76%) as a bright yellow oil, bp 90-95 °C/1.2 mmHg (lit.,[280] bp 74-78 °C/2 mmHg); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.56-8.54 (m, 1H, Ar), 7.65 (tt, *J* = 7.5, 2.0 Hz, 1H, Ar), 7.28 (d, *J* = 7.5 Hz, 1H, Ar), 7.21-7.16 (m, 1H, Ar), 3.86 (s, 2H, C*H*$_2$CO$_2$Me), 3.73 (s, 3H, CO_2Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.0 (C=O), 154.3 (*ipso*-Ar), 149.5 (Ar), 136.6 (Ar), 123.8 (Ar), 122.1 (Ar), 52.1 (*C*H$_2$CO$_2$Me), 43.7 (CO_2*Me*). Spectroscopic data consistent with those reported in the literature.[281]

Lab Book Reference: JDF9_826

Methyl 2-(piperidin-2-yl)acetate 405

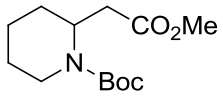


405

$PtO_2.H_2O$ (49 mg, 0.20 mmol, 0.006 eq.) was added to a stirred solution of pyridine **410** (5.00 g, 33.1 mmol, 1.0 eq.) in MeOH (50 mL) and 6M $HCl_{(aq)}$ (9 mL). Then, the reaction flask evacuated under reduced pressure and back filled with N_2 three times. After a final evacuation, H_2 was charged at 2 atm and the reaction mixture was stirred vigorously at rt for 24 h. The mixture was filtered through Celite® and washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure. Then, the residue was dissolved in 2M $NH_4OH_{(aq)}$ (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the piperidine **405** (4.30 g, 83%) as a clear oil, bp 90-94 °C/5.0 mmHg (lit.,[282] bp 101-102 °C/5 mmHg); ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H, CO_2Me), 3.04–2.97 (m, 1H, NCH), 2.87 (dddd, *J* = 10.5, 7.5, 5.0, 2.5 Hz, 1H, NCH), 2.62 (td, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.36 (dd, *J* = 14.5, 3.5 Hz, 1H, C*H*$_A$H$_B$CO$_2$Me), 2.31 (dd, *J* = 14.5, 6.5 Hz, 1H, CH$_A$*H*$_B$CO$_2$Me), 1.98 (br s, 1H, NH), 1.78–1.68 (m, 1H, CH_2), 1.62–1.50 (m, 2H, CH_2), 1.44–1.26 (m, 2H, CH_2), 1.20–1.05 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 172.8 (C=O), 53.2 (NCH), 51.5 (CO_2*Me*), 46.8 (*C*H$_2$CO$_2$Me), 41.4 (NCH_2), 32.6 (CH_2), 26.0 (CH_2), 24.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[283]

Lab Book Reference: JDF9_897

***tert*-Butyl 2-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate 408**

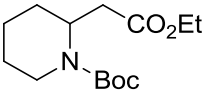


408

A solution of di-*tert*-butyl dicarbonate (7.16 g, 32.8 mmol, 1.2 eq.) in CH_2Cl_2 (20 mL) was added dropwise a stirred solution of piperidine **405** (4.3 g, 27.4 mmol, 1.0 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 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 9:1-4:1 petrol-EtOAc as eluent gave *N*-Boc piperidine **408** (6.9 g, 97%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76–4.58 (m, 1H, NCH), 3.98 (br d, *J* = 12.5 Hz, 1H, NCH), 3.63 (s, 3H, CO_2Me), 2.77 (br t, *J* = 12.5 Hz, 1H, NCH), 2.59 (dd, *J* = 14.0, 7.5 Hz, 1H CH_AH$_B$CO$_2$Et), 2.51 (dd, *J* = 14.0, 8.0 Hz, 1H, CH$_A$$H_BCO_2$Et), 1.70–1.55 (m, 4H, CH_2), 1.52–1.33 (m, 2H, CH_2), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.8 (*C*O_2Me), 154.6 (NC=O), 79.4 (*C*Me_3), 51.6 (CO_2*Me*), 47.8 (NCH), 39.1 (NCH_2), 35.0 (CH_2), 28.3 (C*Me*$_3$), 28.2 (CH_2), 25.2 (CH_2), 18.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[223]

Lab Book Reference: JDF9_900

***tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate 374**



374

A solution of di-*tert*-butyl dicarbonate (13.4 g, 61.3 mmol, 1.2 eq.) in CH_2Cl_2 (50 mL) was added dropwise a stirred solution of piperidine **365** (10.0 g, 58.4 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1M $HCl_{(aq)}$ (200 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined

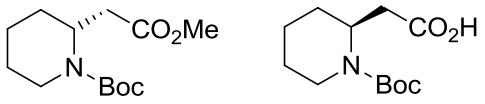
organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-4:1 petrol-EtOAc as eluent gave *N*-Boc piperidine **374** (15.1 g, 95%) as a colourless oil.

Lab Book Reference: JDF10_928

A solution of di-*tert*-butyl dicarbonate (11.1 g, 50.7 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) was added dropwise a stirred solution of piperidine **365** (8.69 g, 50.7 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1M $HCl_{(aq)}$ (200 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *N*-Boc piperidine **374** (13.7 g, 99%) as a colourless oil, which was sufficiently pure by ^{1}H NMR spectroscopy.

Lab Book Reference: JDF12_1103

(*R*)-*tert*-Butyl 2-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (*R*)-408 and (*S*)-2-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)acetic acid (*S*)-409



(*R*)-**408** (*S*)-**409**

Using general procedure G, methyl ester **408** (257 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate $buffer_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at rt for 48 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**408** (104 mg, 41%, 88:12 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**408** 17.1 min, (*S*)-**408** 19.3 min, and acid (*S*)-**409** (103 mg, 42%, 87:13 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid, mp 93-95 °C (lit.,[254] 95 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 11.5, 7.0 Hz, 1H, NCH), 3.99 (d, *J* = 13.0 Hz, 1H, NCH), 2.79 (t, *J* = 13.0 Hz, 1H, NCH), 2.66 (dd, *J* = 14.5, 7.0 Hz, 1H, $CH_ACH_BCO_2H$), 2.57 (dd, *J* = 14.5, 7.0 Hz, 1H, $CH_ACH_BCO_2H$), 1.74–1.38 (m, 6H, CH_2), 1.45 (s, 9H, CMe_3); NMR (100.6 MHz, $CDCl_3$) *δ* 176.4 (COOH), 154.9 (NC=O), 79.9 (CMe_3), 47.5 (NCH), 39.2

(NCH_2 or CH_2COOH), 35.3 (NCH_2 or CH_2COOH), 28.3 (CMe_3), 25.1 (CH_2), 18.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[254]

Lab Book Reference: JDF10_909

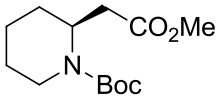
Using general procedure G, methyl ester **408** (257 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate $buffer_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at 35 °C for 48 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**408** (120 mg, 47%, 97:3 er by CSP-HPLC) as a clear oil, $[\alpha]_D$ +9.0 (*c* 1.0 in $CHCl_3$) (lit.,[284] $[\alpha]_D$ +8.1 (*c* 2.0 in $CHCl_3$ for >99:1 er); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**408** 15.5 min, (*S*)-**408** 17.5 min, and acid (*S*)-**409** (98 mg, 40%, >99:1 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid, $[\alpha]_D$ –11.8 (*c* 0.9 in MeOH) (lit.,[254] $[\alpha]_D$ –8 (*c* 1.53 in MeOH).

Lab Book Reference: JDF10_907

Using general procedure G, methyl ester **408** (257 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate $buffer_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at 50 °C for 28 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**408** (116 mg, 45%, 90:10 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**408** 16.6 min, (*S*)-**408** 18.9 min, and acid (*S*)-**409** (94 mg, 39%, 96:4 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_910

(*S*)-*tert*-Butyl 2-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (*S*)-408



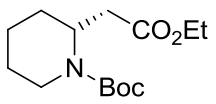
(*S*)-**408**

(Trimethylsilyl)diazomethane (113 µL of a 2.0 M solution in Et_2O, 0.216 mmol, 1.03 eq.) was added to a stirred solution of carboxylic acid (*S*)-**409** (50 mg, 0.210 mmol, 1.0

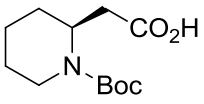
eq.) in THF (3 mL) and MeOH (1 mL) at at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, the solvent was removed under reduced pressure. The residue was partitioned between water (5 mL) and Et_2O (5 ml). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the methyl ester (*S*)-**408** (50 mg, 93%, >99:1 er by CSP-HPLC) as a pale yellow oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**408** 18.1 min, (*S*)-**408** 20.2 min.

Lab Book Reference: JDF4_317

(*R*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (*R*)-374 and (*S*)-2-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)acetic acid (*S*)-409



(*R*)-**374**



(*S*)-**409**

Using general procedure G, ethyl ester **374** (271 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate $buffer_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at rt for 24 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**374** (127 mg, 47%, 97:3 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 15.5 min, (*S*)-**374** 16.6 min, and acid (*S*)-**409** (104 mg, 44%, 98:2 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_915

Using general procedure G, ethyl ester **374** (271 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate $buffer_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at rt for 48 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**374** (113 mg, 42%, >99:1 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 14.7 min, (*S*)-**374** not observed, and acid (*S*)-**409** (112 mg, 46%, 92:8 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_920

Using general procedure G, ethyl ester **374** (271 mg, 1.0 mmol), lipase (250 mg), 0.1 M phosphate buffer$_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at 35 °C for 24 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**374** (112 mg, 42%, >99:1 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 15.3 min, (*S*)-**374** 16.2 min, and acid (*S*)-**409** (103 mg, 42%, 96:4 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_921

Using general procedure G, ethyl ester **374** (271 mg, 1.0 mmol), lipase (125 mg), 0.1 M phosphate buffer$_{(aq)}$ (8 mL), H_2O (8 mL), and THF (2 mL), at 35 °C for 72 h, extracted with Et_2O (3 × 10 mL) gave ester (*R*)-**374** (112 mg, 42%, >99:1 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 16.0 min, (*S*)-**374** not observed, and acid (*S*)-**409** (107 mg, 44%, 95:5 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_929

Using general procedure G, ethyl ester **374** (2.71 g, 10.0 mmol), lipase (2.50 g), 0.1 M phosphate buffer$_{(aq)}$ (40 mL), H_2O (40 mL), and THF (10 mL), at 35 °C for 48 h, extracted with Et_2O (3 × 50 mL) gave ester (*R*)-**374** (1.23 g, 45%, >99:1 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 17.4 min, (*S*)-**374** not observed, and acid (*S*)-**409** (1.18 g, 45%, 96:4 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

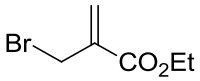
Lab Book Reference: JDF10_934

Using general procedure G, ethyl ester **374** (13.6 g, 50.0 mmol), lipase (12.5 g), 0.1 M phosphate buffer$_{(aq)}$ (200 mL), H_2O (200 mL), and THF (50 mL), at 35 °C for 64 h,

extracted with Et_2O (3 × 100 mL) gave ester (*R*)-**374** (6.23 g, 46%, >99:1 er by CSP-HPLC) as a clear oil, CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**374** 15.2 min, (*S*)-**374** not observed, and acid (*S*)-**409** (5.33 g, 44%, 96:4 er by CSP-HPLC of a derivative (*S*)-**408**) as a white solid.

Lab Book Reference: JDF10_960

Ethyl 2-(bromomethyl)acrylate 375

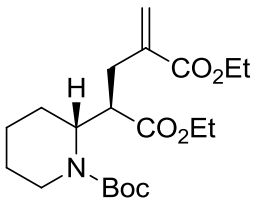


375

A solution of K_2CO_3 (14.8 g, 107 mmol, 1.2 eq.) in H_2O (15 mL) was added dropwise to a stirred solution of triethyl phosphonoacetate **411** (20.0 g, 17.7 mL, 89.2 mmol, 1.0 eq.) and formaldehyde (37% aqueous solution, 29.2 mL, 360 mmol, 4.0 eq.) at rt under air. The resulting mixture was stirred at rt for 15 min. Then, Et_2O (75 mL) and brine (75 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude alcohol **412**. PBr_3 (14.5 g, 5.0 mL, 53.5 mmol, 0.6 eq.) was added dropwise to a stirred solution of crude alcohol **412** in Et_2O (100 mL) at 0 °C under Ar. The resulting solution was warmed to rt and stirred at rt for 16 h. Then, sat $NaHCO_{3(aq)}$ (200 mL) was added slowly with stirring and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave acrylate **375** (10.8 g, 63%) as a clear oil, bp 75-80 °C/3.5 mmHg (lit.,[285] bp 55-61 °C/2 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 1.0 Hz, 1H, C=CH_AH_B), 5.94 (d, *J* = 1.0 Hz, 1H, C=CH_AH_B), 4.26 (q, *J* = 7.0 Hz, 2H, CH_2Me), 4.17 (s, 2H, CH_2Br), 1.32 (t, *J* = 7.0 Hz, 3H, CH_2Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 174.8 (C=O), 137.5 (*C*=CH_2), 138.9 (C=*C*H_2), 61.2 (*C*H_2Me), 29.4 (CH_2Br), 14.1 (CH_2Me). Spectroscopic data consistent with those reported in the literature.[285]

Lab Book Reference: JDF10_957

(*R*)-Diethyl 2-((*R*)-1-(*tert*-butoxycarbonyl)piperidin-2-yl)-4-methylenepentanedioate (*R*,*R*)-376



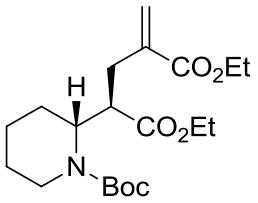
(*R*,*R*)-**376**

LHMDS (5.83 mL of a 1.0 M solution in THF, 5.83 mmol, 1.4 eq.) was added dropwise to a stirred solution of *N*-Boc ester (*R*)-**374** (1.13 g, 4.16 mmol, 1.0 eq.) in THF (30 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, acrylate **375** (1.13 g, 805 µL, 5.83 mmol, 1.4 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (50 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 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 petrol-EtOAc as eluent gave *N*-Boc ester (*R*,*R*)-**376** (1.55 g, 97%, >99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; $[\alpha]_D$ +49.5 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) 2972, 2936, 2894, 1697 (C=O, CO_2Et), 1654 (C=O, Boc), 1606 ($C=CH_2$), 1453, 1425, 1396, 1370, 1346, 1316, 1283, 1257, 1231, 1196, 1136, 1071, 1011, 971, 941, 911, 825, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J* = 1.0 Hz, 1H, C=C$H_A$$H_B$), 5.60 (d, *J* = 1.0 Hz, 1H, C=C$H_A$$H_B$), 4.56-4.28 (m, 1H, NCH), 4.28-4.12 (m, 2H, CH_2Me), 4.12-3.79 (m, 3H, CH_2Me and NCH), 3.21 (td, *J* = 11.0, 3.5 Hz, 1H, C*H*CO_2Et), 2.93 (br s, 1H, NCH), 2.64-2.37 (m, 2H, CH_2C=CH_2), 1.83 (d, *J* = 11.5 Hz, 1H, CH_2), 1.68–1.48 (m, 5H, CH_2), 1.41 (s, 9H, CMe_3), 1.30 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.17 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 172.9 (*C*O_2Et), 172.8 (*C*O_2Et), 166.5 (*C*O_2Et), 154.3 (NC=O), 137.6 (*C*=CH_2), 127.2 (C=*C*H_2), 79.3 (*C*Me_3), 60.8 (*C*H_2Me), 60.2 (*C*H_2Me), 53.2 (NCH), 52.0 (NCH), 44.9 (*C*HCO_2Et), 44.4 (*C*HCO_2Et), 40.1 (NCH_2), 38.9 (NCH_2), 32.6 (*C*H_2C=CH_2), 28.3 (C*Me*$_3$), 26.0 (CH_2), 25.2 (CH_2), 19.0 (CH_2), 14.1 (CH_2*Me*); MS (ESI) *m/z* 406 [$(M + Na)^+$, 100], 384 [$(M + H)^+$, 60]; HRMS *m/z* calcd for $C_{20}H_{33}NO_6$ $(M + H)^+$ 384.2381, found 384.2376 (+1.0

ppm error); CSP-HPLC: Chiralcel AD-H (98:2 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*,*S*)-**376** 13.2 min, (*R*,*R*)-**376** 14.8 min.

Lab Book Reference: JDF10_950

Diethyl 2-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)-4-methylenepentanedioate 376

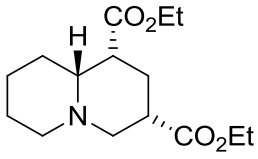


376

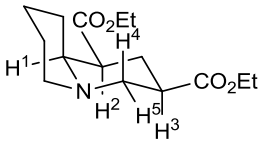
LHMDS (1.4 mL of a 1.0 M solution in THF, 1.4 mmol, 1.4 eq.) was added dropwise to a stirred solution of *N*-Boc ester **374** (271 mg, 1.0 mmol, 1.0 eq.) in THF (8 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, acrylate **375** (270 g, 193 µL, 1.4 mmol, 1.4 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (20 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 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 petrol-EtOAc as eluent gave *N*-Boc ester **376** (358 mg, 94%) as a colourless oil.

Lab Book Reference: JDF9_868

(1*R*,3*S*,9a*R*)-Diethyl octahydro-1H-quinolizine-1,3-dicarboxylate (*R*,*S*,*R*)-379



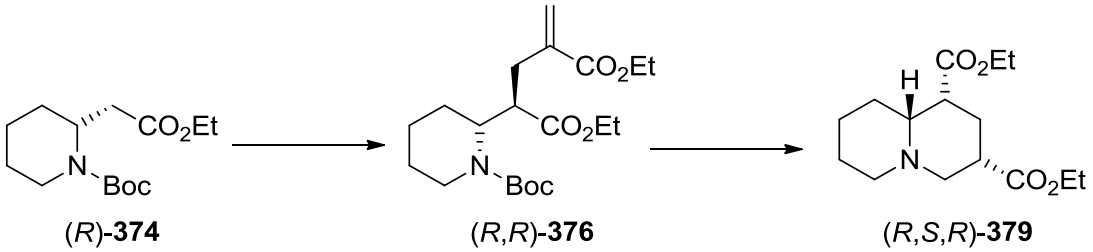
(*R*,*S*,*R*)-**379**



Trifluoroacetic acid (1.5 mL, 19.6 mmol) was added to a stirred solution of *N*-Boc ester (*R*,*R*)-**376** (1.49 g, 3.89 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the volatiles were removed under reduced pressure and EtOH (30 mL) and K_2CO_3 (5.37 g, 38.9 mmol, 10 eq.) were added. The resulting mixture was stirred at rt under Ar for 16 h. Then, the solvent was removed under reduced pressure. Water (50 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 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 97:3 CH_2Cl_2-MeOH as eluent gave di-ester (*R*,S,*R*)-**379** (890 mg, 81%) as a colourless oil, R_F (97:3 CH_2Cl_2-MeOH) 0.2; $[\alpha]_D$ +3.8 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2974, 2938, 2892, 2816, 1698 (C=O), 1424, 1348, 1331, 1244, 1196, 1135, 1067, 1041, 1015, 738, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 4.13 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 3.30 (ddd, *J* = 12.5, 4.5, 2.5 Hz, 1H, NCH, H^1), 3.06 (t, *J* = 11.5 Hz, 1H, NCH, H^4), 3.02-2.92 (m, 2H, NCH), 2.76 (dt, *J* = 13.0, 4.5 Hz, 1H, NCH, H^2), 2.70 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH, H^5), 2.56 (tt, *J* = 11.5, 4.0 Hz, 1H, H^3), 2.07 (dt, *J* = 13.5, 3.5 Hz, 1H, CH_2), 1.91-1.80 (m, 1H, CH_2), 1.80-1.63 (m, 3H, CH_2), 1.47 (qt, *J* = 13.0, 4.0 Hz, 1H, CH_2), 1.26 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.25 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.22-1.14 (m, 1H, CH_2), 1.01-0.93 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 173.7 (C=O), 172.7 (C=O), 60.5 (*C*H_2Me), 60.5 (*C*H_2Me), 57.2 (NCH), 54.9 (NCH_2), 46.5 (NCH_2), 45.2 (CH), 41.8 (CH), 25.2 (CH_2), 23.7 (CH_2), 18.6 (CH_2), 18.2 (CH_2), 14.2 (CH_2*Me*), 14.2 (CH_2*Me*); MS (ESI) *m/z* 284 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{25}NO_4$ $(M + H)^+$ 284.1856, found 284.1850 (+2.6 ppm error).

Lab Book Reference: JDF10_956

(1*R*,3*S*,9a*R*)-Diethyl octahydro-1H-quinolizine-1,3-dicarboxylate (*R*,*S*,*R*)-379

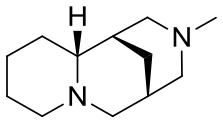


(*R*)-**374** (*R*,*R*)-**376** (*R*,*S*,*R*)-**379**

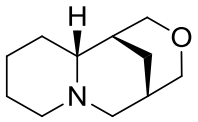
LHMDS (13.3 mL of a 1.0 M solution in THF, 13.3 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc ester (*R*)-**374** (3.0 g, 11.1 mmol, 1.0 eq.) in THF (70 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, acrylate **375** (2.56 g, 1.89 mL, 5.83 mmol, 1.2 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (100 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude *N*-Boc ester (*R*,*R*)-**376** which was used in the next step without further purification (≥90% purity by ^{1}H NMR spectroscopy). Trifluoroacetic acid (5.0 mL, 65.3 mmol) was added to a stirred solution of *N*-Boc ester (*R*,*R*)-**376** (max. 11.1 mmol, 1.0 eq.) in CH_2Cl_2 (100 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the volatiles were removed under reduced pressure and EtOH (100 mL) and K_2CO_3 (15.3 g, 111 mmol, 10 eq.) were added. The resulting mixture was stirred at rt under Ar for 16 h. Then, the solvent was removed under reduced pressure. Water (100 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 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 97:3 CH_2Cl_2-MeOH as eluent gave di-ester (*R*,S,*R*)-**379** (2.51g, 80%) as a colourless oil.

Lab Book Reference: JDF12_1112 and 1114

3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine 26 and Decahydro-1,5-methanopyrido[2,1-d][1,5]oxazocine 413



26



413

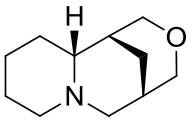
A solution of di-ester **379** (1.41 g, 5.0 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (755 mg, 20.0 mmol, 4.0 eq.) in THF (20 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 1 h. After cooling to 0 °C the mixture was diluted with Et_2O (30 mL), water (755 µL), 20% $NaOH_{(aq)}$ (1.51 mL) and water (755 µL) were sequentially added dropwise and the mixture stirred for 30 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (100 mL). The filter cake was suspended in EtOAc (50 mL) and stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (100 mL). The combined filtrate was concentrated under reduced pressure to give the crude diol **381**. MsCl (1.15 g, 790 µL, 10.0 mmol, 2.0 eq.) was added dropwise to a stirred solution of the crude diol **381** and Et_3N (1.52 g, 2.09 mL, 15.0 mmol, 3.0 eq.) in CH_2Cl_2 (30 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. Water (20 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude di-mesylate **382**. Crude di-mesylate **382** was dissolved in methyl amine (20 mL of a 8 M solution in EtOH) under Ar. The resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. 20% $NaOH_{(aq)}$ (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product containing a 5:1 mixture of sparteine surrogate **26** and tetrahydropyran **413** (by ^1H NMR spectroscopy). Purification by Kugelrohr distillation gave diamine a 5:1 mixture of diamine **26** and tetrahydropyran **413** (765 mg) as a colourless oil.

Lab Book Reference: JDF10_952

di-mesylate **382** (278 mg, 0.78 mmol, 1.0 eq.) was dissolved in methyl amine (10 mL of a 8 M solution in EtOH) under Ar. The resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. 20% $NaOH_{(aq)}$ (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product containing a 9:1 mixture of sparteine surrogate **26** and tetrahydropyran **413** (by ^{1}H NMR spectroscopy) (120 mg).

Lab Book Reference: JDF10_978

Decahydro-1,5-methanopyrido[2,1-d][1,5]oxazocine 413



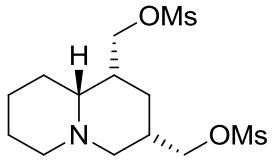
413

A solution of di-mesylate **413** (174 mg, 0.49 mmol, 1.0 eq.) in 20% $KOH_{(aq)}$ (10 mL) was heated and stirred at reflux for 16 h. Upon cooling to rt, Et_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1 CH_2Cl_2-MeOH then 89:10:1 CH_2Cl_2-MeOH-35% $NH_4OH_{(aq)}$ as eluent gave tetrahydropyran **413** (22 mg, 25%) as a pale yellow oil, R_F (89:10:1 CH_2Cl_2-MeOH-35% $NH_4OH_{(aq)}$) 0.2; IR (ATR) 2927, 2853, 1462, 1442, 1287, 1272, 1203, 1149, 1136, 1118, 1099, 1072, 1045, 1033, 885, 854, 823, 806, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (br d, *J* = 11.5 Hz, 1H, OCH), 4.00 (br d, *J* = 11.5 Hz, 1H, OCH), 3.73 (dt, *J* = 11.0, 2.5 Hz, 1H, OCH), 3.58 (dd, *J* = 11.5, 2.5 Hz, 1H, OCH), 3.00 (d, *J* = 11.0 Hz, 1H, NCH), 2.94–2.83 (m, 1H, NCH), 2.34 (dt, *J* = 11.0, 2.5 Hz, 1H, NCH), 2.03 (d, *J* = 11.0 Hz, 1H, NCH), 1.94–1.50 (m, 8H, NCH + 2CH, +

5CH_2), 1.44–1.20 (m, 3H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 71.4 (OCH_2), 67.3 (OCH_2), 66.1 (NCH), 60.6 (NCH_2), 57.7 (NCH_2), 35.5 (CH), 33.3 (CH_2), 30.8 (CH), 30.6 (CH_2), 25.5 (CH_2), 24.9 (CH_2); MS (ESI) *m/z* 182 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{19}NO$ $(M + H)^+$ 182.1539, found 182.1545 (–3.2 ppm error).

Lab Book Reference: JDF10_998

Octahydro-1H-quinolizine-1,3-diyl)bis(methylene) dimethanesulfonate 382



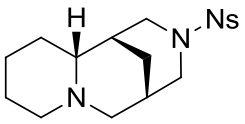
382

A solution of di-ester **379** (490 mg, 1.73 mmol, 1.0 eq.) in THF (2 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (262 mg, 6.91 mmol, 4.0 eq.) in THF (3 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 1 h. After cooling to 0 °C the mixture was diluted with Et_2O (10 mL), water (262 µL), 20% $NaOH_{(aq)}$ (524 µL) and water (262 µL) were sequentially added dropwise and the mixture stirred for 30 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (50 mL). The filter cake was suspended in EtOAc (20 mL) and stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (50 mL).The combined filtrate was concentrated under reduced pressure to give the crude diol **381**. MsCl (418 mg, 288 µL, 3.65 mmol, 2.1 eq.) was added dropwise to a stirred solution of the crude diol **381** and Et_3N (699 mg, 936 µL, 6.91 mmol, 4.0 eq.) in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 x 5 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 9:1 CH_2Cl_2-MeOH as eluent gave di-ester **382** (522 mg, 85%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; IR (ATR) 2932, 1347, 1332, 1243, 1168, 946, 827, 733 cm^{-1}; ^{1}H

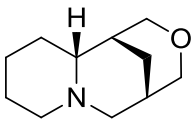
NMR (400 MHz, $CDCl_3$) δ 4.20-4.12 (m, 3H, CH_2OMs and CH_AH$_B$OMs), 4.06 (dd, *J* = 10.0, 7.0 Hz, 1H, CH$_A$$H_B$OMs), 3.03 (s, 3H, OMs), 3.03 (s, 3H, OMs), 2.97-2.74 (m, 4H, NCH), 2.54 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.32-2.09 (m, 2H, CH), 1.87 (d, *J* = 11.5 Hz, 1H, CH), 1.73-1.36 (m, 4H, CH), 1.35-1.14 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 72.1 (*C*H_2OMs), 70.8 (*C*H_2OMs), 58.3 (NCH), 55.4 (NCH$_2$), 49.8 (NCH$_2$), 38.6 (CH or Me), 37.4 (CH or Me), 37.4 (CH or Me), 35.9 (CH or Me), 25.2 (CH$_2$), 25.1 (CH$_2$), 20.3 (CH$_2$), 19.8 (CH$_2$); MS (ESI) *m/z* 356 (M + H)$^+$; HRMS *m/z* calcd for $C_{13}H_{26}N_2O_6S_2$ (M + H)$^+$ 356.1196, found 356.1182 (+3.5 ppm error).

Lab Book Reference: JDF11_1052

3-((2-Nitrophenyl)sulfonyl)decahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine 417 and Decahydro-1,5-methanopyrido[2,1-d][1,5]oxazocine 413



417



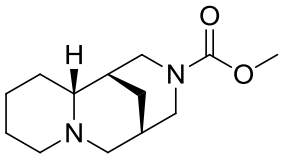
413

DIAD (146 mg, 142 µL, 0.71 mmol, 2.0 eq.) was added dropwise to a stirred solution of diol **381** (70 mg, 0.35 mmol, 1.0 eq.), 2-nitrobenzenesulfonamide (142 mg, 0.71 mmol, 2.0 eq.) and PPh_3 (185 mg, 0.71 mmol, 2.0 eq.) in THF at 0 °C under Ar. The resulting solution was warmed to rt and stirred at rt for 16 h. Then, the mixture was concentrated under reduced pressure and Et_2O (10 mL) was added. The resulting white precipitate was removed by filtration and washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1-9:1 CH_2Cl_2-MeOH then 89:10:1 CH_2Cl_2-MeOH:-35% $NH_4OH_{(aq)}$ as eluent gave bispidine **417** (13 mg, 10%) as a pale yellow oil, R_F (19:1 CH_2Cl_2-MeOH) 0.1; IR (ATR) 2928, 1739, 1542, 1375, 1346, 1175, 1149, 1122, 1104, 1008, 946, 760, 746, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36-8.12 (m, 1H, Ar), 7.71-7.50 (m, 3H, Ar), 3.99 (d, *J* = 12.5 Hz, 1H, NCH), 3.76 (d, *J* = 12.5 Hz, 1H, NCH), 3.18 (ddd, *J* = 12.0, 3.5, 2.0 Hz, 1H, NCH), 3.03 (dd, *J* = 12.5, 3.5 Hz, 1H, NCH), 2.89 (br d, *J* = 10.0 Hz, 1H, NCH), 2.71 (br d, *J* = 10.0 Hz, 1H, NCH), 2.30 (br s, 1H, NCH), 2.13-1.13 (m, 12H, NCH + CH + CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*

148.5 (*ipso*-Ar), 134.3 (*ipso*-Ar), 134.1 (Ar), 132.8 (Ar), 131.3 (Ar), 123.9 (Ar), 65.0 (NCH), 60.3 (NCH_2), 56.9 (NCH_2), 50.0 (NCH_2), 45.5 (NCH_2), 33.7 (CH), 32.2 (CH_2), 30.0 (CH_2), 28.9 (CH), 25.4 (CH_2), 24.6 (CH_2); MS (ESI) *m/z* 366 $(M + H)^+$; HRMS *m/z* calcd for $C_{17}H_{23}N_3O_4S$ $(M + H)^+$ 366.1482, found 366.1492 (–2.8 ppm error), and tetrahydropyran **413** (40 mg, 63%) as a pale yellow oil.

Lab Book Reference: JDF11_1010

(1*S*,5*S*,11a*R*)-Methyl octahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine-3(2H)-carboxylate (*S*,*S*,*R*)-419



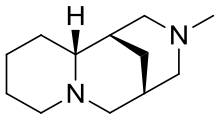
(*S*,*S*,*R*)-**419**

A solution of di-ester (*R*,*S*,*R*)-**379** (2.35 g, 8.29 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (1.26 g, 33.2 mmol, 4.0 eq.) in THF (30 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 1 h. After cooling to 0 °C, the mixture was diluted with Et_2O (50 mL). Water (1.26 mL), 20% $NaOH_{(aq)}$ (2.52 mL) and water (1.26 mL) were sequentially added dropwise and the mixture stirred for 30 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (100 mL). The filter cake was suspended in EtOAc (50 mL) and stirred for 30 min. The solids were removed by filtration through Celite® and washed with EtOAc (100 mL). The combined filtrate was concentrated under reduced pressure to give the crude diol (*R*,*S*,*R*)-**381**. MsCl (1.99 g, 1.38 mL, 17.4 mmol, 2.1 eq.) was added dropwise to a stirred solution of the crude diol (*R*,*S*,*R*)-**381** and Et_3N (3.36 g, 4.62 mL, 33.2 mmol, 4.0 eq.) in CH_2Cl_2 (20 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 16 h. Water (50 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude di-mesylate (*R*,*S*,*R*)-**382**. Freshly distilled allylamine (10 mL) was added to di-mesylate (*R*,*S*,*R*)-**382** at rt under Ar. The

resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. Then, 20% $NaOH_{(aq)}$ (20 mL) and $CHCl_3$ (20 mL) were added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude allyl bispidine (*S*,*R*,*R*)-**418**. Methyl chloroformate (2.35 g, 1.92 mL, 24.9 mmol, 3.0 eq.) was added to a stirred solution of crude allyl bispidine (*S*,*R*,*R*)-**418** in $CHCl_3$ (30 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, 1M $HCl_{(aq)}$ (20 mL) was added and the two layers separated. The organic layer was extracted with 1M $HCl_{(aq)}$ (3 × 20 mL). Then, the pH of the aqueous layer was adjusted to pH 12 with 20% $NaOH_{(aq)}$. The aqueous was extracted with Et_2O (5 × 30 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 9:1 CH_2Cl_2-MeOH as eluent gave methyl carbamate (*S*,*S*,*R*)-**419** (1.21 g, 61%) as a pale yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.1; $[\alpha]_D$ –25.6 (*c* 1.0 in $CHCl_3$); IR (ATR) 2917, 1697 (C=O), 1473, 1441, 1412, 1374, 1330, 1309, 1288, 1262, 1231, 1188, 1131, 1120, 1121, 1101, 1071, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 4.43 (dd, *J* = 13.5, 1.5 Hz, 0.45H, NCH), 4.34-4.20 (m, 1H, NCH), 4.08 (dd, *J* = 13.5, 1.5 Hz, 0.55H, NCH), 3.69 (s, 1.65H, CO_2Me), 3.64 (s, 1.35H, CO_2Me), 3.05 (dt, *J* = 13.0, 3.0 Hz, 0.45H, NCH), 2.97 (dt, *J* = 13.0, 3.0 Hz, 0.55H, NCH), 2.92-2.76 (m, 2H, NCH), 2.66 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.61 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.28-2.12 (m, 1H, NCH), 1.93 (br s, 0.45H, NCH), 1.91 (br s, 0.55H, NCH), 1.86-1.55 (m, 6H, NCH, CH and CH_2), 1.53- 1.11 (m, 5H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 156.4 (*C*O_2Me), 65.5 (CO_2*Me*), 65.5 (CO_2*Me*), 61.1 (NCH), 60.8 (NCH_2), 57.2 (NCH_2), 57.0 (NCH_2), 52.2 (NCH), 52.1 (NCH), 48.9 (NCH_2), 48.8 (NCH_2), 44.9 (NCH_2), 44.6 (NCH_2), 34.5 (CH), 34.1 (CH_2), 34.0 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 29.6 (CH), 29.5 (CH), 26.0 (CH_2), 25.7 (CH_2), 24.9 (CH_2), 24.9 (CH_2); MS (ESI) *m/z* 237 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{21}N_2O_2$ $(M + H)^+$ 237.1598, found 237.1593 (+2.3 ppm error).

Lab Book Reference: JDF12_1118 and 1121

(1*S*,5*R*,11a*R*)-3-Methyldecahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocine (–)-26

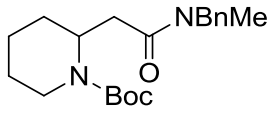


(–)-**26**

A solution of methyl carbamate (*S*,*R*,*R*)-**419** (1.12 g, 4.70 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (535 mg, 14.1 mmol, 3.0 eq.) in THF (20 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at reflux for 16 h. After cooling to 0 °C, the mixture was diluted with Et_2O (30 mL). Water (535 µL), 20% $NaOH_{(aq)}$ (1.07 mL) and water (535 µL) were sequentially added dropwise and the mixture stirred for 30 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (100 mL). The filtrate was concentrated under reduced pressure to give the (–)-sparteine surrogate (–)-**26** (880 mg, 97%, 99:1 by CSP-GC) as a colourless oil, $[\alpha]_D$ –28.4 (*c* 1.0 in EtOH) (lit.,[213] $[\alpha]_D$ +26.5 (*c* 1.0 in EtOH for (+)-**26**); IR (ATR) 2928, 2854, 2755, 2734, 2722, 2693, 1463, 1440, 1374, 1321, 1280, 1267, 1223, 1158, 1147, 1125, 1112, 1082, 1066, 1046, 1029, 992, 882, 838, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.05-2.95 (m, 2H, NCH), 2.94-2.81 (m, 2H, NCH), 2.24 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, NCH), 2.19-2.12 (m, 1H, NCH), 2.15 (s, 3H, NMe), 1.97 (dd, *J* = 11.5, 3.0 Hz, 1H, NCH), 1.90 (br d, *J* = 11.0 Hz, 1H, NCH), 1.83 (dd, *J* = 5.5, 3.0 Hz, 1H, NCH), 1.81-1.45 (m, 8H, CH), 1.37-1.22 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 66.5 (NCH), 60.5 (NCH_2), 60.5 (NCH_2), 57.7 (NCH_2), 56.3 (NCH_2), 47.5 (NMe), 35.3 (CH), 34.0 (CH_2), 30.9 (CH_2), 30.7 (CH), 25.8 (CH_2), 25.2 (CH_2); MS (ESI) *m/z* 195 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{22}N_2$ $(M + H)^+$ 195.1856, found 195.1860 (–1.8 ppm error); CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**26** 22.8 min, (–)-**26** 23.1 min. Spectroscopic data consistent with those reported in the literature.[213]

Lab Book Reference: JDF12_1124

***tert*-Butyl 2-(2-(benzyl(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate 423**



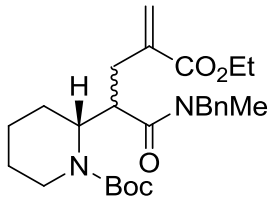
423

Lithium hydroxide (706 mg, 29.5 mmol, 4.0 eq.) was added to a stirred solution of *N*-Boc ester **374** (2.0 g, 7.37 mmol, 1.0 eq.) in 4:1:1 THF-MeOH-water (60 mL) under air. The resulting solution was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure. Then, water (30 mL) was added and the pH was adjusted to pH 4-5 with 1M $HCl_{(aq)}$. The aqueous was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give crude carboxylic acid as a white solid. Methyl chloroformate (696 mg, 570 µL, 7.37 mmol, 1.0 eq.) was added to a stirred solution of crude carboxylic acid and Et_3N (745 mg, 1.03 mL, 7.37 mmol, 1.0 eq.) in THF at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, *N*-methylbenzylamine (982 mg, 1.05 ml, 8.11 mmol, 1.1 eq.) was added dropwise and the resulting solution stirred at 0 °C for 1.5 h. Then, saturated $NaHCO_{3(aq)}$ (20 mL) and Et_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 20 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 1:1 petrol-EtOAc as eluent gave *N*-Boc amide **423** (2.12 g, 83%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.4; IR (ATR) 2984, 2942, 2863, 1707, 1682 (C=O, Boc), 1641 (C=O, Amide), 1476, 1451, 1400, 1363, 1267, 1252, 1160, 1139, 1098, 1072, 1042, 953, 874, 734, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.39-7.20 (m, 4H, Ph), 7.15 (br d, *J* = 7.5 Hz, 1H, Ph), 4.75-4.57 (m, 2H, C*H*$_2$Ph), 4.57-4.37 (m, 1H, NCH), 3.96 (br s, 1H, NCH), 2.99 (s, 1.65H, NMe), 2.91 (s, 1.35H, NMe), 2.89-2.65 (m, 2H, NCH + C*H*$_A$H$_B$CO), 2.63-2.43 (m, 1H, CH$_A$*H*$_B$CO), 1.78-1.69 (m, 1H, CH_2), 1.68-1.54 (m, 4H, CH_2), 1.50-1.33 (m, 1H, CH_2), 1.44 (s, 4.95H, CMe_3), 1.41 (s, 4.05H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 171.0 (CH_2*C*=O), 170.6 (CH_2*C*=O), 154.8 (C=O), 154.8 (C=O), 137.3 (*ipso*-Ph), 136.7 (*ipso*-Ph), 128.8 (Ph), 128.5 (Ph), 128.0 (Ph), 127.5 (Ph), 127.2 (Ph), 126.2 (Ph), 79.4 (*C*Me_3), 79.4 (*C*Me_3), 53.4 (*C*H_2Ph), 50.6 (*C*H_2Ph), 47.9 (NCH), 47.6 (NCH), 39.5 (NCH_2), 35.0 (NMe), 34.4 (*C*H_2CO), 34.1 (*C*H_2CO), 33.8

(NMe), 28.4 (C*Me*$_3$), 28.3 (C*Me*$_3$), 27.6 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 18.8 (CH_2), 18.7 (CH_2); MS (ESI) *m/z* 369 [$(M + Na)^+$, 100], 347 [$(M + H)^+$, 20]; HRMS *m/z* calcd for $C_{20}H_{31}N_2O_3$ $(M + H)^+$ 347.2329, found 347.2329 (–0.3 ppm error).

Lab Book Reference: JDF10_997

tert-Butyl-2-(1-(benzyl(methyl)amino)-4-(ethoxycarbonyl)-1-oxopent-4-en-2-yl)piperidine-1-carboxylate 422

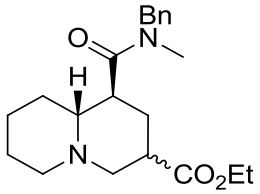


422

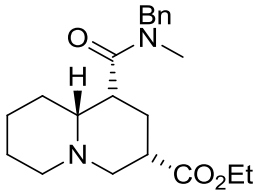
LHMDS (2.81 mL of a 1.0 M solution in THF, 2.81 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc amide **423** (809 mg, 2.34 mmol, 1.0 eq.) in THF (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, acrylate **375** (542 mg, 387 µg, 2.81 mmol, 1.2 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (20 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 7:3 petrol-EtOAc as eluent gave a mixture of diastereomeric *N*-Boc esters **422** (786 mg, 69%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.36-7.01 (m, 5H, Ph), 6.23-6.07 (m, 1H, C=CH_AH$_B$), 5.81-5.57 (m, 1H, C=CH$_A$$H_B$), 4.84-3.90 (m, 6H), 3.81-3.58 (m, 1H), 2.88-2.72 (m, 3H, NMe), 2.65-2.45 (m, 2H), 1.89 (br d, *J* = 11.0 Hz, 1H), 1.73-1.52 (m, 5H), 1.51-1.40 (m, 10H, CMe_3 + CH), 1.27 (t, *J* = 7.0 Hz, 2.2H, CH_2*Me*), 1.21 (t, *J* = 7.0 Hz, 0.8H, CH_2*Me*); MS (ESI) *m/z* 481 $(M + Na)^+$; HRMS *m/z* calcd for $C_{26}H_{38}N_2NaO_5$ $(M + H)^+$ 481.2673, found 481.2655 (+3.8 ppm error).

Lab Book Reference: JDF10_1000

Ethyl 1-(benzyl(methyl)carbamoyl)octahydro-1H-quinolizine-3-carboxylate 424 and Ethyl 1-(benzyl(methyl)carbamoyl)octahydro-1H-quinolizine-3-carboxylate 421



424



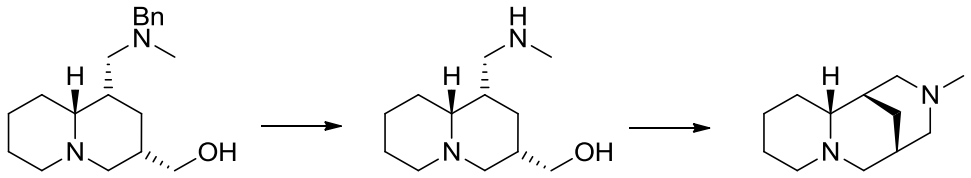
421

Trifluoroacetic acid (3 mL, 39.2 mmol) was added to a stirred solution of diastereomeric *N*-Boc esters **422** (786 mg, 1.71 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the volatiles were removed under reduced pressure and EtOH (20 mL) and K_2CO_3 (2.37 g, 17.1 mmol, 10 eq.) were added. The resulting mixture was stirred at rt under Ar for 16 h. Then, the solvent was removed under reduced pressure. Water (50 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained a 1:4 mixture of **424** and **421** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 19:1 to 9:1 CH_2Cl_2-MeOH as eluent gave bicyclic amide **424** (125 mg, 20%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.4; IR (ATR) 2932, 1725 (C=O, Ester), 1638 (C=O, Amide), 1451, 1411, 1368, 1315, 1298, 1252, 1179, 1149, 1139, 1107, 1073, 1047, 1028, 729, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.39-7.19 (m, 5H, Ph), 4.92 (d, *J* = 14.5 Hz, 0.4H, CH_AH$_B$Ph), 4.62 (d, *J* = 14.5 Hz, 0.6H, CH_AH$_B$Ph), 4.57 (d, *J* = 14.5 Hz, 0.6H, CH$_A$$H_B$Ph), 4.48 (d, *J* = 14.5 Hz, 0.4H, CH$_A$$H_B$Ph), 4.23-4.06 (m, 2H, C$H_2$Me), 3.18 (br t, *J* = 10.5 Hz, 1H, NCH), 3.05 (s, 1.8H, NMe), 2.91 (s, 1.2H, NMe), 2.99-2.82 (m, 1H, NCH), 2.73 (br t, *J* = 11.0 Hz, 1H, NCH), 2.69-2.60 (m, 1H, NCH), 2.38-2.28 (m, 1H, NCH), 2.28-2.15 (m, 2H, CHCO), 2.03 (td, *J* = 11.0, 4.0 Hz, 0.5H, CH_2), 1.98 (td, *J* = 11.0, 4.0 Hz, 0.5H, CH_2), 1.82-1.39 (m, 5H, CH_2), 1.34-1.20 (m, 1H, CH_2), 1.25 (t, *J* = 7.0 Hz, 1.8H, CH_2*Me*), 1.15 (t, *J* = 7.0 Hz, 1.2H, CH_2*Me*), 1.11-0.84 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 174.8 (C=O), 174.6 (C=O), 174.0 (C=O), 173.8 (C=O), 137.5 (*ipso*-Ph), 137.0 (*ipso*-Ph), 128.7 (Ph), 128.5 (Ph), 127.8 (Ph), 127.4 (Ph), 127.2

(Ph), 126.6 (Ph), 63.8 (NCH), 60.4 (*C*H_2Me), 57.1 (NCH_2 or CH_2Ph), 57.0 (NCH_2 or CH_2Ph), 56.4 (NCH_2 or CH_2Ph), 56.4 (NCH_2 or CH_2Ph), 52.9 (NCH_2), 50.6 (NCH_2), 42.0 (*C*HCO or NMe), 39.0 (*C*HCO or NMe), 34.8 (*C*HCO or NMe), 33.6 (*C*HCO or NMe), 30.4 (CH_2), 30.4 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 24.2 (CH_2), 24.2 (CH_2), 14.1 (CH_2*Me*), 14.1 (CH_2*Me*); MS (ESI) *m/z* 359 $(M + H)^+$; HRMS *m/z* calcd for $C_{21}H_{30}N_2O_3$ $(M + H)^+$ 359.2329, found 359.2328 (+0.1 ppm error), and bicyclic amide **421** (442 mg, 72%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; IR (ATR) 2927, 1726 (C=O, Ester), 1639 (C=O, Amide), 1495, 1450, 1410, 1367, 1319, 1255, 1188, 1153, 1093, 1080, 1056, 1030, 733, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.40-7.24 (m, 3H, Ph), 7.24-7.19 (m, 1H, Ph), 7.12 (br d, *J* = 7.0 Hz, 1H, Ph), 4.77 (d, *J* = 14.5 Hz, 0.4H, C*H*$_2$Ph), 4.62-4.52 (m, 1.6H, C*H*$_2$Ph), 4.20-4.09 (m, 2H, C*H*$_2$Me), 3.22-2.98 (m, 6H, NCH + C*H*CO), 3.03 (s, 1.8H, NMe), 2.91 (s, 1.2H, NMe), 2.82-2.53 (m, 2H, C*H*CO + CH_2), 2.19-1.63 (m, 5H, CH_2), 1.50-1.29 (m, 1H, CH_2), 1.26 (t, *J* = 7.0 Hz, 1.8H, CH_2*Me*), 1.25 (t, *J* = 7.0 Hz, 1.2H, CH_2*Me*), 1.20-1.05 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 173.0 (C=O), 172.9 (C=O), 172.1 (C=O), 171.4 (C=O), 137.1 (*ipso*-Ph), 136.8 (*ipso*-Ph), 129.0 (Ph), 128.6 (Ph), 128.0 (Ph), 127.6 (Ph), 126.1 (Ph), 126.6 (Ph), 60.8 (*C*H_2Me), 60.8 (*C*H_2Ph), 56.9 (NCH), 56.5 (NCH), 54.5 (*C*H_2Ph), 53.2 (*C*H_2Ph), 51.0 (NCH_2), 45.8 (NCH_2), 42.2 (*C*HCO or NMe), 40.9 (*C*HCO or NMe), 34.9 (*C*HCO or NMe), 34.3 (*C*HCO or NMe), 29.7 (CH_2), 24.7 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 18.6 (CH_2), 18.3 (CH_2), 14.1 (CH_2*Me*); HRMS *m/z* calcd for $C_{21}H_{30}N_2O_3$ $(M + H)^+$ 359.2329, found 359.2330 (–0.3 ppm error),

Lab Book Reference: JDF11_1030

3-methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine 26



425 **420** **26**

A solution of bicyclic ester **421** (442 mg, 1.23 mmol, 1.0 eq.) in THF (4 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (233 mg, 6.15 mmol, 5.0 eq.) in THF (6 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at rt for 2 h. After cooling to 0 °C, the mixture was diluted with Et_2O (20 mL). Water (233 µL), 20% $NaOH_{(aq)}$ (466 µL) and water (233 µL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (50 mL). The filtrate was concentrated under reduced pressure to give the amino alcohol **425** (342 mg, 92%) as a white solid, mp 101-103 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 4H, Ph), 7.28-7.23 (m, 1H, Ph), 3.78-3.66 (m, 1H, C*H*$_2$Ph or OCH_2), 3.66-3.54 (m, 2H, C*H*$_2$Ph or OCH_2), 3.28 (br d, *J* = 12.5 Hz, 1H, C*H*$_2$Ph or OCH_2), 2.82 (br d, *J* = 11.5 Hz, 1H, NCH), 2.75 (br s, 1H, OH), 2.60 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.35-2.11 (m, 3H, NCH), 2.09 (s, 3H, NMe), 1.97 (br s, 3H, NCH + CH), 1.76 (br d, *J* = 12.0 Hz, 1H, CH), 1.71-1.17 (m, 8H, CH). The crude product was used in the next step without further purification (≥90% purity by ^{1}H NMR spectroscopy).

Lab Book Reference: JDF11_1036

20% $Pd(OH)_2/C$ (50 mg) was added to a stirred solution of crude amino alcohol **425** (430 mg, 1.42 mmol, 1.0 eq.) and ammonium formate (447 mg, 7.1 mmol, 5.0 eq.) in EtOH (20 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 2 h. After cooling to rt, the mixture was filtered through Celite® and washed with EtOH (50 mL). The filtrate was evaporated under reduced pressure to give crude secondary alcohol **420** (246 mg, 81%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.63 (m, 1H, OC*H*$_A$H$_B$), 3.54 (dd, *J* = 11.5, 7.0 Hz, 1H, OCH$_A$*H*$_B$), 2.80 (br d, *J* = 12.0 Hz,

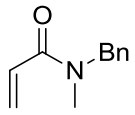
1H, NCH), 2.76-2.54 (m, 3H, NCH), 2.41 (s, 3H, NMe), 2.35-2.14 (m, 3H, NCH), 1.96-1.69 (m, 4H, CH or OH or NH), 1.64-1.19 (m, 8H, CH or OH or NH). The crude product was used in the next step without further purification (≥90% purity by ^{1}H NMR spectroscopy).

Lab Book Reference: JDF11_1038

Carbon tetrabromide (576 mg, 1.74 mmol, 1.5 eq.) was added a solution of secondary alcohol **420** (246 mg, 1.15 mmol, 1.0 eq.), PPh_3 (456 mg, 1.74 mmol, 1.5 eq.) and Et_3N (351 mg, 484 µL, 3.47 mmol, 3.0 eq.) in $CHCl_3$ (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16. Then, 1M $HCl_{(aq)}$ (10 mL) was added and the layer separated. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). Then, the pH of the aqueous layer was adjusted to pH 12 with 20% $NaOH_{(aq)}$. The aqueous was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine **26** (171 mg, 76%) as a colourless oil.

Lab Book Reference: JDF11_1039

***N*-Benzyl-*N*-methylacrylamide 431**



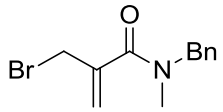
431

Acryloyl chloride **430** (4.53 g, 4.06 mL, 50 mmol, 1.0 eq.) was added dropwise to a stirred solution of *N*-methylbenzylamine (6.06 g, 6.45 ml, 50 mmol, 1.0 eq.) and Et_3N (5.06 g, 6.97 ml, 50 mmol, 1.0 eq.) in THF (100 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2.5 h then warmed to rt. Then, water (100 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 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 1:1 petrol-EtOAc as eluent gave acrylamide **431**

(5.46 g, 62%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.2; IR (ATR) 2933, 1645 (C=O), 1611 (CH=CH_2), 1494, 1477, 1450, 1414, 1402, 1379, 1356, 1258, 1220, 1186, 1116, 1098, 1077, 1056, 978, 792, 731, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.40-7.23 (m, 4H, Ph), 7.21-7.14 (m, 1H, Ph), 6.64 (dd, 0.5H, *J* = 16.5, 10.5 Hz, C*H*=CH_2), 6.58 (dd, 0.5H, *J* = 16.5, 10.5 Hz, C*H*=CH_2), 6.40 (dd, *J* = 16.5, 1.5 Hz, 0.5H, CH=CH_AH_B), 6.40 (dd, *J* = 16.5, 1.5 Hz, 0.5H, CH=CH_AH_B), 5.74 (dd, *J* = 10.5, 1.5 Hz, 0.5H, CH=CH_AH_B), 5.68 (dd, *J* = 10.5, 1.5 Hz, 0.5H, CH=CH_AH_B), 4.66 (s, 1H, CH_2Ph), 4.60 (s, 1H, CH_2Ph), 3.01 (s, 1.5H, NMe), 2.99 (s, 1.5H, NMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 167.2 (C=O), 166.6 (C=O), 137.2 (*ipso*-Ph), 136.9 (*ipso*-Ph), 129.0 (*C*H=CH_2 or Ph), 128.7 (*C*H=CH_2 or Ph), 128.4 (CH=*C*H_2), 128.4 (CH=*C*H_2), 128.2 (*C*H=CH_2 or Ph), 127.8 (*C*H=CH_2 or Ph), 127.7 (*C*H=CH_2 or Ph), 127.5 (*C*H=CH_2 or Ph), 126.5 (*C*H=CH_2 or Ph), 53.5 (*C*H_2Ph), 51.2 (*C*H_2Ph), 35.0 (NMe), 34.2 (NMe); MS (ESI) *m/z* 198 [$(M + Na)^+$, 100], 176 [$(M + H)^+$, 60]; HRMS *m/z* calcd for $C_{11}H_{13}NO$ $(M + H)^+$ 176.1070, found 176.1068 (+1.2 ppm error). Spectroscopic data consistent with those reported in the literature.[286]

Lab Book Reference: JDF11_1079

_N_-Benzyl-2-(bromomethyl)-_N_-methylacrylamide 429



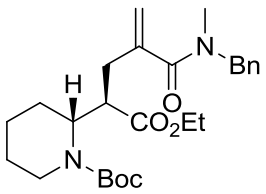
429

Acrylamide **431** (5.46 g, 31.2 mmol, 1.0 eq.) was added to a stirred solution of paraformaldehyde (4.68 g, 156 mmol, 5.0 eq.), DABCO (3.50 g, 31.2 mmol, 1.0 eq.) and phenol (734 mg, 7.8 mmol, 0.25 eq.) in 7:3 H_2O-^{t}BuOH (4 mL) at rt under Ar. The resulting mixture was stirred and heated at 80 °C for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure. Then, CH_2Cl_2 (100 mL) was added and mixture was filtered through Celite® and washed with CH_2Cl_2 (100 mL). The filtrate was evaporated under reduced pressure. Filtration through a plug of silica eluting with 9:1 CH_2Cl_2-MeOH gave crude alcohol **432** (6.7 g). PBr_3 (5.06 g, 1.76 mL, 18.7 mmol, 0.6 eq.) was added dropwise to a stirred solution of crude alcohol **432** in Et_2O (50 mL)

at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated $NaHCO_{3(aq)}$ (100 mL) was added slowly with stirring and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 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 1:1 petrol-EtOAc as eluent gave acrylamide **429** (3.35 g, 40%) as a colourless oil that solidified upon standing, mp 51-53 °C; R_F (1:1 petrol-EtOAc) 0.3; IR (ATR) 1641 (C=O), 1612 (C=CH_2), 1491, 1455, 1429, 1410, 1391, 1361, 1321, 1301, 1258, 1211, 1129, 1094, 959, 933, 895, 782, 739, 713, 699, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.42-7.20 (m, 5H, Ph), 5.57 (br s, 0.6H, C=C$H_A$$H_B$), 5.46 (br s, 0.4H, C=C$H_A$$H_B$), 5.23 (br s, 1H, C=C$H_A$$H_B$), 4.72 (br s, 0.8H, C$H_2$Ph), 4.68 (br s, 1.2H, C$H_2$Ph), 4.28 (s, 2H, CH_2Br), 3.03 (s, 1.8H, NMe), 2.95 (s, 1.2H, NMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 169.8 (C=O), 169.3 (C=O), 140.0 (*C*=CH_2), 139.9 (*C*=CH_2), 136.5 (*ipso*-Ph), 128.8 (Ph), 128.6 (Ph), 127.9 (Ph), 127.5 (Ph), 127.4 (Ph), 126.6 (Ph), 118.0 (C=*C*H_2), 118.0 (C=*C*H_2), 54.6 (*C*H_2Ph), 50.4 (*C*H_2Ph), 36.3 (NMe), 33.4 (CH_2Br), 32.9 (CH_2Br); MS (ESI) *m/z* 290 [$(M + Na)^+$, 100], 268 [$(M + H)^+$, 60]; HRMS *m/z* calcd for $C_{12}H_{14}BrNO$ $(M + H)^+$ 268.0332, found 268.0336 (–1.7 ppm error).

Lab Book Reference: JDF11_1085

tert-Butyl 2-(4-(benzyl(methyl)carbamoyl)-1-ethoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate 428



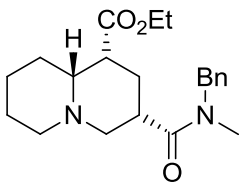
428

LHMDS (1.20 mL of a 1.0 M solution in THF, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc ester **374** (271 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of acrylamide **429** (321 mg, 1.20 mmol, 1.2 eq.) in THF (1 mL) was added dropwise and

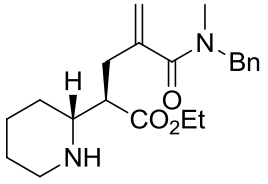
the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (20 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 petrol-EtOAc as eluent gave *N*-Boc ester **428** (426 mg, 93%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.3; IR (ATR) 2932, 1731 (C=O, Ester), 1687 (C=O, Boc), 1645 (C=O, Amide), 1618 (C=CH_2), 1476, 1450, 1413, 1364, 1306, 1274, 1249, 1158, 1096, 1028, 920, 867, 729, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.39-7.14 (m, 5H, Ph), 5.33 (br s, 0.6H, C=CH_AH_B), 5.21 (br s, 0.4H, C=CH_AH_B), 5.14 (br s, 1H, C=CH_AH_B), 4.78-4.22 (m, 3H, NCH + CH_2Ph), 4.15-3.91 (m, 3H, CH_2Me + NCH), 3.13 (br s, 1H, NCH), 2.96 (br s, 1H, C$H$$CO_2$Et), 2.92 (s, 3H, NMe), 2.75-2.44 (m, 2H, CH_2C=CH_2), 1.85-1.71 (m, 2H, CH_2), 1.66-1.48 (m, 4H, CH_2), 1.42 (s, 9H, CMe_3), 1.16 (br t, *J* = 6.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 173.1 (C=O), 173.0 (C=O), 154.3 (C=O, Boc), 141.7 (*C*=CH_2), 136.9 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.4 (Ph), 116.7 (C=*C*H_2), 79.4 (*C*Me_3), 60.4 (*C*H_2Me), 54.5 (NCH), 50.4 (*C*H_2Ph), 43.4 (C*H*CO_2Et), 40.0 (NCH_2), 36.4 (NMe), 34.3 (*C*H_2C=CH_2), 28.3 (C*Me*$_3$), 25.9 (CH_2), 25.2 (CH_2), 19.0 (CH_2), 14.1 (CH_2*Me*); MS (ESI) *m/z* 481 [(M + Na)$^+$, 100], 459 [(M + H)$^+$, 30]; HRMS *m/z* calcd for $C_{26}H_{38}N_2O_5$ (M + H)$^+$ 459.2853, found 459.2860 (–1.4 ppm error).

Lab Book Reference: JDF11_1087

Ethyl 3-(benzyl(methyl)carbamoyl)octahydro-1H-quinolizine-1-carboxylate 427 and Ethyl 3-(benzyl(methyl)carbamoyl)octahydro-1H-quinolizine-1-carboxylate 433



427



433

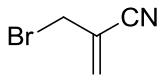
Trifluoroacetic acid (1 mL, 13.1 mmol) was added to a stirred solution of *N*-Boc ester **428** (329 mg, 0.72 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting

solution was stirred at rt under Ar for 16 h. Then, the volatiles were removed under reduced pressure and EtOH (10 mL) and K_2CO_3 (991 mg, 7.17 mmol, 10 eq.) were added. The resulting mixture was stirred at rt for 16 h. Then, the solvent was removed under reduced pressure. Water (20 mL) and CH_2Cl_2 (20 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained a 1:4 mixture of **427** and **433** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1 to 19:1 CH_2Cl_2-MeOH as eluent gave bicyclic amide **427** (52 mg, 20%) as a colourless oil, R_F (97:3 CH_2Cl_2-MeOH) 0.2; IR (ATR) 2933, 2857, 1727 (C=O, Ester), 1635 (C=O, Amide), 1495, 1450, 1414, 1352, 1261, 1194, 1169, 1144, 1094, 1079, 1027, 732, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.39-7.26 (m, 3H, Ph), 7.22-7.13 (m, 2H, Ph), 4.61 (d, *J* = 14.5 Hz, 1H, C*H*$_A$H$_B$Ph), 4.52 (d, *J* = 14.5 Hz, 1H, CH$_A$*H*$_B$Ph), 4.15 (q, *J* = 7.0 Hz, 1.3H, C*H*$_2$Me), 4.11 (q, *J* = 7.0 Hz, 0.7H, C*H*$_2$Me), 3.61 (br d, *J* = 11.5 Hz, 0.65H, NCH), 3.54-3.42 (m, 1H, NCH), 3.39 (d, *J* = 11.5 Hz, 0.35H, NCH), 3.30-2.99 (m, 4H, NCH + CHCO), 2.98 (s, 1.95H, NMe), 2.95 (s, 1.05H, NMe), 2.83-2.62 (m, 1H, NCH or CHCO), 2.07-1.73 (m, 6H, CH_2), 1.65-1.41 (m, 2H, CH_2), 1.25 (t, *J* = 7.0 Hz, 1.95H, CH_2*Me*), 1.22 (t, *J* = 7.0 Hz, 1.05H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) *δ* 172.2 (C=O), 171.1 (C=O), 136.9 (*ipso*-Ph), 136.3 (*ipso*-Ph), 129.0 (Ph), 128.7 (Ph), 127.9 (Ph), 127.7 (Ph), 127.5 (Ph), 126.4 (Ph), 61.0 (*C*H$_2$Me), 60.7 (*C*H$_2$Me), 57.4 (NCH), 57.3 (NCH), 54.4 (NCH$_2$ or *C*H$_2$Ph), 54.3 (NCH$_2$ or *C*H$_2$Ph), 53.2 (NCH$_2$ or *C*H$_2$Ph), 47.0 (NCH$_2$ or *C*H$_2$Ph), 46.6 (NCH$_2$ or *C*H$_2$Ph), 44.3 (*C*HCO), 44.0 (*C*HCO), 38.3 (*C*HCO), 37.9 (*C*HCO), 34.8 (NMe), 34.3 (NMe), 24.2 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 23.2 (CH_2), 18.3 (CH_2*Me*), 18.2 (CH_2*Me*); MS (ESI) *m/z* 359 (M + H)$^+$; HRMS *m/z* calcd for $C_{21}H_{30}N_2O_3$ (M + H)$^+$ 359.2329, found 359.2319 (+2.5 ppm error), and secondary amine **433** (165 mg, 64%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.2; IR (ATR) 2982, 2937, 1725 (C=O, Ester), 1648 (C=O, Amide), 1618 (C=CH$_2$), 1494, 1450, 1396, 1254, 1159, 1122, 1094, 1029, 919, 856, 729, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.39-7.11 (m, 5H, Ph), 5.32 (br s, 0.5H, C=C*H*$_A$H$_B$), 5.22 (br s, 0.5H, C=C*H*$_A$H$_B$), 5.14 (br s, 1H, C=CH$_A$*H*$_B$), 4.61 (br s, 2H, C*H*$_2$Ph), 4.10-3.92 (m, 2H, C*H*$_2$Me), 3.09 (br d, *J* = 9.5 Hz, 1H, NCH), 2.92 (br s, 3H, NMe), 2.83-2.45 (m, 6H, NCH$_2$ + COCH + C*H*$_2$C=CH$_2$ + NH), 1.87-1.77 (m, 1H, CH_2), 1.73 (br d, *J* = 12.5 Hz, 1H, CH_2), 1.62-1.49 (m, 1H, CH_2), 1.40–1.30 (m, 2H, CH_2), 1.28-1.09 (m, 4H, CH_2 + CH_2*Me*); ^{13}C

NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 173.9 (C=O), 172.2 (C=O), 171.4 (C=O), 141.9 (*C*=CH_2), 136.8 (*ipso*-Ph), 136.6 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.0 (Ph), 127.4 (Ph), 126.5 (Ph), 117.0 (C=*C*H_2), 116.4 (C=*C*H_2), 60.5 (*C*H_2Me), 58.2 (NCH), 50.3 (*C*HCO), 46.9 (NCH_2), 36.2 (NMe), 33.1 (CH_2), 32.7 (CH_2), 30.0 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 14.2 (CH_2*Me*); MS (ESI) *m/z* 359 $(M + H)^+$; HRMS *m/z* calcd for $C_{21}H_{30}N_2O_3$ $(M + H)^+$ 359.2329, found 359.2311 (+3.8 ppm error).

Lab Book Reference: JDF11_1090

2-(Bromomethyl)acrylonitrile 436

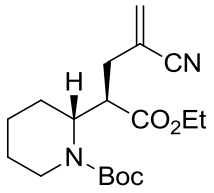


436

A solution of K_2CO_3 (7.8 g, 56.4 mmol, 2.0 eq.) in H_2O (8 mL) was added dropwise to a stirred solution of diethyl cyanomethylphosphonate **434** (5.0 g, 4.6 mL, 28.2 mmol, 1.0 eq.) and formaldehyde (37% aqueous solution, 9.2 mL, 113 mmol, 4.0 eq.) at rt under air. The resulting mixture was stirred at rt for 1 h. Then, Et_2O (75 mL) and brine (75 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude alcohol **435**. PBr_3 (4.6 g, 1.59 mL, 16.9 mmol, 0.6 eq.) was added dropwise to a stirred solution of crude alcohol **435** in Et_2O (40 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. Then, saturated $NaHCO_{3(aq)}$ (100 mL) was added slowly with stirring and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave acrylonitrile **436** (1.20 g, 29%) as a clear oil, R_F (7:3 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H, C=C$H_A$$H_B$), 6.02 (s, 1H, C=C$H_A$$H_B$), 4.00 (s, 2H, CH_2Br); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.3 (C=*C*H_2), 120.2 (*C*=CH_2 + CN), 29.4 (CH_2Br). Spectroscopic data consistent with those reported in the literature.[287]

Lab Book Reference: JDF12_1111

***tert*-Butyl 2-(4-cyano-1-ethoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate 437**

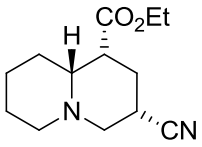


437

LHMDS (1.20 mL of a 1.0 M solution in THF, 1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc ester **374** (271 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of acrylonitrile **436** (175 mg, 1.20 mmol, 1.2 eq.) in THF (1 mL) was added dropwise and the resulting solution was stirred at –78 °C for 4 h and allowed to warm to rt over 16 h. Water (20 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 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 9:1 to 7:3 petrol:Et_2O as eluent gave *N*-Boc ester **437** (243 mg, 72%) as a colourless oil, R_F (8:2 petrol:Et_2O) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (br s, 1H, C=CH_AH$_B$), 5.79 (br s, 1H, C=CH$_A$$H_B$), 4.40 (br s, 1H, NCH), 4.18-3.86 (m, 3H, CH_2Me + NCH), 3.20 (td, *J* = 11.5, 2.5 Hz, 1H, NCH), 2.96 (br t, *J* = 13.5 Hz, 1H, C*H*CO_2Et or CH_2C=CH_2), 2.72-2.54 (br t, *J* = 13.5 Hz, 1H, C*H*CO_2Et or CH_2C=CH_2), 2.33 (br d, *J* = 14.0 Hz, 1H, C*H*CO_2Et or CH_2C=CH_2), 1.77-1.44 (m, 6H, CH_2), 1.41 (s, 9H, CMe_3), 1.21 (t, *J* = 7.0 Hz, 3H, CH_2*Me*);

Lab Book Reference: JDF12_1113

Ethyl 3-cyanooctahydro-1H-quinolizine-1-carboxylate 438



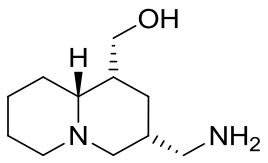
438

Trifluoroacetic acid (1.0 mL, 13.1 mmol) was added to a stirred solution of *N*-Boc ester **437** (217 mg, 0.65 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting

solution was stirred at rt for 16 h. Then, the volatiles were removed under reduced pressure and EtOH (10 mL) and K_2CO_3 (898 mg, 6.5 mmol, 10 eq.) were added. The resulting mixture was stirred at rt under Ar for 16 h. Then, the solvent was removed under reduced pressure. Water (20 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 98:2 CH_2Cl_2-MeOH as eluent gave bicyclic ester **438** (108 mg, 70%) as a white solid, mp 57-58 °C; R_F (98:2 CH_2Cl_2-MeOH) 0.1; IR (ATR) 2938, 2860, 2251 (CN), 1729 (C=O), 1447, 1378, 1351, 1320, 1264, 1197, 1171, 1143, 1080, 1027, 1012, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 3.26-3.16 (m, 1H, NCH), 3.12 (t, *J* = 12.0 Hz, 1H, NCH), 3.01-2.82 (m, 2H, NCH), 2.77-2.62 (m, 3H, NCH + CH), 2.15-2.07 (m, 1H, CH_2), 1.94-1.81 (m, 2H, CH_2), 1.79-1.59 (m, 2H, CH_2), 1.54-1.39 (m, 1H, CH_2), 1.25 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.24-1.17 (m, 1H, CH_2), 1.01 (br dd, *J* = 13.5, 2.5 Hz, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.6 (C=O), 120.5 (CN), 60.7 (*C*H_2Me), 57.1 (NCH), 55.0 (NCH_2), 47.6 (NCH_2), 44.5 (*C*HCO_2Et), 27.5 (*C*HCN), 25.0 (CH_2), 24.7 (CH_2), 19.0 (CH_2), 18.5 (CH_2), 14.1 (CH_2*Me*); MS (ESI) *m/z* 237 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{20}N_2O_2$ $(M + H)^+$ 237.1598, found 237.1593 (+2.3 ppm error),

Lab Book Reference: JDF12_1115

Attempted Synthesis of 3-(aminomethyl)octahydro-1H-quinolizin-1-yl)methanol 439



439

A solution of nitrile **438** (103 mg, 0.43 mmol, 1.0 eq.) in THF (2 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (66 mg, 1.74 mmol, 4.0 eq.) in THF (3 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt

and then stirred at rt for 1 h. After cooling to 0 °C, the mixture was diluted with Et_2O (50 mL). Water (66 µL), 20% $NaOH_{(aq)}$ (122 µL) and water (66 µL) were sequentially added dropwise and the mixture stirred for 30 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL).The filtrate was concentrated under reduced pressure to give the crude product which contained a complex mixture of decomposition products.

Lab Book Reference: JDF12_1120

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
aq.	aqueous
Ar	aryl
atm	atmospheres
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Cbz	carboxybenzyl
CIPE	complex induced proximity effect
cm^{-1}	wavenumber
COD	1,5-cyclooctadiene
CSP-GC	chiral stationary phase gas chromatography
CSP-HPLC	chiral stationary phase high performance liquid chromatography
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DavePhos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DPEPhos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppe	ethylenebis(diphenylphosphine)
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTR	dynamic thermodynamic resolution
E^+	electrophile
eq.	equivalent(*S*)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl

FDA	Food and Drug Administration
Fmoc	9-fluorenylmethyloxycarbonyl
g	gram(*S*)
GC	gas chromatography
glyme	dimethoxyethane
h	hour(*S*)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HFIP	hexafluoro-2-propanol
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
IPA	isopropyl alcohol
IR	infra-red
J	coupling constant in Hz
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LiDMAE	lithiated dimethylethanolamine
m	multiplet
M	molar
m/z	mass to charge ratio

M^+	molecular ion
Me	methyl
mg	milligrams
min	minutes
mL	millilitre
mmol	millimole
mp	melting point
MS	mass spectrometry
MS	molecular sieves
Ms	mesyl
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl
PEPPSI-*i*-Pr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Petrol	petroleum ether (fraction which boils at 40-60 ^oC)
Ph	phenyl
PhFl	9-phenylfluoren-9-yl
Pin	pinacol
PMP	para-methoxyphenyl
ppm	parts per million
Pr	propyl
p-Tol	*p*-tolyl

q	quartet
QPhos	1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
R	alkyl group
R_F	retention factor
rt	room temperature
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	singlet
SET	single electron transfer
SnAP	tin amine protocol
(+)-sp	(+)-sparteine
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMCDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
Tr	trityl
Trisyl	2,4,6-triisopropylbenzenesulfonyl
Ts	tosyl

UV	ultraviolet
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter Seven: References

(1) Schlenk, W.; Holtz, J. *Chem. Ber.* **1917**, *50*, 262.
(2) Ziegler, K.; Colonius, H. *Liebigs Ann.* **1930**, *479*, 135.
(3) Eisch, J. J. *Organometallics* **2002**, *21*, 5439.
(4) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Thieme, **2002**.
(5) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139.
(6) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2001**, *4*, 119.
(7) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727.
(8) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322.
(9) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(10) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.
(11) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092.
(12) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(13) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
(14) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed* **2004**, *43*, 2206.
(15) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553.
(16) Beak, P.; McKinnie, B. G.; Reitz, D. B. *Tetrahedron Lett.* **1977**, *18*, 1839.
(17) Reitz, D. B.; Beak, P.; Tse, A. *J. Org. Chem.* **1981**, *46*, 4316.
(18) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080.
(19) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.
(20) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.
(21) Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2.
(22) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chanrasekhar, J.; Schleyer, P. V. R. *J. Org. Chem.* **1981**, *46*, 4108.
(23) Seebach, D.; Enders, D. *Angew. Chem. Int. Ed* **1975**, *14*, 15.
(24) Seebach, D.; Isabelle, M. P. H.; Max, A. S. *Helv Chim Acta* **1987**, *70*, 1357.
(25) Meyers, A. I.; Hellring, S. *J. Org. Chem.* **1982**, *47*, 2229.
(26) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(27) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263.
(28) Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538.
(29) Metallinos, C.; Dudding, T.; Zaifman, J.; Chaytor, J. L.; Taylor, N. J. *J. Org. Chem.* **2007**, *72*, 957.
(30) Metallinos, C.; Xu, S. *Org. Lett.* **2009**, *12*, 76.
(31) Hodgson, D.; Kloesges, J. *Angew. Chem. Int. Ed* **2010**, *49*, 2900.
(32) Hodgson, D. M.; Pearson, C. I.; Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1098.
(33) Hodgson, D. M.; Pearson, C. I.; Kazmi, M. *Org. Lett.* **2014**.
(34) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197.
(35) Kocienski, P. J. *Protecting Groups*; Thieme, **1994**.
(36) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092.
(37) Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron Lett.* **1968**, *9*, 2087.
(38) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *9*, 4097.
(39) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.
(40) Hoppe, D.; Zschage, O. *Angew. Chem. Int. Ed* **1989**, *28*, 69.
(41) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed* **1990**, *29*, 1422.

(42) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(43) Wiberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231.
(44) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577.
(45) Hermet, J.-P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830.
(46) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148.
(47) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875.
(48) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
(49) Harrison, J. R.; Obrien, P.; Porter, D. W.; Smith, N. M. *Chem. Commun.* **2001**, *0*, 1202.
(50) Wiberg, K. B.; Bailey, W. F. *Angew. Chem. Int. Ed* **2000**, *39*, 2127.
(51) Dixon, A., J; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141.
(52) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893.
(53) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607.
(54) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.
(55) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.
(56) Sott, R.; Håkansson, M.; Hilmersson, G. *Organometallics* **2006**, *25*, 6047.
(57) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(58) Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872.
(59) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176.
(60) Gelardi, G.; Barker, G.; O'Brien, P.; Blakemore, D. C. *Org. Lett.* **2013**, *15*, 5424.
(61) Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed* **2002**, *41*, 716.
(62) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(63) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378.
(64) McGrath, M. J.; O'Brien, P. *Synthesis* **2006**, 2233.
(65) Barker, G.; O'Brien, P.; Campos, K. R. *Arkivoc* **2011**, *5*, 217.
(66) Bilke, J. L.; O'Brien, P. *J. Org. Chem.* **2008**, *73*, 6452.
(67) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935.
(68) Rayner, P. J.; O'Brien, P.; Horan, R. A. J. *J. Am. Chem. Soc.* **2013**, *135*, 8071.
(69) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276.
(70) Rayner, P. J. *PhD Thesis, University of York,* **2013**
(71) Coldham, I.; Patel, J. J.; Sanchez-Jimenez, G. *Chem. Commun.* **2005**, 3083.
(72) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.
(73) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.
(74) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578.
(75) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(76) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E. *Chem. Commun.* **2007**, 4534.
(77) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715.
(78) Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E. *Chem. Commun.* **2008**, 4174.
(79) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216.
(80) Beng, T. K.; Tyree, W. S.; Parker, T.; Su, C.; Williard, P. G.; Gawley, R. E. *J. Am. Chem. Soc.* **2012**, *134*, 16845.
(81) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(82) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **1999**, *2*, 155.
(83) Beng, T. K.; Gawley, R. E. *Heterocycles* **2012**, *84*, 697.
(84) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3464.
(85) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75*, 4069.
(86) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175.
(87) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847.
(88) Li, S.; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969.
(89) Dieter, R. K.; Chen, N.; Yu, H.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109.
(90) Karl Dieter, R.; Sharma, R. R. *Tetrahedron Lett.* **1997**, *38*, 5937.
(91) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302.
(92) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715.
(93) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.
(94) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.
(95) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260.
(96) Dieter, R. K.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221.
(97) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.
(98) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C.-y. *J. Org. Chem.* **2008**, *73*, 4986.
(99) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.
(100) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923.
(101) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem. Eur. J.* **2010**, *16*, 4082.
(102) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2010**, *13*, 394.
(103) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774.
(104) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241.
(105) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946.
(106) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat. Chem.* **2013**, *5*, 667.
(107) "Top 200 Pharmaceutical Products by Worldwide Sales in 2012", http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200%20Pharmaceutical%20Products%20by%20US%20Retail%20Sales%20in%202012_0.pdf
(108) McDermott, B. P.; Campbell, A. D.; Ertan, A. *Synlett* **2008**, *6*, 875.
(109) Al-Aseer, M. A.; Smith, S. G. *J. Org. Chem.* **1984**, *49*, 2608.
(110) Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715.
(111) Sun, X.; Kenkre, S. L.; Remenar, J. F.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 4765.
(112) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.
(113) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *124*, 264.
(114) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919.
(115) Sheikh, N. S.; Leonori, D.; Barker, G.; Firth, J. D.; Campos, K. R.; Meijer, A. J. H. M.; O'Brien, P.; Coldham, I. *J. Am. Chem. Soc.* **2012**, *134*, 5300.
(116) Li, X.; Leonori, D.; Sheikh, N. S.; Coldham, I. *Chem. Eur. J.* **2013**, *19*, 7724.

(117) Grainger, D. M.; Campbell Smith, A.; Vincent, M. A.; Hillier, I. H.; Wheatley, A. E. H.; Clayden, J. *Eur. J. Org. Chem.* **2012**, *2012*, 731.
(118) Lefranc, J.; Fournier, A. M.; Mingat, G.; Herbert, S.; Marcelli, T.; Clayden, J. *J. Am. Chem. Soc.* **2012**, *134*, 7286.
(119) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734.
(120) Rossi, F.; Corcella, F.; Caldarelli, F. S.; Heidempergher, F.; Marchionni, C.; Auguadro, M.; Cattaneo, M.; Ceriani, L.; Visentin, G.; Ventrella, G.; Pinciroli, V.; Ramella, G.; Candiani, I.; Bedeschi, A.; Tomasi, A.; Kline, B. J.; Martinez, C. A.; Yazbeck, D.; Kucera, D. J. *Org. Process Res. Dev.* **2008**, *12*, 322.
(121) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12276.
(122) Barker, G. *PhD Thesis, University of York*, **2011**
(123) Gelardi, G. *PhD Thesis, University of York*, **2014**
(124) Lautens, M.; Fillion, E.; Sampat, M. *J. Org. Chem.* **1997**, *62*, 7080.
(125) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.
(126) Bey, A. E.; Weyenberg, D. R. *J. Org. Chem.* **1966**, *31*, 2036.
(127) Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.
(128) Cooke, M. P. *J. Org. Chem.* **1986**, *51*, 951.
(129) Seyferth, D.; Vick, S. C. *J. Organomet. Chem.* **1978**, *144*, 1.
(130) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103.
(131) Coldham, I.; Leonori, D.; Beng, T. K.; Gawley, R. E. *Chem. Commun.* **2009**, *0*, 5239.
(132) Husmann, R.; Jörres, M.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 12549.
(133) Bauer, J. O.; Stiller, J.; Marqués-López, E.; Strohfeldt, K.; Christmann, M.; Strohmann, C. *Chem. Eur. J.* **2010**, *16*, 12553.
(134) Jentzsch, K. I.; Min, T.; Etcheson, J. I.; Fettinger, J. C.; Franz, A. K. *J. Org. Chem.* **2011**, *76*, 7065.
(135) Berkheij, M.; van der Sluis, L.; Sewing, C.; den Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema Bakker, W. I.; van den Hoogenband, A.; van Maarseveen, J. H. *Tetrahedron Lett.* **2005**, *46*, 2369.
(136) Vieth, M.; Siegel, M. G.; Higgs, R. E.; Watson, I. A.; Robertson, D. H.; Savin, K. A.; Durst, G. L.; Hipskind, P. A. *J. Med. Chem.* **2003**, *47*, 224.
(137) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, 57, 5845.
(138) James, T.; Simpson, I.; Grant, J. A.; Sridharan, V.; Nelson, A. *Org. Lett.* **2013**, *15*, 6094.
(139) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096.
(140) Guercio, G.; Bacchi, S.; Perboni, A.; Leroi, C.; Tinazzi, F.; Bientinesi, I.; Hourdin, M.; Goodyear, M.; Curti, S.; Provera, S.; Cimarosti, Z. *Org. Process Res. Dev.* **2009**, *13*, 1100.
(141) Garrido, F.; Mann, A.; Wermuth, C.-G. *Tetrahedron Lett.* **1997**, *38*, 63.
(142) Miller, K. A.; Shanahan, C. S.; Martin, S. F. *Tetrahedron* **2008**, *64*, 6884.
(143) Chackalamannil, S.; Davies, R.; McPhail, A. T. *Org. Lett.* **2001**, *3*, 1427.
(144) Fukatsu, K.; Nakayama, Y.; Tarui, N.; Mori, M.; Matsumoto, H.; Kurasawa, O.; Banno, H. *Eur. Appl., to Takeda Pharmaceutical Company Limited, EP 1661898A1*, **2006**
(145) Okamura, N.; Habay, S. A.; Zeng, J.; Chamberlin, A. R.; Reinscheid, R. K. *J. Pharmacol. Exp. Ther.* **2008**, *325*, 893.

(146) Garvey, D., S.; Larosa, G., J.; Greenwood, J., Robert; Brewer, M., L.; Quach, T.; Cote, J., B.; Berman, J. *Int. Appl., to Bikam Pharmaceuticals Inc., WO 2010/147653 A1*, **2010**
(147) Robinson, S. P.; Sheikh, N. S.; Baxter, C. A.; Coldham, I. *Tetrahedron Lett.* **2010**, *51*, 3642.
(148) Chu, D. T. W.; Nordeen, C. W.; Hardy, D. J.; Swanson, R. N.; Giardina, W. J.; Pernet, A. G.; Plattner, J. J. *J. Med. Chem.* **1991**, *34*, 168.
(149) Ognyanov, V. I.; Balan, C.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y.-X.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2006**, *49*, 3719.
(150) Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 4177.
(151) Maity, P.; Konig, B. *Org. Lett.* **2008**, *10*, 1473.
(152) Reider, P. J. *CHIMEA* **1997**, *51*, 306.
(153) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823.
(154) Andersson, H.; Banchelin, T. S.-L.; Das, S.; Gustafsson, M.; Olsson, R.; Almqvist, F. *Org. Lett.* **2010**, *12*, 284.
(155) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279.
(156) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2007**, *10*, 329.
(157) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236.
(158) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem. Int. Ed* **2013**, *52*, 1705.
(159) Karppanen, E. J.; Koskinen, A. M. P. *Molecules* **2010**, *15*, 6512.
(160) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511.
(161) Jamison, T. F.; Lubell, W. D.; Dener, J. M.; Krisché, M. J.; Rapoport, H. *Org. Synth.* **1993**, *71*, 220.
(162) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.
(163) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317.
(164) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229.
(165) Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532.
(166) Goldsmith, P.; Hancox, T.; Hudson, N.; Pegg, N.; Kulagowski, J.; Nadin, A.; Price, S. *Int. Appl., to Hoffman La Roche, WO 200953716*, **2009**
(167) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653.
(168) Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754.
(169) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825.
(170) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325.
(171) Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116.
(172) Newsome, S. *MChem. dissertation, University of York,* **2012**
(173) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749.
(174) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed* **2007**, *46*, 2768.
(175) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
(176) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
(177) Batsanov, A. S.; Grosjean, C.; Schütz, T.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 6276.

(178) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369.
(179) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.
(180) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.
(181) Liu, Y.; Wang, J.; Li, H.; Wu, J.; Feng, G.; Dai, W.-M. *Synlett* **2010**, 2184.
(182) Cumming, J.; Wellington Faull, A.; Waterson, D. *US. Appl., to AstraZeneca AB, US 2010/0152197A1*, **2010**
(183) Trapella, C.; Pela, M.; Del Zoppo, L.; Calo, G.; Camarda, V.; Ruzza, C.; Cavazzini, A.; Costa, V.; Bertolasi, V.; Reinscheid, R. K.; Salvadori, S.; Guerrini, R. *J. Med. Chem.* **2011**, *54*, 2738.
(184) Obiedzinski, M. *MSc. dissertation, University of York*, **2009**
(185) Taylor, R. R. R.; Twin, H. C.; Wen, W. W.; Mallot, R. J.; Lough, A. J.; Gray-Owen, S. D.; Batey, R. A. *Tetrahedron* **2010**, *66*, 3370.
(186) Gawley, R. E.; Eddings, D. B.; Santiago, M.; Vicic, D. A. *Org. Biomol. Chem.* **2006**, *4*, 4285.
(187) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.
(188) Chambournier, G.; Gawley, R. E. *Org. Lett.* **2000**, *2*, 1561.
(189) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.
(190) Warshawsky, A. M.; Patel, M. V.; Chen, T.-M. *J. Org. Chem.* **1997**, *62*, 6439.
(191) Opalka, C. J.; Dambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766.
(192) Wang, H.-L.; Katon, J.; Balan, C.; Bannon, A. W.; Bernard, C.; Doherty, E. M.; Dominguez, C.; Gavva, N. R.; Gore, V.; Ma, V.; Nishimura, N.; Surapaneni, S.; Tang, P.; Tamir, R.; Thiel, O.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2007**, *50*, 3528.
(193) Kurz, J. L.; El-Nasr, M. M. S. *J. Am. Chem. Soc.* **1982**, *104*, 5823.
(194) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673.
(195) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337.
(196) Liniger, M.; Estermann, K.; Altmann, K.-H. *J. Org. Chem.* **2013**, *78*, 11066.
(197) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed* **2007**, *46*, 7491.
(198) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531.
(199) Johansson, Magnus J.; Schwartz, Lennart O.; Amedjkouh, M.; Kann, Nina C. *Eur. J. Org. Chem.* **2004**, *2004*, 1894.
(200) Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336.
(201) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833.
(202) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem. Int. Ed* **2008**, *47*, 6367.
(203) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789.
(204) Germain, A. R.; Bruggemeyer, D. M.; Zhu, J.; Genet, C.; O'Brien, P.; Porco, J. A. *J. Org. Chem.* **2011**, *76*, 2577.
(205) O'Brien, P. *Chem. Commun.* **2008**, 655.
(206) http://pipeline.corante.com/archives/2010/06/16/sparteine_and_other_fine_chemical_shortages.php

(207) www.chemistry-blog.com/2010/06/11/where-has-all-the-sparteine-gone/
(208) Marrière, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121.
(209) Scheiber, P.; Nemes, P. *Liebigs Ann.* **1994**, *1994*, 1033.
(210) Sternbach, L. H.; Kaiser, S. *J. Am. Chem. Soc.* **1952**, *74*, 2215.
(211) Leonard, N. J.; Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457.
(212) R. Harrison, J.; O'Brien, P.; W. Porter, D.; M. Smith, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, *0*, 3623.
(213) Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977.
(214) Porter, D. *PhD Thesis, University of York,* **2000**
(215) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316.
(216) Abu Zarga, M. H.; Shamma, M. *Tetrahedron Lett.* **1980**, *21*, 3739.
(217) Dumont, R.; Brossi, A.; Silverton, J. V. *J. Org. Chem.* **1986**, *51*, 2515.
(218) Schlenk, W. *Angew. Chem. Int. Ed* **1965**, *4*, 139.
(219) Toda, F.; Tanaka, K.; Ueda, H.; Oshima, T. *J. Chem. Soc., Chem. Commun.* **1983**, 743.
(220) Canipa, S. *PhD Thesis, University of York,* **2008**
(221) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
(222) Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron: Asymmetry* **1990**, *1*, 147.
(223) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903.
(224) Ledoux, S.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1999**, *40*, 9019.
(225) Hermet, J.-P. R.; Viterisi, A.; Wright, J. M.; McGrath, M. J.; O'Brien, P.; Whitwood, A. C.; Gilday, J. *Org. Biomol. Chem.* **2007**, *5*, 3614.
(226) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193.
(227) Gray, D.; Gallagher, T. *Angew. Chem. Int. Ed* **2006**, *45*, 2419.
(228) Breuning, M.; Steiner, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1978.
(229) Breuning, M.; Steiner, M.; Mehler, C.; Paasche, A.; Hein, D. *J. Org. Chem.* **2009**, *74*, 1407.
(230) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem.* **1998**, *63*, 3492.
(231) Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron Lett.* **2002**, *43*, 7155.
(232) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron Lett.* **2005**, *46*, 7121.
(233) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Org. Lett.* **2004**, *6*, 493.
(234) Goldberg, N. N.; Perfetti, B. M.; Levine, R. *J. Am. Chem. Soc.* **1953**, *75*, 3843.
(235) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391.
(236) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem. Int. Ed* **2004**, *43*, 6528.
(237) Rome, K.; Hobday, K. *Unpublished Results*
(238) DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621.
(239) Gray, D.; Concellón, C.; Gallagher, T. *J. Org. Chem.* **2004**, *69*, 4849.
(240) Enders, D.; Wiedemann, J. *Liebigs Ann.* **1997**, *1997*, 699.
(241) Baenziger, M.; Gobbi, L.; Riss, B. P.; Schaefer, F.; Vaupel, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2231.
(242) O'Brien, P.; Porter, D. W.; Smith, N. M. *Synlett* **2000**, 1336.

(243) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.
(244) Breuning, M.; Steiner, M. *Synthesis* **2006**, 1386.
(245) Blot, J.; Bardou, A.; Bellec, C.; Fargeau-Bellassoued, M. C.; Célérier, J. P.; Lhommet, G.; Gardette, D.; Gramain, J. C. *Tetrahedron Lett.* **1997**, *38*, 8511.
(246) David, O.; Calvet, S.; Chau, F.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *J. Org. Chem.* **2004**, *69*, 2888.
(247) Toy, M. S.; Price, C. C. *J. Am. Chem. Soc.* **1960**, *82*, 2613.
(248) Callens, R.; Gire, R.; Pousset, C. *Int. Appl., to Solvay, WO 2009/080708 A1*, **2009**
(249) Humljan, J.; Kotnik, M.; Contreras-Martel, C.; Blanot, D.; Urleb, U.; Dessen, A. a.; Šolmajer, T.; Gobec, S. *J. Med. Chem.* **2008**, *51*, 7486.
(250) Toone, E. J.; Jones, J. B. *Can. J. Chem.* **1987**, *65*, 2722.
(251) Chung, H.-k.; Kim, H.-w.; Chung, K.-H. *Heterocycles* **1999**, *51*, 2983.
(252) Liljeblad, A.; Kavenius, H.-M.; Tähtinen, P.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2007**, *18*, 181.
(253) Ghanem, A.; Aboul-Enein, H. Y. *Chirality* **2005**, *17*, 1.
(254) Pousset, C.; Callens, R.; Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3407.
(255) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(256) Straathof, A. J. J.; Jongejan, J. A. *Enzyme Microb. Technol.* **1997**, *21*, 559.
(257) Haggis, G. A.; Owen, L. N. *J. Chem. Soc.* **1953**, 399.
(258) Fray, A. H.; Augeri, D. J.; Kleinman, E. F. *J. Org. Chem.* **1988**, *53*, 896.
(259) Gelmi, M. L.; Cattaneo, C.; Pellegrino, S.; Clerici, F.; Montali, M.; Martini, C. *J. Org. Chem.* **2007**, *72*, 9811.
(260) Yen, C.-F.; Liao, C.-C. *Angew. Chem. Int. Ed* **2002**, *41*, 4090.
(261) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246.
(262) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed* **2005**, *44*, 1706.
(263) Davoust, M.; Briere, J.-F.; Metzner, P. *Org. Biomol. Chem.* **2006**, *4*, 3048.
(264) Madelaine, C.; Valerio, V.; Maulide, N. *Angew. Chem. Int. Ed* **2010**, *49*, 1583.
(265) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281.
(266) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726.
(267) Carpino, L. A.; Mansour, E. M. E.; Cheng, C. H.; Williams, J. R.; MacDonald, R.; Knapczyk, J.; Carman, M.; Lopusinski, A. *J. Org. Chem.* **1983**, *48*, 661.
(268) Herrin, T. R.; Pauvlik, J. M.; Schuber, E. V.; Geiszler, A. O. *J. Med. Chem.* **1975**, *18*, 1216.
(269) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283.
(270) Vechorkin, O.; Proust, V. r.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756.
(271) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920.
(272) Price, M. D.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2002**, *67*, 7769.
(273) Lee, J. H.; Choi, Y. H.; Lim, Y. J.; Lee, B. S.; Chi, D. Y.; Jin, C. *Bioorg. Med. Chem.* **2007**, *15*, 3499.
(274) Yamanaka, H.; Annaka, M.; Kondo, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 4309.
(275) O'Ferrall, R. A. M.; Murray, B. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2461.
(276) Fürstner, A.; Kennedy, J. W. J. *Chem. Eur. J.* **2006**, *12*, 7398.
(277) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394.

(278) Harington, C. R.; Moggridge, R. C. G. *J. Chem. Soc.* **1940**, 706.
(279) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613.
(280) Dummel, R. J.; Wrinkle, W.; Mosher, H. S. *J. Am. Chem. Soc.* **1956**, *78*, 1936.
(281) Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.
(282) Beckett, A. H.; Lingard, R. G.; Theobald, A. E. E. *J. Med. Chem.* **1969**, *12*, 563.
(283) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2423.
(284) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.
(285) Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995.
(286) Szabó, A.; Hermecz, I. *J. Org. Chem.* **2001**, *66*, 7219.
(287) Csuk, R.; Höring, U.; Schaade, M. *Tetrahedron* **1996**, *52*, 9759.