“High” Temperature Asymmetric Lithiation of *N*-Boc Heterocycles: Synthesis of Tetra-Substituted Pyrrolidines

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Abstract

This thesis describes the study of new methodologies for the asymmetric synthesis of *N*-Boc heterocycles using lithiation chemistry, with the main focus on *N*-Boc pyrrolidine.

The "high" temperature asymmetric lithiation-trapping of five-membered heterocycles *N*-Boc pyrrolidine and *N*-Boc imidazolidine and six-membered heterocycles *N*-Boc piperidine and *N*-Boc piperazine is described in Chapter Two. It was found that lithiated *N*-Boc pyrrolidine is configurationally stable for 1 hour at –40 °C and –30 °C giving high ers (90:10 er). With *N*-Boc imidazolidine, yields above 50% can be achieved using THF as solvent and are supported by VT ^{1}H NMR spectroscopy studies as well as ReactIR™ spectroscopy studies.

In Chapter Three, attempts towards the elucidation of the instability of α-amino sulfoxides are described. The synthetic strategies planned to clarify the possible mechanism causing the elimination of the sulfoxide group were unsuccessful and ultimately, we were unable to understand which process was at the basis of the elimination. As part of these studies, the development of the asymmetric lithiation-trapping of 4-phenyl *N*-Boc pyrrolidine is also described.

Chapter Four describes the development of the asymmetric synthesis of α,α' tri- and tetra-substituted pyrrolidines. The use of ReactIR™ spectroscopy experiments was fundamental for the studies into the interconversion of *N*-Boc rotamers and to achieve good yields of the trapped products. An interesting match/mismatch mechanism for the formation of tri-substituted pyrrolidines is shown, which can give ers of >99:1 er. Finally, the synthesis of several new tetra-substituted pyrrolidines in 70:30-91:9 dr is presented.

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Author's Declaration

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

Giacomo Gelardi

Chapter One: Introduction

Pyrrolidines are a widespread motif in both natural products and pharmaceutically active compounds. An example of a natural compound showing a substituted pyrrolidine core is (–)-kainic acid, which is an agonist for a subtype of glutamate receptors ultimately involved in neuronal apoptosis.[1] The pyrrolidine ring also appears in important pharmaceutical products such as Pfizer's anti-migraine drug eletriptan (Relpax®)[2] and (+)-RP 66803 a cholecystokinin antagonist (Figure 1.1).[3] Different synthetic strategies have been employed to access these substituted pyrrolidines. However, the asymmetric lithiation-trapping methodology represents one of the most efficient and straightforward transformations available to synthetic chemists. The importance of the lithiation chemistry is shown by the possibility of introducing a stereogenic centre using a single synthetic transformation.

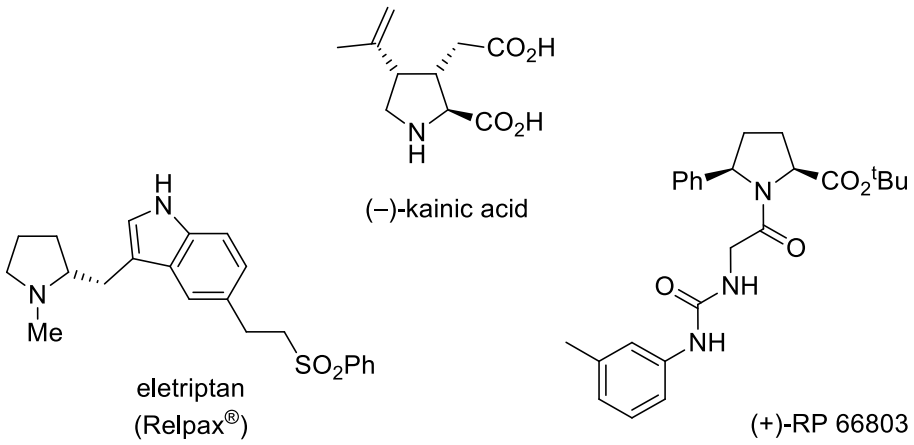
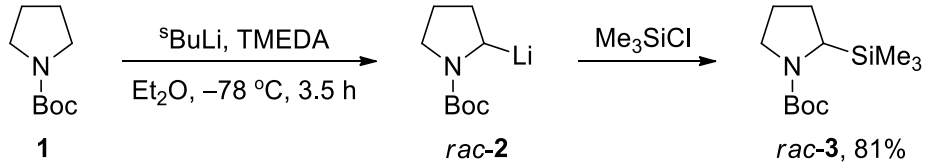


Figure 1.1

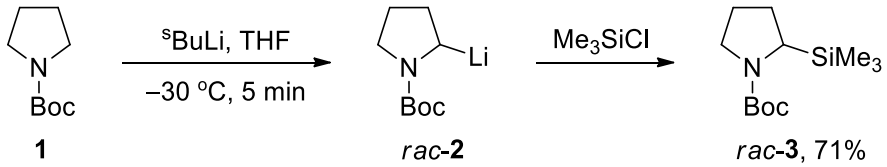
1.1 Brief Overview of Lithiation-Trapping of *N*-Boc Heterocycles

In 1989, Beak and Lee reported that α-substituted nitrogen heterocycles could be easily accessed *via* lithiation chemistry of *N*-Boc protected substrates.[4] They described the lithiation of *N*-Boc pyrrolidine **1** using *s*-BuLi and TMEDA in Et_2O at –78 °C for 3.5 hours which generated lithiated intermediate *rac*-**2**. Trapping with Me_3SiCl gave silyl pyrrolidine *rac*-**3** in 81% yield (Scheme 1.1).



Scheme 1.1

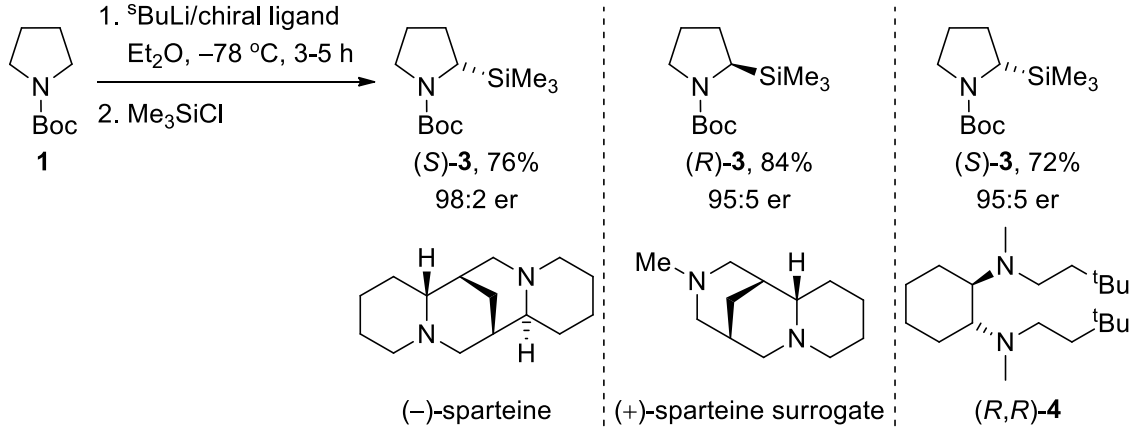
More than a decade later, our group discovered that the racemic lithiation-trapping methodology could also be successfully performed at –30 °C without TMEDA, if THF was used as the solvent.[5] Lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi in THF at –30 °C and trapping with Me_3SiCl afforded *rac*-**3** in 71% yield (Scheme 1.2). The lithiation-trapping chemistry has been also developed on six-membered *N*-Boc heterocycles such as *N*-Boc piperidine[4,6,7] and *N*-Boc piperazine.[8,9]



Scheme 1.2

The racemic lithiation-trapping protocol was soon followed by the development of asymmetric lithiation-trapping methodology with the employment of chiral ligands. Beak and Kerrick showed that the use of (–)-sparteine in the lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and trapping with Me_3SiCl gave silyl pyrrolidine (*S*)-**3** (76% yield) in 98:2 er (Scheme 1.3).[10,11] The key intermediate was a configurationally stable chiral organolithium species. Chiral ligands other than (–)-sparteine were also developed. Our group first presented the (+)-sparteine surrogate and subsequently diamine (*R*,*R*)-**4**, which could afford a 95:5 er of silyl pyrrolidine (*R*)-**3** and (*S*)-**3**

respectively.[12,13] These methodologies with related synthetic applications have also been independently reviewed by Beak and Maes.[14,15]

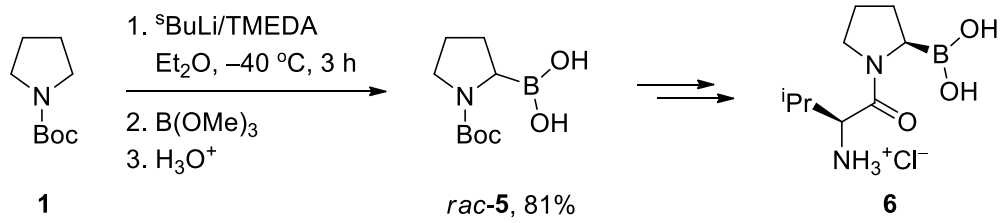


Scheme 1.3

These results shown in this section are just a brief overview of the lithiation-trapping methodology of *N*-Boc heterocycles. More details are presented at the relevant points in later chapters.

1.2 Synthetic Applications of *N*-Boc α-Lithiation Methodology

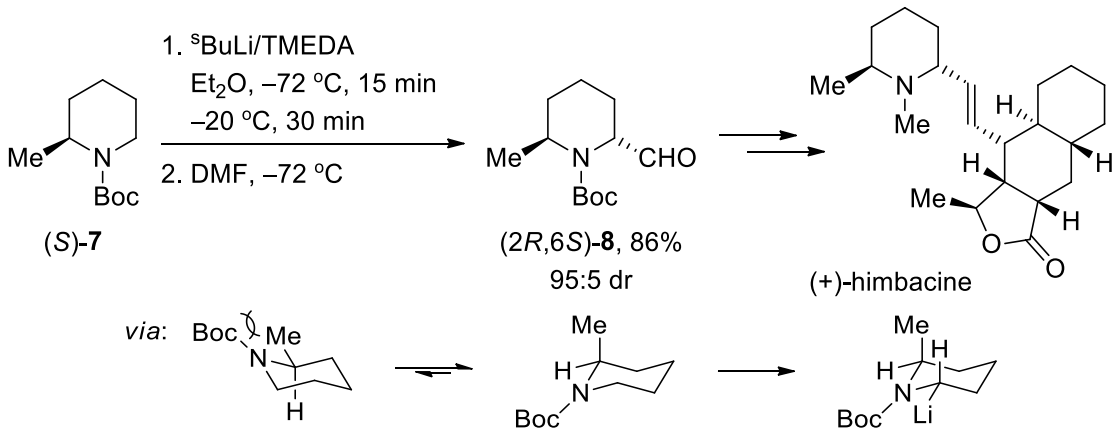
There are numerous applications of Beak's *N*-Boc α-lithiation-trapping methodology. In this section, some selected examples are presented with a focus on the synthetic applications. Researchers at Boehringer Ingelheim Pharmaceuticals described the synthesis of dipeptides based on proline boronic acids, such as **6**, which could have potential applications in the treatment of human immunodeficiency virus.[16] The common intermediate in the synthetic pathway, boronic pyrrolidine *rac*-**5**, was accessed in 81% yield by lithiating *N*-Boc pyrrolidine **1** with *s*-BuLi and TMEDA in Et_2O at –40 °C for 3 hours and trapping with trimethyl borate (Scheme 1.4).



1 *rac*-**5**, 81% **6**

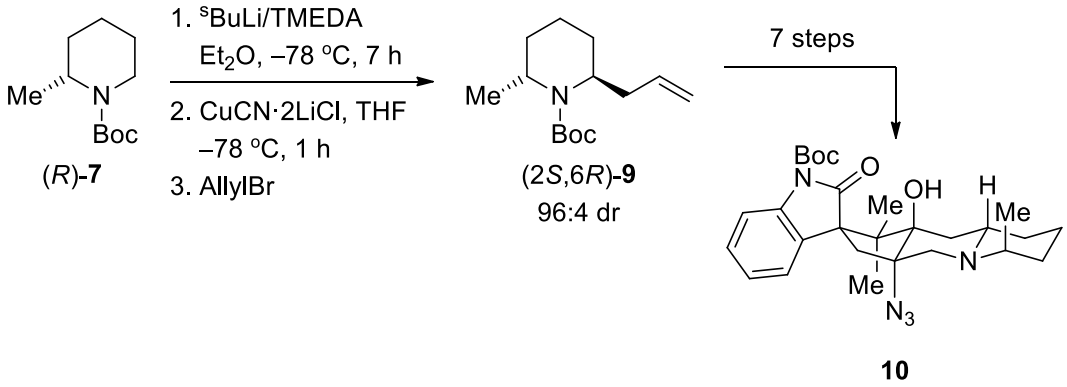
Scheme 1.4

The use of the lithiation chemistry has been applied to other *N*-Boc heterocycles. Chackalamannil *et al*. lithiated 2-methyl *N*-Boc piperidine (*S*)-**7** with *s*-BuLi and TMEDA in Et_2O and trapped with DMF to synthesise (2*R*,6*S*)-**8** in 86% yield and 95:5 dr (Scheme 1.5).[17] The *trans* geometry between methyl group and the aldehyde was due to allylic $A_{1,3}$ strain[18] which forced the α-substituent to be axial. Subsequent equatorial lithiation gave the observed relative stereochemistry.[7] Aldehyde (2*R*,6*S*)-**8** was further processed to ultimately give (+)-himbacine, studied for the treatment of Alzheimer's disease.



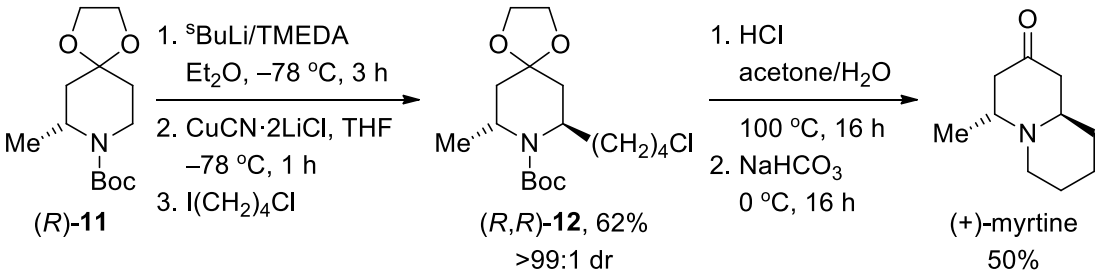
Scheme 1.5

The same substrate, but the opposite enantiomer, (*R*)-**7**, was used by Sorensen to form allyl derivative (2*R*,6*S*)-**9** (96:4 dr), in synthetic studies towards the citrinadins core architecture **10** (Scheme 1.6).[19] In this case, the lithiation of (*R*)-**7** with *s*-BuLi/TMEDA in Et_2O was followed by transmetallation to an organocuprate intermediate with a mixture of CuCN·2LiCl. Final trapping with allyl bromide gave (2*R*,6*S*)-**9**, with the electrophile introduced *trans* to the methyl group. Allyl (2*R*,6*S*)-**9** was further processed without purification and the dr was determined in subsequent products.



Scheme 1.6

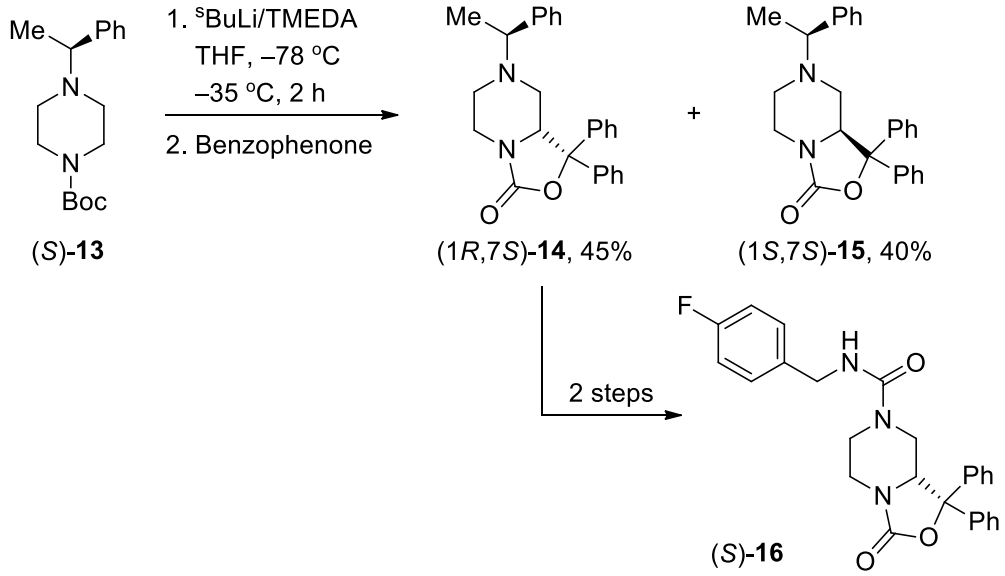
A similar lithiation-copper transmetallation sequence was employed in a synthesis of the natural alkaloid (+)-myrtine.[20] Lithiation-transmetallation of ketal *N*-Boc piperidine (*R*)-**11** and trapping of the organocuprate intermediate with 1-chloro-4-iodobutane gave piperidine (*R,R*)-**12** in 62% and >99:1 dr, which was then deprotected and cyclised to (+)-myrtine in 50% yield (Scheme 1.7)



Scheme 1.7

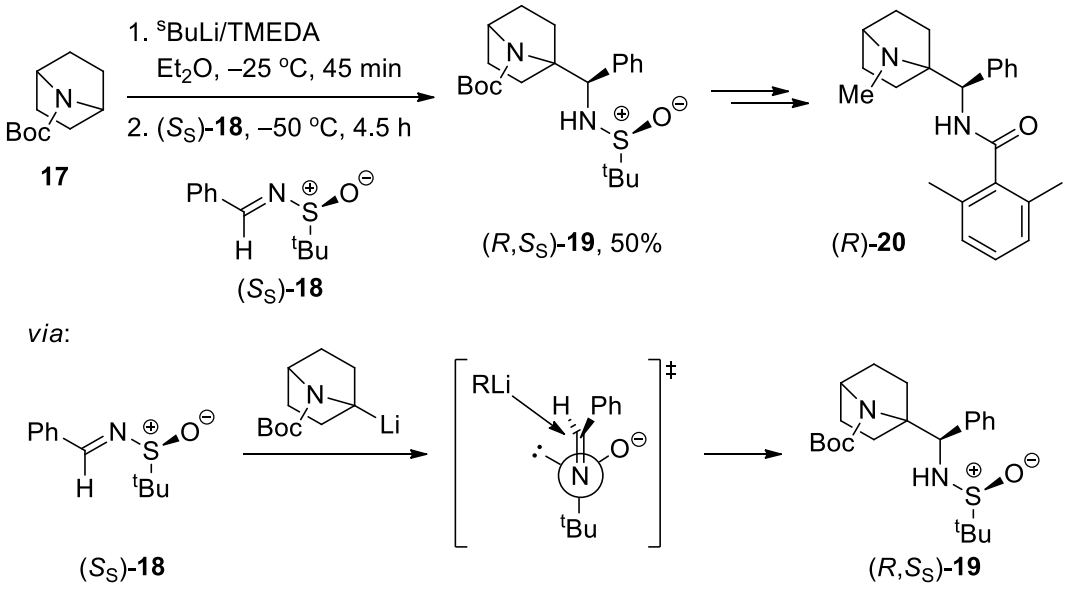
Racemic lithiation-trapping was applied to *N*-Boc piperazine (*S*)-**13** by Guerrini *et al*. in the synthesis of (*S*)-**16**, an antagonist of neuropeptide S receptor (NPSR) which is involved in the regulation of several functions in the central nervous system.[21] Lithiation of *N*-Boc piperazine (*S*)-**13** with *s*-BuLi and TMEDA in THF and trapping with benzophenone gave two separable diastereoisomers (1*R*,7*S*)-**14** (45% yield) and

(1*S*,7*S*)-**15** (40% yield) (Scheme 1.8). Since the stereogenic centre was far from the lithiation position, there was little diastereoselectivity in this reaction.



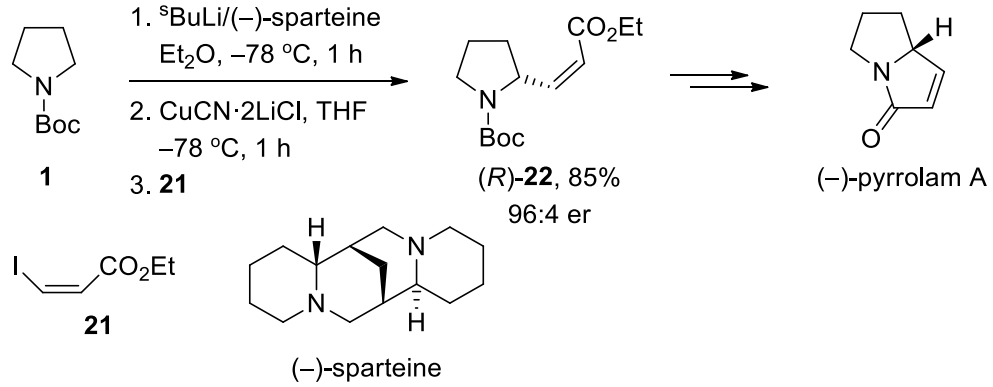
Scheme 1.8

Interestingly, the lithiation-trapping procedure has been successfully employed with an azabicyclic substrate by researchers at AstraZeneca in the synthesis of (*R*)-**20**, a GlyT1 uptake receptor inhibitor.[22] *N*-Boc azabicycle **17** was lithiated with *s*-BuLi and TMEDA at –25 °C and then trapped with sulfinamide (S_S)-**18** to give (R,S_S)-**19** (50% yield) (Scheme 1.9). In this case, diastereoselective addition of the organolithium to the imine was controlled by the sulfinamide chiral auxiliary. Further elaboration of (R,S_S)-**19** formed the active compound, (*R*)-**20**.



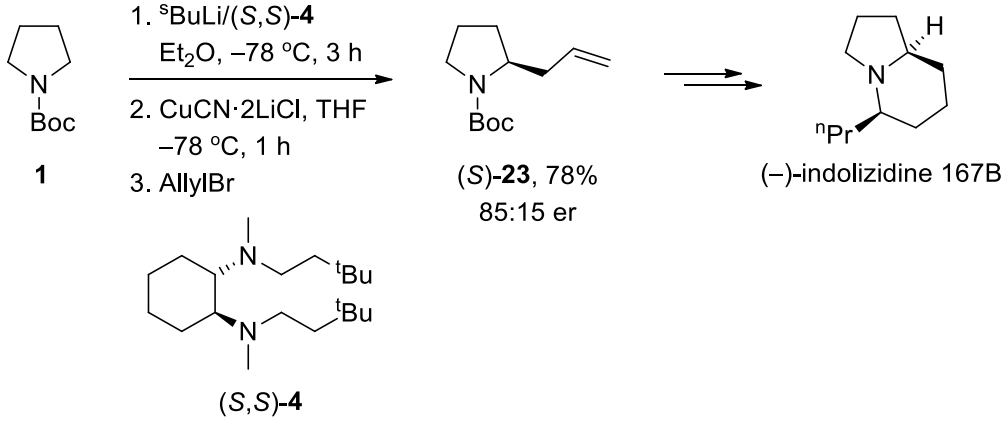
Scheme 1.9

The asymmetric lithiation-trapping methodology represents an attractive alternative to the racemic protocol for the total synthesis of natural products. As an example, the Dieter group reported the asymmetric lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and (–)-sparteine followed by CuCN·2LiCl transmetallation and trapping with ethyl 3-iodopropenoate **21**. Vinyl pyrrolidine (*R*)-**22** was isolated in 85% yield and 96:4 er (Scheme 1.10). Subsequent deprotection and cyclisation gave (–)-pyrrolam A.[23] A range of bicyclic alkaloids were also synthesised using a similar procedure, as described by the same group.[24]



Scheme 1.10

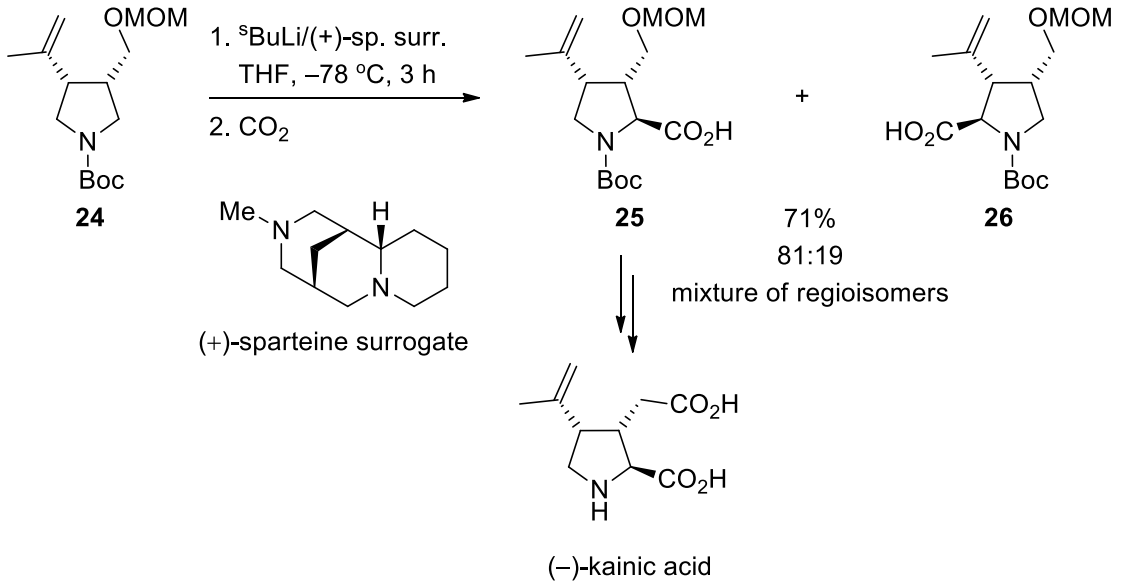
The lithiation-allylation procedure was used by our group in the synthesis of alkaloid (–)-indolizidine 167B.[13] Allyl intermediate (*S*)-**23** was obtained in 78% yield and 85:15 er, by treatment of *N*-Boc pyrrolidine **1** with *s*-BuLi and chiral diamine (*S*,*S*)-**4** at –78 °C followed by lithium-copper transmetallation and allylation (Scheme 1.11).



Scheme 1.11

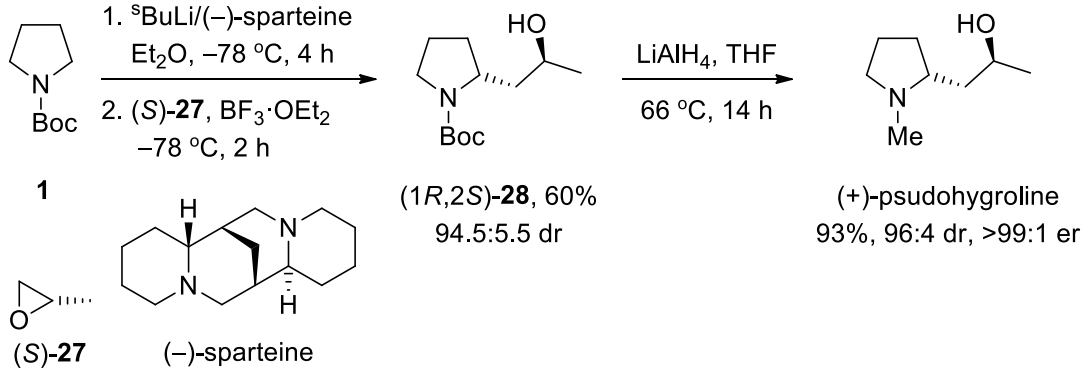
Another interesting natural product, with a poly-substituted pyrrolidine core, is (–)-kainic acid.[25] Fukuyama showed that asymmetric lithiation of substituted *N*-Boc

pyrrolidine **24** with *s*-BuLi and the (+)-sparteine surrogate followed by trapping with CO_2 gave an 81:19 mixture of regioisomers **25** and **26** in 71% yield (Scheme 1.12).[1] Further processing of **25** subsequently gave (–)-kainic acid.



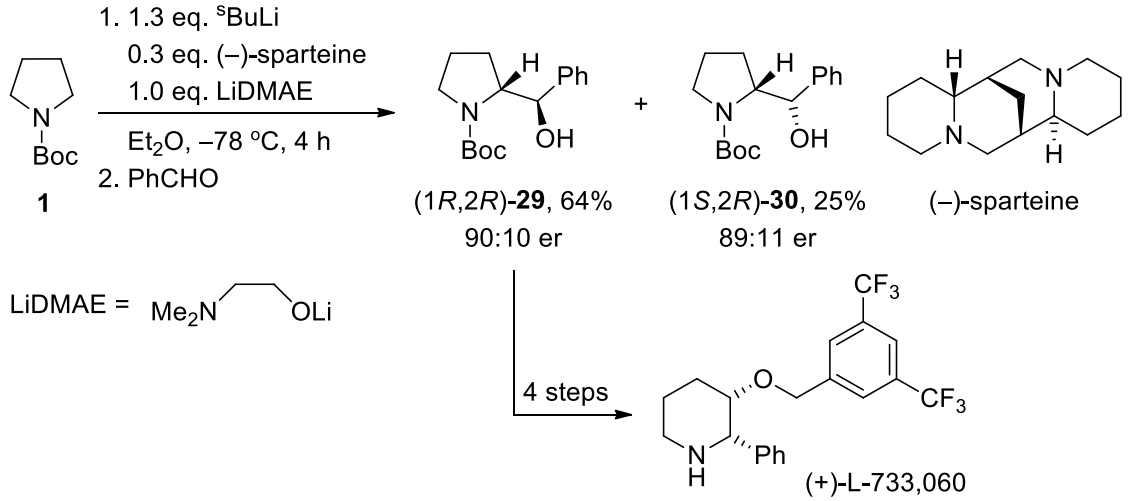
Scheme 1.12

More recently, Altmann *et al*. reported the synthesis of the hygrolines and pseudohygrolines *via* the asymmetric lithiation-trapping methodology by combining chiral ligands and chiral epoxides.[26] As an example, lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and (–)-sparteine and trapping with propylene oxide (*S*)-**27** afforded alcohol (1*R*,2*S*)-**28** (60% yield) in 94.5:5.5 dr. Subsequent reduction of the Boc group with $LiAlH_4$ gave (+)-pseudohygroline in 93% yield, 96:4 dr and >99:1 er (Scheme 1.13). The use of epoxides as electrophiles in the lithiation-trapping of *N*-Boc pyrrolidine **1** was first revealed by Mani and Deng.[27]



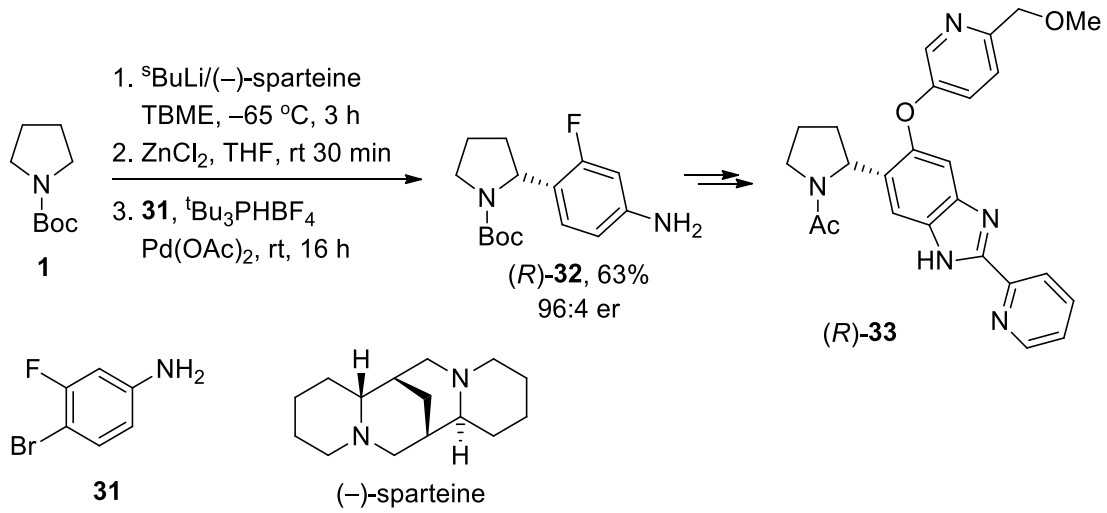
Scheme 1.13

In 2009, our group described the formation of piperidine heterocycles *via* a ring expansion procedure from α-substituted pyrrolidines.[28] These pyrrolidine intermediates were attained using a lithiation-trapping methodology which used 0.3 eq. of (–)-sparteine. Hence, *N*-Boc pyrrolidine **1** was lithiated with *s*-BuLi and (–)-sparteine (0.3 eq.) in the presence of an additive (LiDMAE). Trapping with PhCHO gave alcohols (1*R*,2*R*)-**29** (90:10 er) and (1*S*,2*R*)-**30** (89:11 er) in 64% and 25% yield respectively (Scheme 1.14). Alcohol (1*R*,2*R*)-**29** was then converted into piperidine (+)-L-733,060 which is a potent substance P-NK1 receptor antagonist.



Scheme 1.14

Campos at Merck was the first to show that the lithiation-trapping chemistry could be useful to access α-arylated products such as glucokinase activator (*R*)-**33**.[29] The synthesis of (*R*)-**33** was achieved by elaboration of arylated pyrrolidine (*R*)-**32**. In this case, the lithiation of *N*-Boc pyrrolidine **1** was performed on a 7.2 mol scale. Pyrrolidine (*R*)-**32** (63% yield and 96:4 er) was formed using the lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and (–)-sparteine in TBME, followed by treatment with $ZnCl_2$ and Pd-Negishi catalysed reaction with bromo aniline **31** (Scheme 1.15).



Scheme 1.15

This lithiation-transmetallation-Negishi coupling sequence also allowed the total synthesis of natural products such as (*S*)-nicotine, (*R*)-crispine A and (*R*)-maackiamine, as shown by our group in collaboration with Campos in a subsequent report (Figure 1.2).[30]

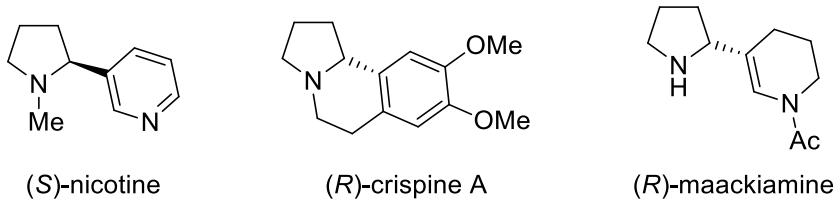
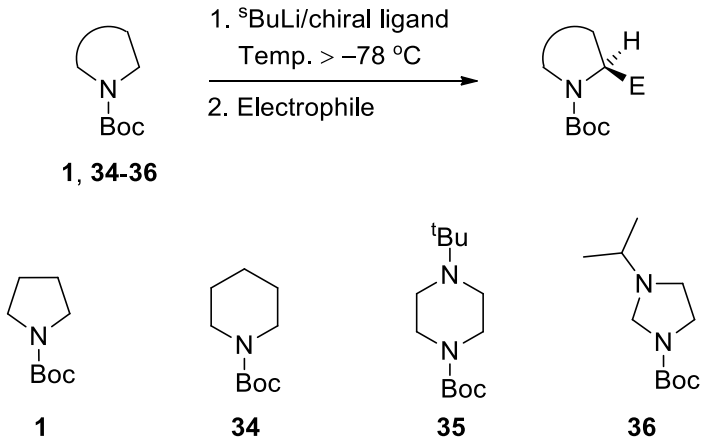


Figure 1.2

The examples reviewed in this section are not an exhaustive list of the synthetic applications of the lithiation-trapping methodology. However, the versatility of the lithiation chemistry is demonstrated through the selection of representative examples. It was shown that lithiation-trapping methodology has been successfully used by pharmaceutical companies for the synthesis of potential drug compounds. In one case, it has been also employed in a large-scale reaction by process chemists at Merck. Moreover, several academic groups have applied the lithiation chemistry in the total synthesis of natural products.

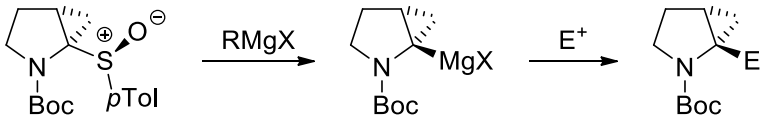
1.3 Outline of the Project

In the first part of the project (Chapter Two), we planned to explore the asymmetric lithiation-trapping of *N*-Boc heterocycles at temperatures > –78 °C. In particular, our interest was to discover the effect of "high" temperatures on the enantioselective outcome of the asymmetric lithiation methodology. The initial investigation was developed with *N*-Boc pyrrolidine **1** and then extended to *N*-Boc piperidine **34**, *N*-Boc piperazine **35** and *N*-Boc imidazolidine **36** (Scheme 1.16).



Scheme 1.16

One of the major limitations of the asymmetric α-lithiation and electrophilic trapping methodology of *N*-Boc heterocycles is the impossibility of accessing enantiopure products. Typically, enantioselectivities of ≤95:5 er are obtained with this chemistry. To overcome this limitation, our group has put some effort into the synthesis of stable α-amino sulfoxides such as *anti*-(*R*,*R*,S_S)-**37**, with the aim to access *N*-Boc heterocycles **39** in >99:1 er using asymmetric lithiation chemistry.[31] The enantiopure sulfoxide *anti*-(*R*,*R*,S_S)-**37** would act as a precursor for chiral Grignard reagent (*R*,*R*)-**38** *via* sulfoxide-magnesium exchange (Scheme 1.17).



Scheme 1.17

In order to explore other *N*-Boc α-amino sulfoxides, the attempted syntheses of sulfoxides **40**-**43** are described in Chapter Three (Figure 1.3).

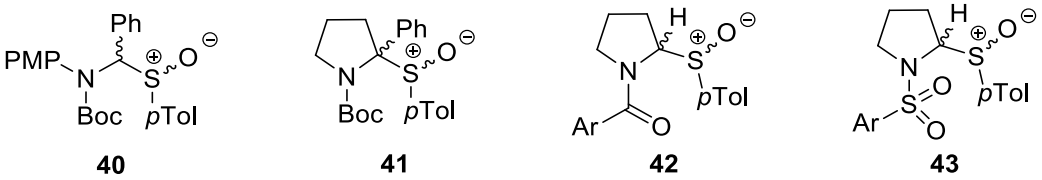
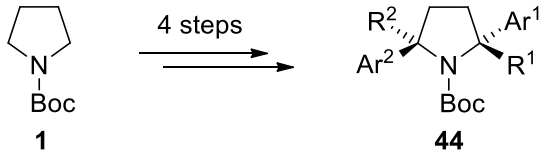


Figure 1.3

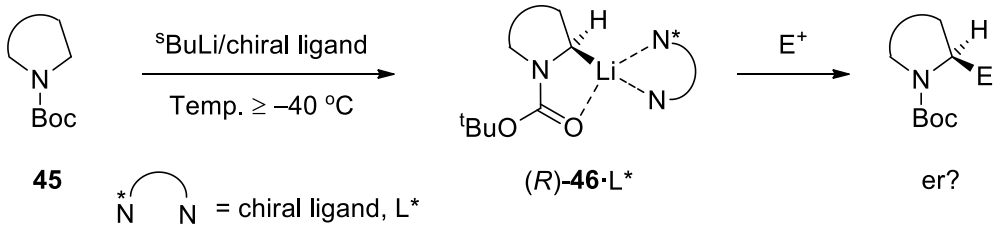
Ultimately, we planned to use the asymmetric lithiation-trapping methodology for the synthesis of α,α'-tetra-substituted pyrrolidines **44**. We proposed that such compounds could be accessed *via* two sequential asymmetric lithiation-Negishi coupling reactions and benzylic lithiation steps (Scheme 1.18). ReactIR™ spectroscopy studies were planned in order to optimise the lithiation-trapping of di- and tri-substituted pyrrolidines.



Scheme 1.18

Chapter Two: Asymmetric Synthesis of *N*-Boc Heterocycles at Temperatures Above –78 °C

An exploration of the asymmetric lithiation of *N*-Boc heterocycles performed at temperatures above –78 °C will be presented in this chapter. The ultimate objective of this part of the project was to investigate whether the asymmetric lithiation could be performed successfully at temperatures ≥ –40 °C with high levels of enantioselectivity (Scheme 2.1). The selection of –40 °C as the lowest temperature in this study, was due to the fact that cooling down a process-scale reaction to temperatures below –40 °C vastly increases the energetic cost of the process.[32] Thus, temperatures of –78 °C could make the lithiation methodology unsuitable for use in process-scale reactions. In addition, higher temperatures might allow shorter lithiation times to be used and this could further reduce the energy cost and increase the sustainability of the process. Finally, the aim of this investigation was to find the highest temperature which could give products in high enantioselectivities, ideally ≥80:20 er, and good yields.



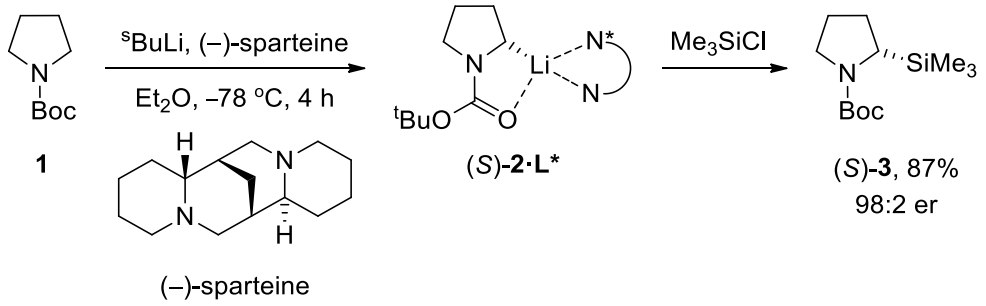
Scheme 2.1

2.1 Asymmetric Synthesis of *N*-Boc Pyrrolidines Using Organolithium Methodology

Enantioenriched α-substituted *N*-Boc pyrrolidines can be accessed using lithiation chemistry *via* two predominant mechanisms: asymmetric deprotonation and asymmetric substitution.

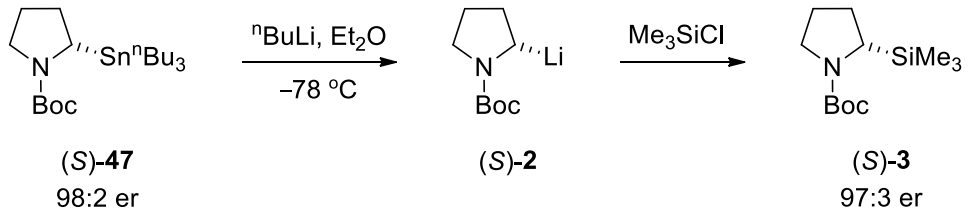
2.1.1 Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine 1

The conditions for the asymmetric lithiation of *N*-Boc pyrrolidine **1** were first reported by Beak and Kerrick in 1991[10] and then in full in 1994.[11] In their protocol, the lithiation of **1** was performed with *s*-BuLi and (–)-sparteine in Et_2O for 4 hours at –78 °C to give the configurationally stable lithiated intermediate (*S*)-**2**·L* (Scheme 2.2). Subsequent trapping with a range of electrophiles gave products in moderate to good yields (35-88%) and high enantioselectivity (79:21-98:2 er). For example, trapping with Me_3SiCl gave silylated product (*S*)-**3** in 87% yield and 98:2 er.



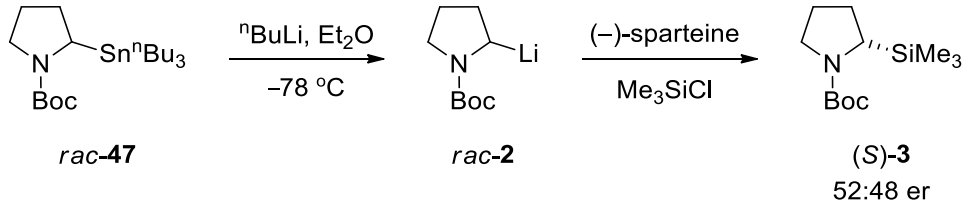
Scheme 2.2

The enantioselectivity of the lithiation originated from asymmetric deprotonation of *N*-Boc pyrrolidine **1**. This was proven with mechanistic studies using tin-lithium transmetallation experiments with stannyl pyrrolidines (*S*)-**47** and *rac*-**47**. With enantioenriched (*S*)-**47** (98:2 er), transmetallation with *n*-BuLi gave lithiated intermediate (*S*)-**2**, which was then trapped with Me_3SiCl to afford silylated pyrrolidine (*S*)-**3** in 97:3 er (Scheme 2.3).



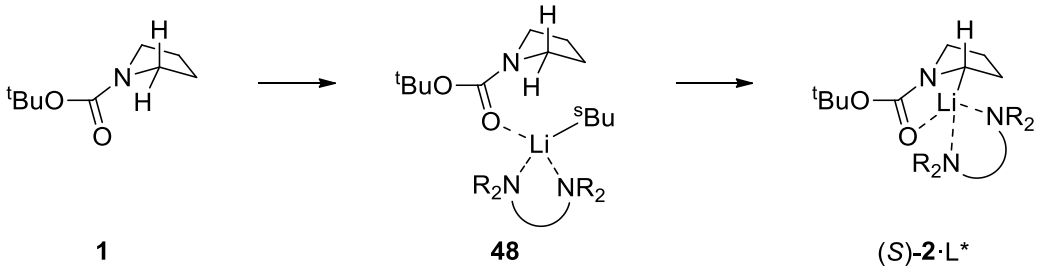
Scheme 2.3

In contrast, when the racemic stannane *rac*-**47** was treated with *n*-BuLi and then (–)-sparteine was added with the electrophile, trapped silylated product (*S*)-**3** was isolated almost as a racemate (52:48 er) (Scheme 2.4). This showed that (–)-sparteine did not affect the substitution step and the enantioselectivity of the reaction was established during the deprotonation.



Scheme 2.4

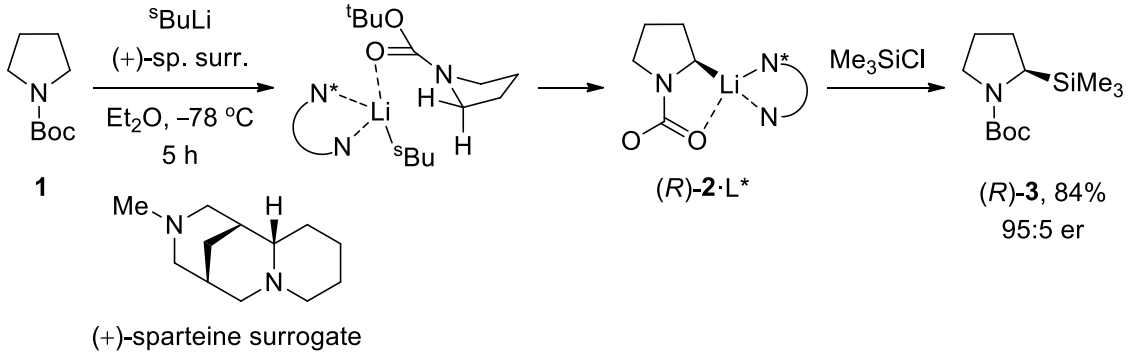
Kinetic studies carried out by Beak and Gallagher suggested that the lithiation reaction proceeds *via* the formation of a pre-lithiation complex **48**.[33] Thus, **48** is formed by coordination of the carbonyl oxygen of *N*-Boc pyrrolidine **48** with the chiral base complex, arising from *s*-BuLi and the chiral ligand (Scheme 2.5). In this example, the stereochemistry depicted is that obtained using (–)-sparteine. Subsequent deprotonation of the *pseudo* equatorial proton leads to lithiated intermediate (*S*)-**2**·L*.



Scheme 2.5

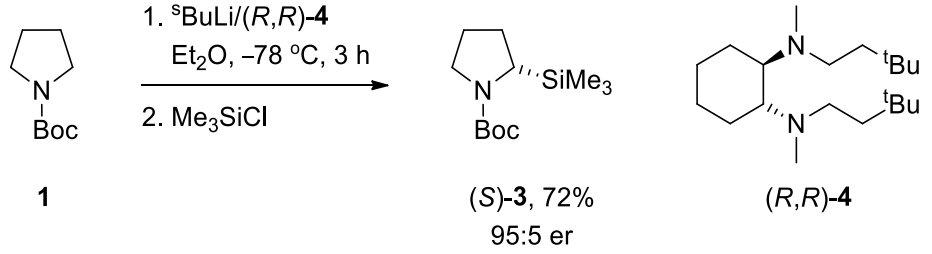
The opposite enantiomeric series could be successfully accessed with the use of a (+)-sparteine surrogate described by our group in 2002.[12] Deprotonation of *N*-Boc pyrrolidine **1** with *s*-BuLi and the (+)-sparteine surrogate in Et_2O at –78 °C for 5 hours

and trapping with Me_3SiCl gave silylated product (*R*)-**3** in 84% yield and 95:5 er (Scheme 2.6). This result showed that the (+)-sparteine surrogate was as effective as (–)-sparteine in the asymmetric lithiation of **1**, inducing high levels of enantioselectivity with the opposite sense of induction.



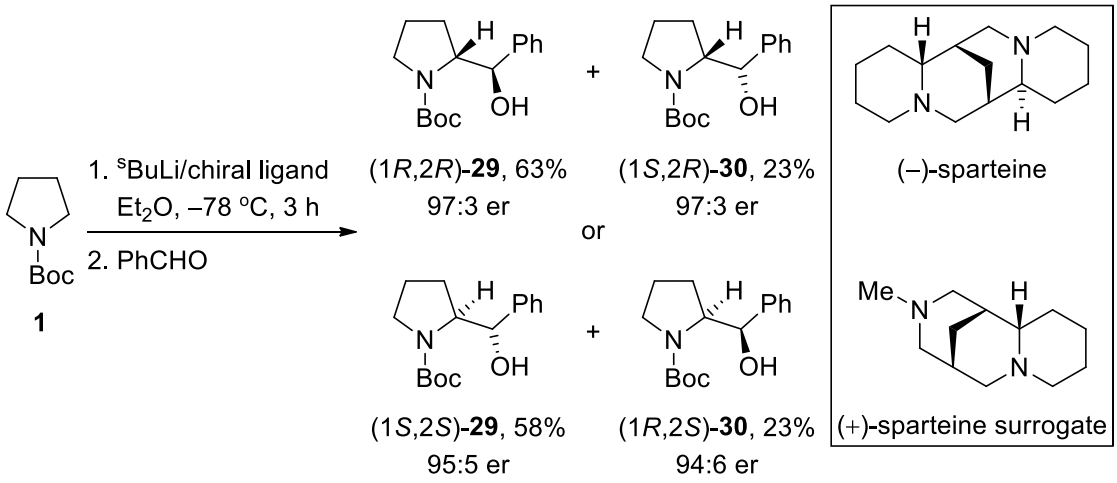
Scheme 2.6

In 2008, O'Brien and Stead reported the use of the cyclohexyl diamine chiral ligand (*R,R*)-**4**,[13] whose synthesis was developed by the Alexakis group.[34-36] The result in Scheme 2.7 showed that the use of (*R,R*)-**4** in the asymmetric lithiation of *N*-Boc pyrrolidine **1** was as effective as (–)-sparteine. In fact, trapping with Me_3SiCl gave (*S*)-**3** (72% yield) in high enantioselectivity (95:5 er).



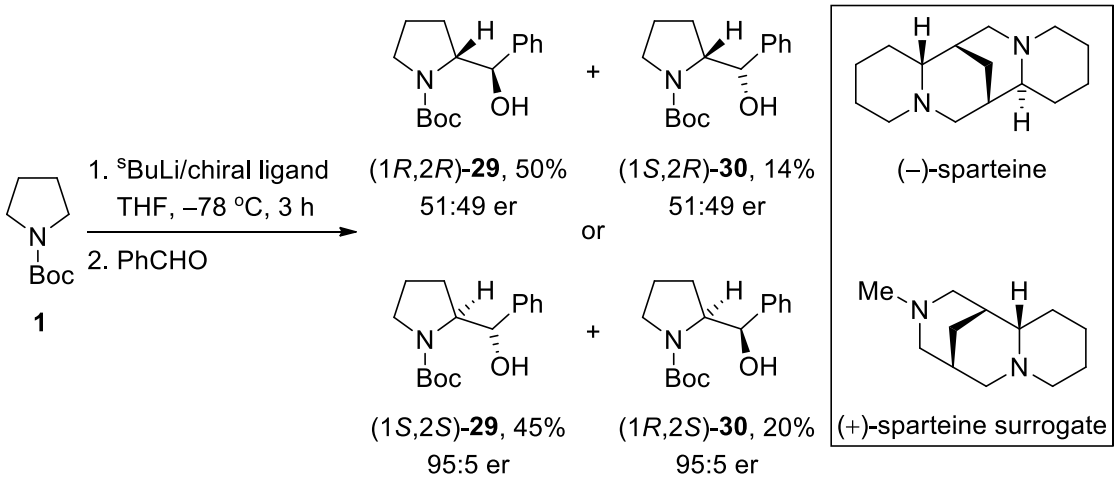
Scheme 2.7

More recently, the asymmetric lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and (–)-sparteine at –78 °C in Et_2O followed by trapping with PhCHO was reported by our group.[37,38] The reaction with this electrophile gave two diastereoisomeric alcohols (1*R*,2*R*)-**29** and (1*S*,2*R*)-**30** in 63% and 23% yield respectively and a high 97:3 er for both (Scheme 2.8). In the same paper, it was also shown that the use of (+)-sparteine surrogate gave access to the opposite enantiomeric alcohols in high er: (1*S*,2*S*)-**29** (58% yield) and (1*R*,2*S*)-**30** (23% yield) were isolated in 95:5 er and 94:6 er respectively.



Scheme 2.8

Interestingly, a solvent effect in the asymmetric lithiation of **1** was also observed. The lithiation of *N*-Boc pyrrolidine **1** was performed under the standard conditions (*s*-BuLi, chiral ligand, 3 hours at −78 °C) in different solvents such as TBME, THF and 2-methyl-THF. The reaction carried out with (+)-sparteine surrogate in THF gave (1*S*,2*S*)-**29** (45% yield) and (1*R*,2*S*)-**30** (20% yield) in a high 95:5 er for both the alcohols (Scheme 2.9). Similar results were also obtained with TBME and 2-methyl-THF.

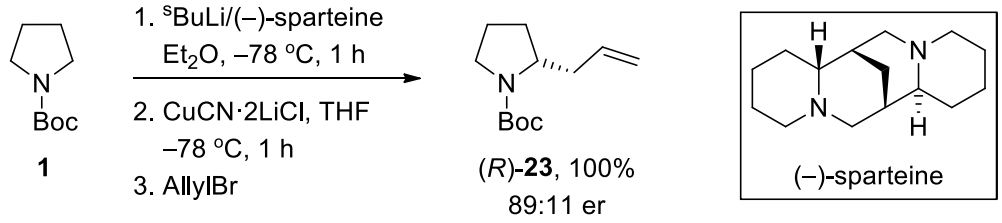


Scheme 2.9

In contrast, the use of (–)-sparteine in THF afforded alcohols (1*S*,2*S*)-**29** (50% yield) and (1*R*,2*S*)-**30** (14% yield) both in a low 51:49 er. Similarly, 2-Methyl-THF gave comparable low enantioselectivities, while the data with TBME matched those obtained with Et_2O.

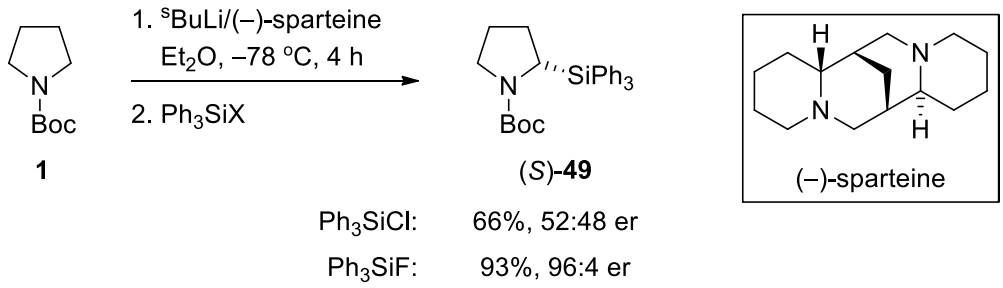
These results were rationalised with ^{6}Li NMR spectroscopy studies performed using *i*-PrLi and the chiral diamines at –80 °C. The experiments carried out in Et_2O-d_{10} showed that both (–)-sparteine and the (+)-sparteine surrogate formed a complex with *i*-PrLi. In contrast, when THF-d_8 was used as solvent, the (+)-sparteine surrogate was still able to complex *i*-PrLi, but (–)-sparteine did not form a complex and the organolithium was solvated by THF molecules.

The asymmetric lithiation-trapping methodology of *N*-Boc pyrrolidine **1** has been used by Dieter for the formation of several vinylic and allylic *N*-Boc pyrrolidines in high er *via* an asymmetric lithiation-copper transmetallation procedure.[39] However, the use of allyl bromide as electrophile resulted in a slightly lower er of allylic pyrrolidine (*R*)-**23** (89:11 er) than Beak had observed with other electrophiles (Scheme 2.10). Furthermore, with diamine (*S*,*S*)-**4** an even lower 85:15 er of (*S*)-**23** was observed.[13]



Scheme 2.10

Interestingly, when a bulky electrophile such as Ph_3SiCl was used, a very low er (52:48 er) of silylated product (*S*)-**49** (66% yield) was obtained (Scheme 2.11).[40] Problems with the reactivity of Ph_3SiCl were also reported by Strohmann, who was unable to synthesise (*S*)-**49** *via* asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1**.[41] However, the use of Ph_3SiF improved both the yield and the er of (*S*)-**49**, which was isolated in 93% yield and 96:4 er.[42]

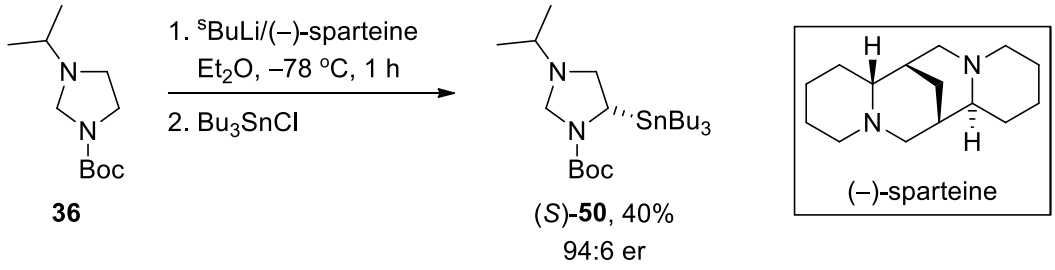


Scheme 2.11

The low er and moderate yield achieved with Ph_3SiCl were ascribed to the steric hindrance of the phenyl groups, which reduced the reactivity of the electrophile. It was assumed that the electrophilic trapping would happen only on warming of the reaction to a temperature where the lithiated intermediate was configurationally unstable, generating (*S*)-**49** in 52:48 er. This problem was not observed with Ph_3SiF which presumably is a faster reacting electrophile.

The allylation and silylation examples showed that slow reacting electrophiles and transmetallations can represent a limitation of the lithiation-trapping methodology.

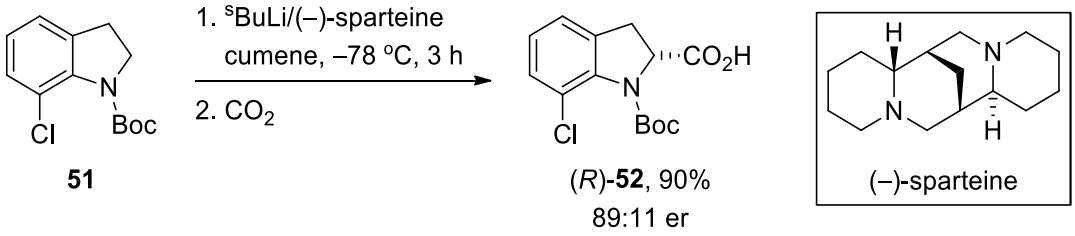
The asymmetric lithiation-trapping methodology was also extended and applied to other five-membered ring heterocycles. Coldham reported the synthesis of α-substituted *N*-Boc imidazolidines in good er from *N*-Boc imidazolidine **36** using *s*-BuLi and (–)-sparteine in Et_2O at –78 °C.[43,44] When Bu_3SnCl was used as electrophile, stannane (*S*)-**50** (40% yield) was isolated in 94:6 er (Scheme 2.12).



36 (*S*)-**50**, 40%, 94:6 er

Scheme 2.12

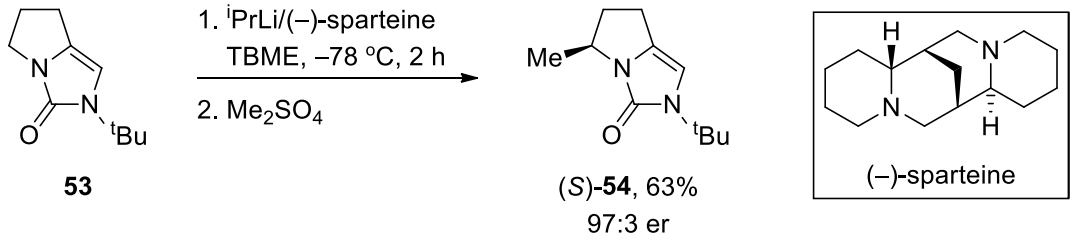
In 1997, Beak *et al*. showed that *N*-Boc indoline **51** could be lithiated with *s*-BuLi/(–)-sparteine in cumene.[45] Trapping with carbon dioxide gave carboxylic acid (*R*)-**52** in a high 90% yield and 89:11 er (Scheme 2.13). In this substrate, the chlorine atom was needed to block *ortho* lithiation on the aromatic moiety.



51 (*R*)-**52**, 90%, 89:11 er

Scheme 2.13

Another example of asymmetric lithiation-trapping on pyrrolidine-like substrates was reported by Metallinos.[46] Lithiation of unsaturated urea **53** with *i*-PrLi and (–)-sparteine in TBME and trapping with Me_2SO_4 afforded methylated (*S*)-**54** (63% yield, 97:3 er) (Scheme 2.14).

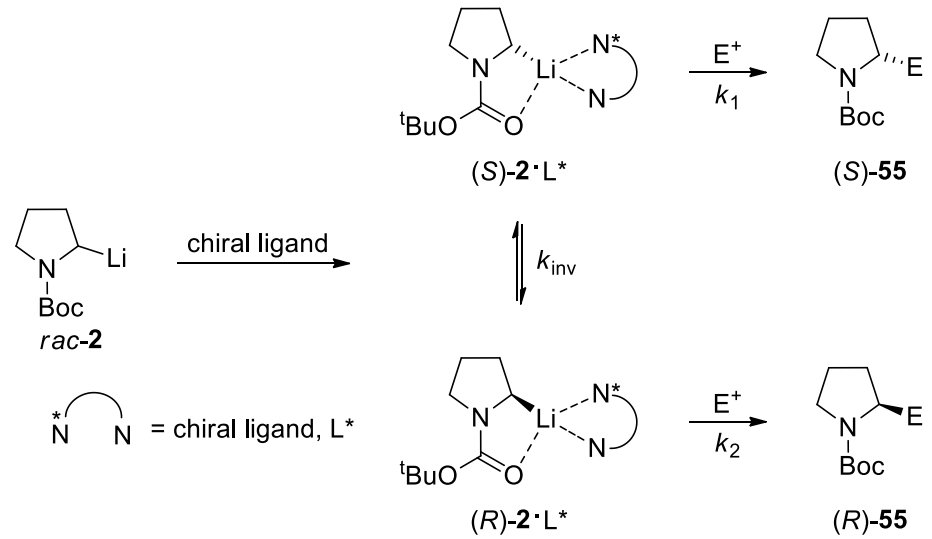


Scheme 2.14

From these reports, it is possible to conclude that the asymmetric lithiation-trapping methodology can be successfully applied to a range of five-membered substrates with a high level of enantioselectivity.

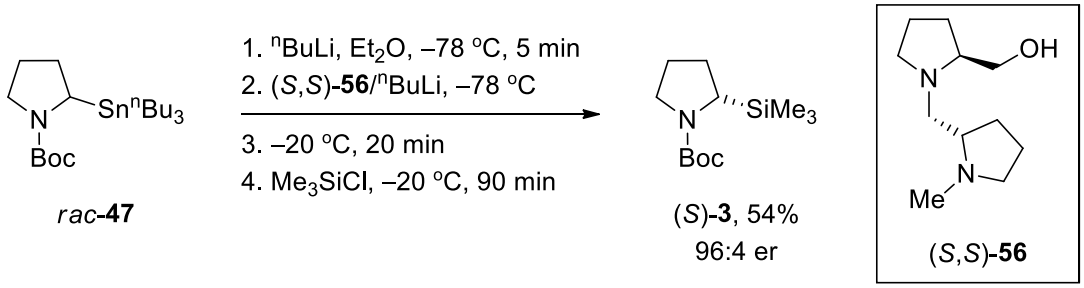
2.1.2 Asymmetric Synthesis of *N*-Boc Pyrrolidines *via* Dynamic Resolution

Enantioenriched 2-substituted *N*-Boc pyrrolidines can also be accessed *via* an asymmetric substitution process, which has been named dynamic resolution. This process relies on the configurational instability of the lithiated intermediate and has been extensively studied by the Coldham group in the past decade.[47-50] In this approach, the racemic lithiated intermediate *rac*-**2**, generated by tin-lithium exchange for example, is treated with a chiral ligand to form a mixture of diastereomeric complexes, (*S*)-**2**·L* and (*R*)-**2**·L* (Scheme 2.15). The mixture is then trapped with an electrophile to give product (*S*)-**55** or (*R*)-**55** with high er. Depending on the rate of interconversion of (*S*)-**2**·L* and (*R*)-**2**·L*, k_{inv}, and the rates of trapping, k_1 and k_2, the observed er can arise *via* two principal mechanisms, a dynamic kinetic resolution and a dynamic thermodynamic resolution.[51]



Scheme 2.15

The dynamic kinetic resolution process requires the rate of interconversion of the diastereomeric complexes (*S*)-**2**·L* and (*R*)-**2**·L* to be faster than the rates of trapping with the electrophile, under the reaction conditions. In other words, $k_{inv} > k_1$ and k_2, and at the same time $k_1 > k_2$, or *vice versa*, for high enantioselectivity. An example of this mechanism was reported by Coldham *et al*. using *N*-Boc stannane *rac*-**47** (Scheme 2.16).[49,50] Stannane *rac*-**47** was transmetallated with *n*-BuLi at –78 °C followed by the addition of a mixture of chiral ligand (*S*,*S*)-**56** and additional *n*-BuLi. The mixture was then warmed to –20 °C for 20 minutes. Finally, slow addition of Me_3SiCl over 90 minutes at –20 °C gave a 54% yield of (*S*)-**3** in 96:4 er.

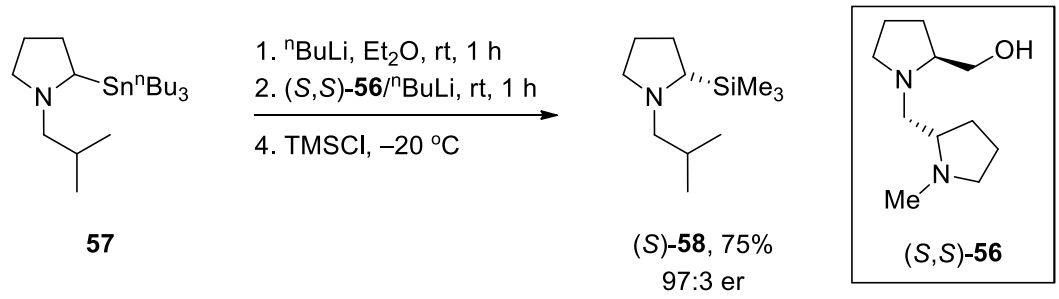


Scheme 2.16

The slow addition of the electrophile was needed to allow the diastereomeric complexes (*S*)-**2**·L* and (*R*)-**2**·L* time to interconvert and equilibrate. In this case, the electrophile reacted preferentially with the (*S*)-**2**·L* complex and thus, the er of this reaction depended on the rate of trapping of the diastereomeric complexes and was independent of the rate of interconversion of (*S*)-**2**·L* and (*R*)-**2**·L*. However, experiments within

this exploration showed that a combination of both dynamic kinetic and dynamic thermodynamic resolution mechanisms could be at the origin of the observed enantioselectivities. In addition, these results showed that the lithiated intermediate was chemically stable at –20 °C for at least 20 minutes. Moreover, with the dynamic kinetic resolution high er of the products could be achieved only when slow trapping electrophiles were used, thus limiting the application of this methodology.

On the other hand, the dynamic thermodynamic resolution process requires the rate of interconversion between (*S*)-**2**·L* and (*R*)-**2**·L* to be slower than the rate of trapping, $k_{inv} < k_1$ and k_2. This would allow the formation of the most stable diastereomeric complex, in thermodynamic equilibrium, which would be frozen by cooling to a lower temperature before trapping with the electrophile. Therefore, (*S*)-**2**·L* and (*R*)-**2**·L* do not equilibrate on the reaction timescale with the electrophile and the er of the product would reflect the diastereomeric ratio of (*S*)-**2**·L* and (*R*)-**2**·L*. To date, there are no reported examples of dynamic thermodynamic resolution using an *N*-Boc pyrrolidine. However, Coldham showed that high enantioselectivities could be obtained starting from stannane **57** with an alkyl group.[50] Transmetallation of **57** with *n*-BuLi at room temperature was followed by treatment with a mixture of (*S*,*S*)-**56** and *n*-BuLi and the complexes formed were left to equilibrate for 1 hour. The temperature was then lowered to –20 °C before the addition of the electrophile and (*S*)-**58** was isolated in 75% yield and 97:3 er (Scheme 2.17).



Scheme 2.17

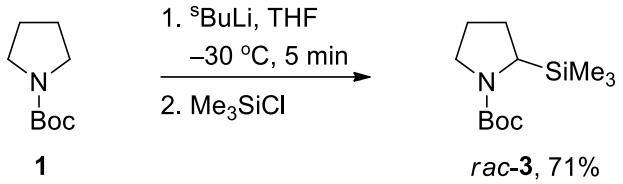
Although several electrophiles were successfully used in the trapping of the lithiated intermediate (>85:15 er), the dynamic thermodynamic resolution gave high er only when *N*-isobutyl or *N*-allyl pyrrolidines were used as substrates. It is worth noting that removal of the *N*-isobutyl group was not possible and that the *N*-allyl group could only be cleaved under harsh conditions.

To conclude this section, the mechanism of the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** has been studied in detail and has been successfully applied to other substrates. In addition, both enantiomeric series of trapped products can be easily accessed in high er (~95:5 er) by choosing the appropriate chiral ligand. In contrast, both of the dynamic resolution processes showed major drawbacks which make this methodology not easy to expand. Hence, the asymmetric lithiation-trapping remains the most useful methodology for the synthesis of α-substituted *N*-Boc pyrrolidines using lithium chemistry.

2.2 High Temperature α-Lithiation and Electrophilic Trapping of *N*-Boc Pyrrolidine 1

When considering temperatures above −78 °C for the asymmetric α-lithiation-trapping of *N*-Boc pyrrolidine **1**, higher temperatures will clearly influence the outcome of the reaction. Specifically, we identified four main factors which depend on the temperature and would affect the yield and the er of the products.

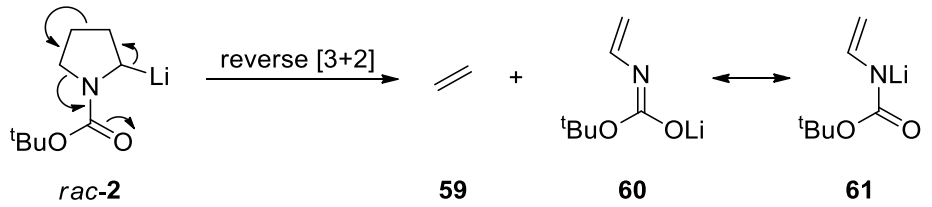
We start by considering the factors which could influence the yield of the lithiation-trapping process. First, the time for full lithiation. It is known, from the results of the racemic high temperature lithiation-trapping of *N*-Boc pyrrolidine **1**, that complete lithiation of **1** could be achieved in short reaction times.[5] In that work, a 5 minute lithiation was enough to achieve products in 49-77% yield, upon treatment of **1** with *s*-BuLi in THF at −30 °C and trapping with a range of electrophiles. For example, trapping with Me_3SiCl gave silyl pyrrolidine *rac*-**3** in 71% yield (Scheme 2.18). Therefore, it is reasonable to expect that the time for full lithiation of **1** will be considerably shorter at higher temperatures than at −78 °C.



1 *rac*-**3**, 71%

Scheme 2.18

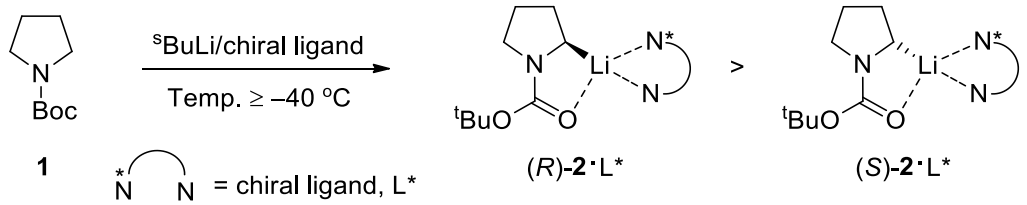
Second, high temperatures may affect the chemically stability of the lithiated *N*-Boc pyrrolidine **2**. It is possible that **2** could undergo a decomposition pathway similar to the one reported for THF with organolithiums.[52,53] Lithiated intermediate *rac*-**2** could be subjected to a reverse [3+2] cycloaddition to form ethylene **59** and lithium imidate **60** (Scheme 2.19). These intermediates would eventually react further with the organolithium (*i.e. s*-BuLi),[54] or with the electrophile.[5] Ultimately, if temperatures higher than −78 °C accelerate the rate of decomposition of **2**, the yield of the trapped product between **1** and the electrophile will be reduced.



rac-**2** **59** **60** **61**

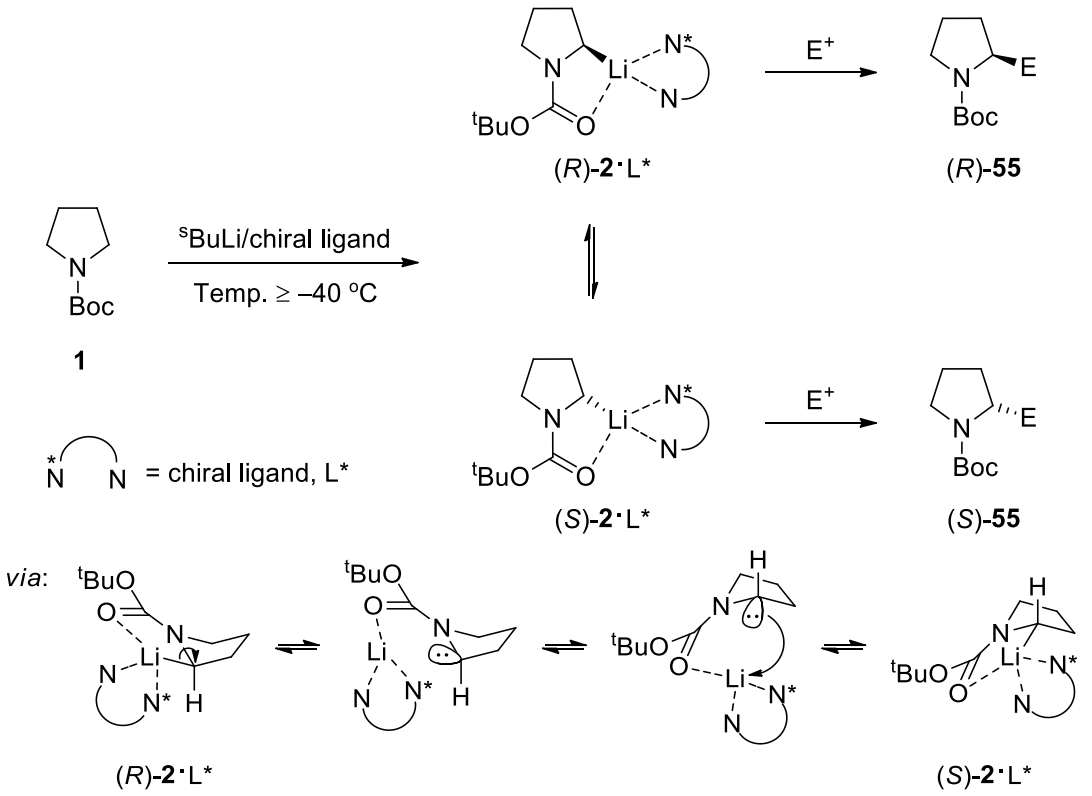
Scheme 2.19

Next, we consider the factors which could influence the er of the product. The er could be affected by the kinetic selectivity arising from the interaction between the *s*-BuLi/chiral ligand complex and *N*-Boc pyrrolidine **1**. Hence, the kinetic selectivity is the expression of the asymmetric deprotonation rates of **1** which selectively forms (*R*)-**2**·L* over (*S*)-**2**·L* (Scheme 2.20), or *vice versa*, and will be dependent on the temperature.



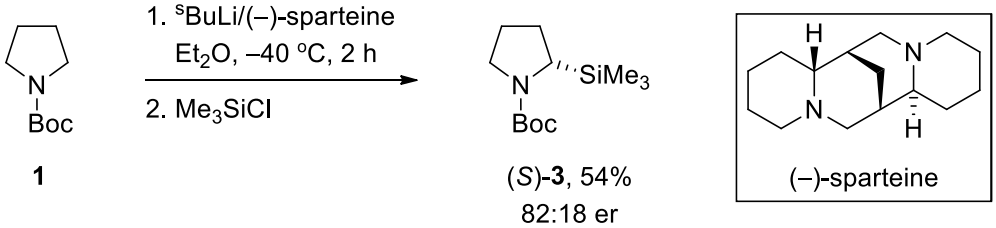
Scheme 2.20

Undoubtedly, (*R*)-**2**·L* and (*S*)-**2**·L* could interconvert and this introduces the second important factor affecting the er: the configurational stability of the lithiated intermediate.[55] Once the mixture of (*R*)-**2**·L* and (*S*)-**2**·L* is formed from the asymmetric deprotonation, the C-Li bond could break and the generated carbanion could invert and attach to the lithium on the opposite face, creating an equilibrium between (*R*)-**2**·L* and (*S*)-**2**·L* *via* the mechanism shown in Scheme 2.21. It is reasonable to think that at temperatures > –40 °C the rate of interconversion of (*R*)-**2**·L* and (*S*)-**2**·L* will be faster than at –78 °C, thus reducing the er of the final product.



Scheme 2.21

To the best of our knowledge, the only asymmetric lithiation-trapping reaction of *N*-Boc pyrrolidine **1** performed at a temperature above –78 °C was reported by Beak in 1994.[11] Lithiation of **1** with *s*-BuLi and (–)-sparteine at –40 °C for 2 hours, followed by electrophilic trapping with Me_3SiCl afforded (*S*)-**3** (54% yield) in 82:18 er (Scheme 2.22). Similar results were obtained when the reaction was carried out in pentane for 4 hours.



Scheme 2.22

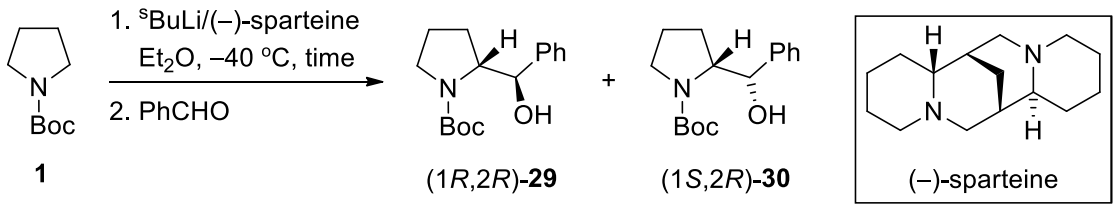
The 82:18 er was considerably lower than the 98:2 er achieved when the reaction was carried out at –78 °C (see Scheme 2.2) and could be due to a partial configurational instability of the lithiated intermediate at –40 °C over 2 hours. In addition, the moderate yield reported could result from some chemical instability of the organolithium under

the reaction conditions. Nevertheless, the enantioselectivity reported was an encouraging result and it was reasonable to believe that high er could be achieved by modulating the lithiation time.

2.2.1 Optimising the Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine 1 at Temperatures ≥ –40 °C Using *s*-BuLi/(–)-Sparteine

The exploration of the asymmetric α-lithiation-trapping of *N*-Boc pyrrolidine **1** at "high" temperature commenced with –40 °C as the reaction temperature. *s*-BuLi and (–)-sparteine in Et_2O were selected as lithiation conditions and PhCHO trapping was used as it was known to give two separable diastereoisomers in good yield (86% total yield) and high enantioselectivity (97:3 er) at –78 °C (see Scheme 2.8). As shown in Scheme 2.23 and Table 2.1, *N*-Boc pyrrolidine **1** was lithiated with *s*-BuLi and (–)-sparteine in Et_2O at –40 °C and then trapped with PhCHO. Reaction times of 1 second, 2 minutes, 20 minutes and 1 hour were investigated. The 1 second lithiation was used to have information on the kinetic selectivity of the chiral base at this temperature, since we assumed that, over such a short time, the lithiated intermediate would be configurationally stable. Longer times of 2 and 20 minutes were selected to explore the time required for full lithiation and finally, the 1 hour reaction should give an indication of the configurationally stability of the lithiated intermediate. In addition, a 1 hour reaction time should be favourable for process-scale reactions where longer times for the addition of the *s*-BuLi are likely to be necessary.

Hence, addition of the electrophile after 1 second gave alcohols (1*R*,2*R*)-**29** (6% yield) and (1*S*,2*R*)-**30** (4% yield) in 92:8 er and 91:9 er respectively (Entry 1); unreacted starting **1** was also recovered (73% yield). The 2 minute lithiation afforded (1*R*,2*R*)-**29** (93:7 er) and (1*S*,2*R*)-**30** (91:9 er) in 84% total yield (Entry 2), while with the 20 minutes lithiation time a 92:8 er for both of the alcohols (87% total yield) was achieved (Entry 3). In Entry 4, electrophilic trapping after 1 hour gave (1*R*,2*R*)-**29** (52% yield) and (1*S*,2*R*)-**30** (27% yield) in 92:8 er and 90:10 er respectively.



Scheme 2.23

Table 2.1: Study of the Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** with (–)-Sparteine at –40 °C

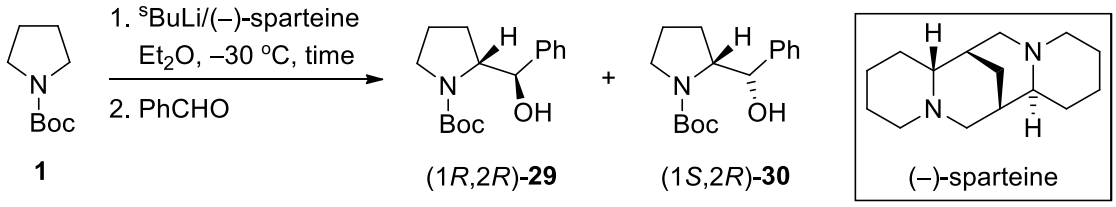
Entry	Time	Yield of (1*R*,2*R*)-29 (%)[a]	er[b]	Yield of (1*S*,2*R*)-30 (%)[a]	er[b]	Total yield (%)
1	1 s	6	92:8	4	91:9	10
2	2 min	58	93:7	26	91:9	84
3	20 min	58	92:8	29	92:8	87
4	1 h	52	92:8	27	90:10	79

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

We were very pleased to observe that a high level of enantioselectivity (90:10-93:7 er) could be achieved at –40 °C. For the 1 second lithiation (Entry 1), the enantioselectivity of the reaction was due to a lower selectivity of the chiral base (*s*-BuLi/(–)-sparteine) with *N*-Boc pyrrolidine **1**, which was ~92:8 er, compared to the –78 °C reaction (97:3 er). Clearly, the low yield (10% total yield) reflected the incomplete lithiation of **1** and was accompanied by recovery of a large amount of starting material. The configurational stability of the lithiated intermediate over a longer period was studied with the longer reaction times (Entry 2-4). Analysing the level of enantioselectivity achieved under these conditions (90:10-93:7 er) and that obtained with the 1 second reaction (~92:8 er), we could establish that the lithiated intermediate was configurationally stable for at least 1 hour at –40 °C. Moreover, the high yields obtained in these examples (79-87% total yield) indicated a chemical stability of the lithiated *N*-Boc pyrrolidine under all the reaction conditions.

Inspired by the high er at –40 °C, higher temperatures were then investigated. A lithiation temperature of –30 °C and reaction times of 1 second, 2 minutes, 20 minutes and 1 hour were explored (Scheme 2.24 and Table 2.2). In Entry 1, 1 second lithiation gave alcohols (1*R*,2*R*)-**29** and (1*S*,2*R*)-**30** (19% total yield) in 89:11 er for both

diastereoisomers; unreacted starting **1** was also recovered in 51% yield. This revealed a kinetic selectivity of ~89:11 er at –30 °C, which was slightly lower than that observed at –40 °C (~92:8 er). Electrophilic trapping after 2 minutes afforded (1*R*,2*R*)-**29** (90:10 er) and (1*S*,2*R*)-**30** (89:11 er) in a high 92% total yield (Entry 2). In the 20 minute reaction, alcohols (1*R*,2*R*)-**29** (49% yield) and (1*S*,2*R*)-**30** (28% yield) were obtained in 88:12 er and 87:13 er respectively (Entry 3) and the 1 hour reaction gave a 72% total yield of (1*R*,2*R*)-**29** (87:13 er) and (1*S*,2*R*)-**30** (84:16 er) (Entry 4).



Scheme 2.24

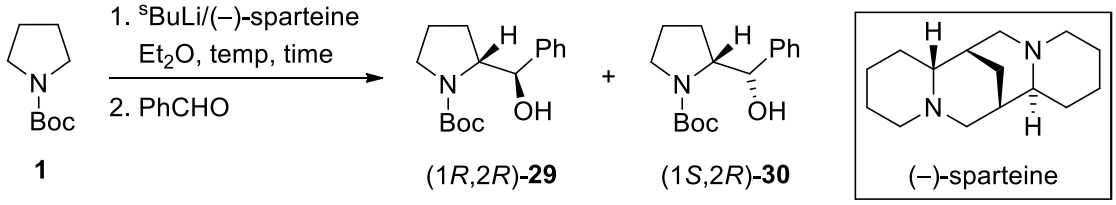
Table 2.2: Study of the Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** with (–)-Sparteine at –30 °C

Entry	Time	Yield of (1*R*,2*R*)-29 (%)[a]	er[b]	Yield of (1*S*,2*R*)-30 (%)[a]	er[b]	Total yield (%)
1	1 s	12	89:11	7	89:11	19
2	2 min	58	90:10	34	89:11	92
3	20 min	49	88:12	28	87:13	77
4	1 h	42	87:13	30	84:16	72

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Increasing the temperature resulted in a progressive, although small, reduction of enantioselectivity from ~90:10 er to ~85:15 er. This was attributed to a lack of configurational stability of the lithiated intermediate over longer reaction times at –30 °C. However, the results of the 2 minute lithiation (Entry 2) showed that the lithiated *N*-Boc pyrrolidine was configurationally stable for 2 minutes. Furthermore, the 92% total yield obtained with only a 2 minute reaction represented the highest yield achieved with a "high" temperature asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** using (–)-sparteine. Nevertheless, the isolated yields of alcohols (1*R*,2*R*)-**29** and (1*S*,2*R*)-**30** diminished with the longer reaction times (Entries 3 and 4), suggesting that the lithiated intermediate was chemically unstable at –30 °C.

Next, to test the limits of the "high" temperature lithiation, even higher temperatures were explored. Thus, lithiation of **1** with *s*-BuLi and (–)-sparteine in Et_2O was carried out at –20 °C, –10 °C and 0 °C (Scheme 2.25 and Table 2.3). When the reaction was performed at –20 °C followed by trapping with PhCHO after 1 minute, alcohols (1*R*,2*R*)-**29** and (1*S*,2*R*)-**30** (86% total yield) were isolated in 86:14 er and 85:15 er respectively (Entry 1). Similar yields (82% total yield) and er (87:13-85:15 er) were obtained with the 2 minute lithiation at –20 °C (Entry 2). At –10 °C, a 30 second lithiation time afforded (1*R*,2*R*)-**29** (43% yield) and (1*S*,2*R*)-**30** (29% yield), both in 80:20 er (Entry 3). Finally, a reaction temperature of 0 °C was explored (Entries 4 and 5). The 10 second lithiation gave 75:25 er of (1*R*,2*R*)-**29** and (1*S*,2*R*)-**30** (67% total yield), while in the 1 minute reaction, alcohols (60% total yield) were obtained in a low 65:35 er for (1*R*,2*R*)-**29** and 62:38 er for (1*S*,2*R*)-**30**.



Scheme 2.25

Table 2.3: Exploration of the Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** with (–)-Sparteine at –20 - 0 °C

Entry	Temp (°C)	Time	Yield of (1*R*,2*R*)-29 (%)[a]	er[b]	Yield of (1*S*,2*R*)-30 (%)[a]	er[b]	Total yield (%)
1	–20	1 min	53	86:14	33	85:15	86
2	–20	2 min	51	87:13	31	85:15	82
3	–10	30 s	43	80:20	29	80:20	72
4	0	10 s	40	75:25	27	75:25	67
5	0	1 min	35	65:35	25	62:38	60

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

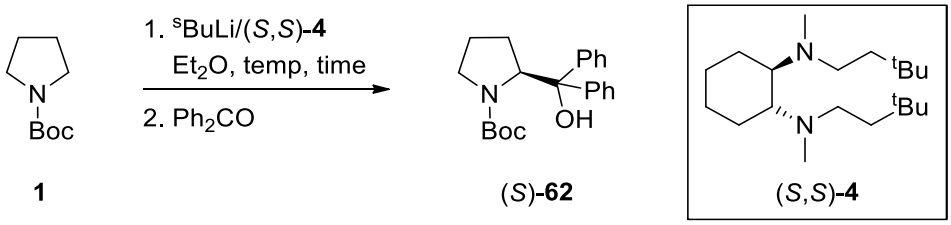
With these higher temperatures, the kinetic selectivity was not determined using the 1 second lithiation. However, it was assumed to be close to the value observed with the shortest reaction time at each temperature. At –20 °C, a slight loss of kinetic selectivity

(~85:15 er) compared with the –40 °C reactions (~92:8 er) or with the –30 °C reactions (~89:11 er) was observed. Nonetheless, the lithiated intermediate was configurationally stable at –20 °C for at least 2 minutes. The results at 0 °C indicate that at this temperature there was a significant decrease in the kinetic selectivity (~75:25 er) and the lithiated intermediate was configurationally labile. In fact, the er reduced to ~65:35 er after only 1 minute. Thus, 0 °C is not a suitable temperature for use in the asymmetric lithiation protocol.

In the exploration of the asymmetric α-lithiation-trapping of *N*-Boc pyrrolidine **1** with (–)-sparteine at "high" temperature, one of the most surprising aspects was the yield in relation to the reaction time. In fact, the 2 minute reactions at –30 °C and at –40 °C gave overall yields of 92% and 84% respectively and an 86% total yield was obtained after only 1 minute at –20 °C.

2.2.2 Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine 1 at Temperatures ≥ –40 °C Using *s*-BuLi/(*S*,*S*)-4

Next, the α-lithiation of *N*-Boc pyrrolidine **1** was explored using Alexakis diamine (*S*,*S*)-**4**, which was known to give excellent results in the asymmetric lithiation protocol (see Scheme 2.7).[13] Unfortunately, the lithiation of **1** with *s*-BuLi and diamine (*S*,*S*)-**4** followed by trapping with PhCHO gave poor yields of isolated products (<20% yield). Hence, the lithiation of **1** was performed using *s*-BuLi and diamine (*S*,*S*)-**4** in Et_2O and benzophenone was used for the electrophilic trapping (Scheme 2.26 and Table 2.4). First, the reaction was performed at –78 °C as a reference. Thus, a 60 minute lithiation at –78 °C gave alcohol (*S*)-**62** in excellent yield and enantioselectivity (82% yield, 95:5 er) (Entry 1). Then, high temperatures of –40 °C and –30 °C were explored (Entries 2-5). A 1 second reaction at –40 °C afforded (*S*)-**62** (15% yield) in 86:14 er and recovered starting pyrrolidine **1** (50% yield) (Entry 2), while trapping after 2 minutes gave (*S*)-**62** in 49% yield (86:14 er) (Entry 3). In Entry 4, alcohol (*S*)-**62** (14% yield) was obtained in 80:20 er with the lithiation at –30 °C for 1 second; starting **1** was also recovered in 55% yield. Finally, a 2 minute reaction at –30 °C gave (*S*)-**62** in 45% yield and 81:19 er with 15% yield of recovered *N*-Boc pyrrolidine **1** (Entry 5).



1 (*S*)-**62** (*S*,*S*)-**4**

Scheme 2.26

Table 2.4: Exploration of the Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** with Alexakis Diamine (*S*,*S*)-**4**

Entry	**Temp (°C)**	**Time**	**Yield of (*S*)-62 (%)[a]**	**er[b]**	**Yield of rec. SM 1 (%)[a]**
1	–78	60 min	82	95:5	-
2	–40	1 s	15	86:14	50
3	–40	2 min	49	86:14	-
4	–30	1 s	14	80:20	55
5	–30	2 min	45	81:19	15

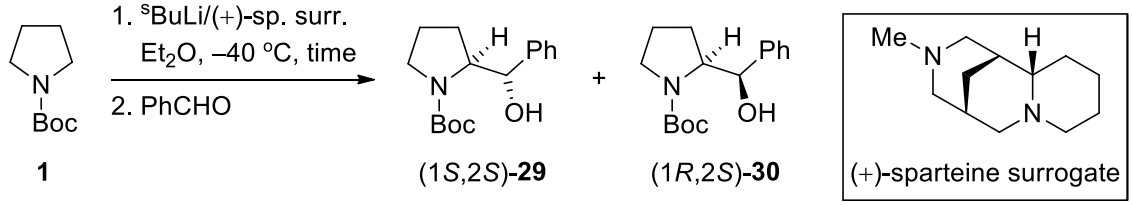
[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC

With diamine (*S*,*S*)-**4** as chiral ligand, the kinetic selectivity at –40 °C and at –30 °C was considerably lower compared to (–)-sparteine. With the 1 second lithiation at –40 °C, 86:14 er was achieved with (*S*,*S*)-**4**, while (–)-sparteine gave ~92:8 er. At –30 °C, 80:20 er was obtained with (*S*,*S*)-**4**, whereas an 89:11 er was attained with (–)-sparteine under the same conditions. Furthermore, the yields of the 2 minute lithiations were significantly lower using benzophenone as electrophile. Due to these considerations, we concluded that Alexakis diamine (*S*,*S*)-**4** was not an effective chiral ligand for the asymmetric α-lithiation at high temperatures and thus, use of diamine (*S*,*S*)-**4** was not further investigated.

2.2.3 *s*-BuLi/(+)-Sparteine Surrogate-Mediated Lithiation-Trapping of *N*-Boc Pyrrolidine 1 at Temperatures ≥ –40 °C

The exploration of the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** was continued using the (+)-sparteine surrogate, which has a more sparteine-like structure and hence, good results were anticipated. First, the lithiation was performed using –40

°C and the lithiated intermediate was trapped with PhCHO (Scheme 2.27 and Table 2.5). A 2 minute lithiation gave a high 95% total yield of alcohols (1*S*,2*S*)-**29** (90:10 er) and (1*R*,2*S*)-**30** (92:8 er) (Entry 1), while electrophilic trapping after 1 hour afforded alcohols (1*S*,2*S*)-**29** and (1*R*,2*S*)-**30** (66% overall yield) in 90:10 er and 91:9 respectively (Entry 2). This result showed that the organolithium was configurationally stable for 1 hour, although the 66% isolated yield suggested partial chemical instability of the lithiated intermediate at –40 °C.



Scheme 2.27

Table 2.5: Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** at –40 °C with (+)-Sparteine Surrogate

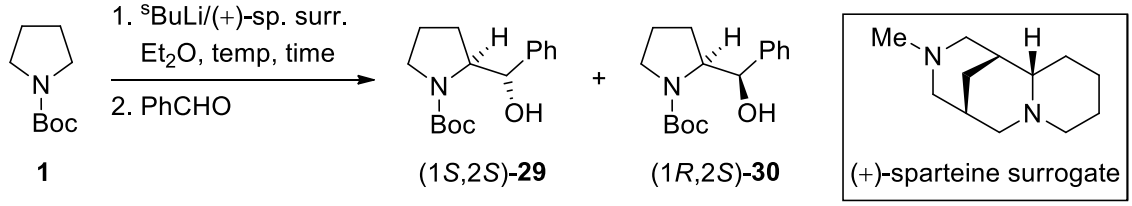
Entry	**Time**	**Yield of (1*S*,2*S*)-29 (%)[a]**	**er[b]**	**Yield of (1*R*,2*S*)-30 (%)[a]**	**er[b]**	**Total yield (%)**
1	2 min	65	90:10	30	92:8	95
2	1 h	46	90:10	20	91:9	66

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Although the kinetic selectivity was not assessed using the 1 second lithiation-trapping sequence, it is reasonable to assume a level comparable to the 2 minute reaction (based on the results with (–)-sparteine in Table 2.1 and 2.2). Considering the er values obtained with the (+)-sparteine surrogate (~90:10 er) and those with (–)-sparteine (~92:8 er, in the opposite sense), it was evident that high and synthetically useful er could also be achieved with the (+)-sparteine surrogate.

Therefore, higher reaction temperatures of –30 °C and –20 °C were investigated (Scheme 2.28 and Table 2.6). Alcohols (1*S*,2*S*)-**29** and (1*R*,2*S*)-**30** were obtained in 94% overall yield and 90:10 er with the 2 minute lithiation-trapping at –30 °C (Entry 1), while a 64% total yield was achieved in the 1 hour reaction at the same temperature, where (1*S*,2*S*)-**29** and (1*R*,2*S*)-**30** were isolated in 89:11 er and 90:10 er respectively (Entry 2). When the reaction temperature was raised to –20 °C, trapping after 2 minutes

gave alcohols (1*S*,2*S*)-**29** (89:11 er) and (1*R*,2*S*)-**30** (91:9 er) in 73% overall yield (Entry 3), while in the 1 hour lithiation, the alcohols were obtained in 60% total yield and 83:17 er and 85:15 er respectively (Entry 4).



Scheme 2.28

Table 2.6: Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** at –30 °C and –20 °C with (+)-Sparteine Surrogate

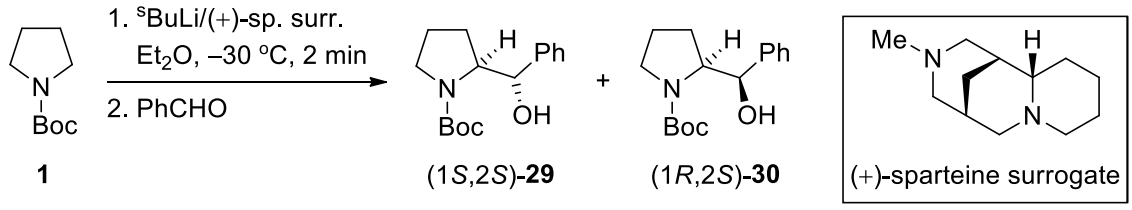
Entry	Temp (°C)	Time	Yield of (1*S*,2*S*)-29 (%)[a]	er[b]	Yield of (1*R*,2*S*)-30 (%)[a]	er[b]	Total yield (%)
1	–30	2 min	67	90:10	27	90:10	94
2	–30	1 h	41	89:11	23	90:10	64
3	–20	2 min	50	89:11	23	91:9	73
4	–20	1 h	40	83:17	20	85:15	60

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Amazingly, high er were achieved in all of the conditions. The results in Entries 1 and 3 showed that the kinetic selectivity at –30 °C and –20 °C using *s*-BuLi/(+)-sparteine surrogate was ~90:10 er. This value was higher than the one at –20 °C using (–)-sparteine (~85:15 er). Furthermore, the 90:10 er achieved with the 1 hour reaction was higher than with (–)-sparteine (~85:15 er), indicating a better configurational stability of the lithiated *N*-Boc pyrrolidine with the (+)-sparteine surrogate at –30 °C. On the other hand, at –20 °C the 83:17 er showed some configurational instability over 1 hour. Finally, the 64% and 60% overall yields obtained from the 1 hour reactions was additional evidence for the chemical instability of the lithiated species as a function of the time at high temperatures.

We briefly explored two other solvents for the reaction. Thus, the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **1** was performed in THF and TBME as solvent, applying

the conditions which gave the best results in Et_2O, namely –30 °C for 2 minutes and trapping with PhCHO. In THF, alcohols (1*S*,2*S*)-**29** (38% yield) and (1*R*,2*S*)-**30** (21% yield) were isolated in 86:14 er (Scheme 2.29, Table 2.7, Entry 2). Better enantioselectivities, but slightly lower yields were obtained performing the lithiation in TBME. In this case, alcohols (1*S*,2*S*)-**29** and (1*R*,2*S*)-**30** were isolated in an overall 43% yield and 89:11 er (Entry 3). These results showed synthetically useful enantioselectivities with both THF and TBME. The use of THF gave higher total yields (59%) than TBME (43%), which was more efficient in the enantioselective outcome (89:11 er).



Scheme 2.29

Table 2.7: High Temperature Asymmetric Lithiation-Trapping of *N*-Boc Pyrrolidine **1** in THF and TBME

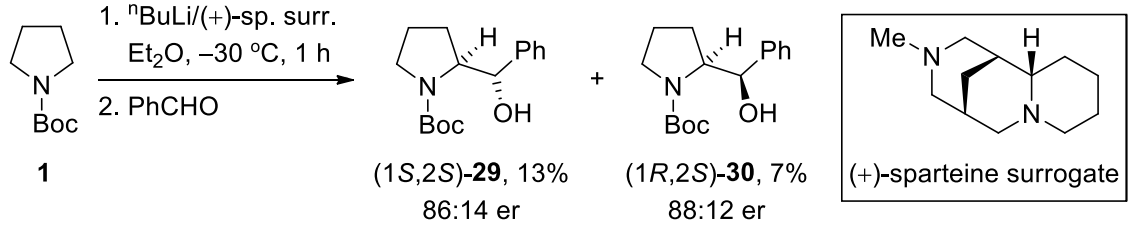
Entry	Solvent	Yield of (1*S*,2*S*)-29 (%)[a]	er[b]	Yield of (1*R*,2*S*)-30 (%)[a]	er[b]	Total yield (%)
1	Et_2O	67	90:10	27	90:10	94
2	THF	38	86:14	21	86:14	59
3	TBME	31	89:11	12	89:11	43

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

These data confirmed that the (+)-sparteine surrogate could complex *s*-BuLi in THF at –30 °C. The loss of er observed in THF (86:14 er) compared to that obtained in Et_2O (90:10 er) could be due to a higher coordination ability of THF, which could displace some of the (+)-sparteine surrogate in the complex with *s*-BuLi. TBME was as good as Et_2O in terms of enantioselectivity, but the yield was not satisfactory.

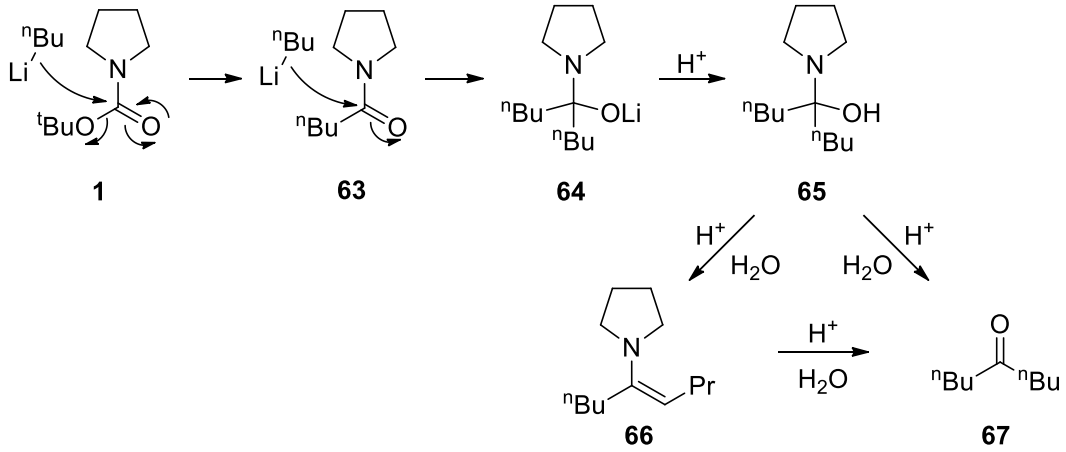
The use of *n*-BuLi was also investigated, since this organolithium reagent is generally preferred to *s*-BuLi by process chemists for process-scale reactions. Hence, *N*-Boc pyrrolidine **1** was lithiated with *n*-BuLi in the presence of (+)-sparteine surrogate at –30 °C for 1 hour. Trapping with PhCHO gave alcohols (1*S*,2*S*)-**29** (13% yield) and

(1*R*,2*S*)-**30** (7% yield) in 86:14 er an 88:12 er respectively; 35% of recovered starting **1** was also obtained after flash column chromatography (Scheme 2.30).



Scheme 2.30

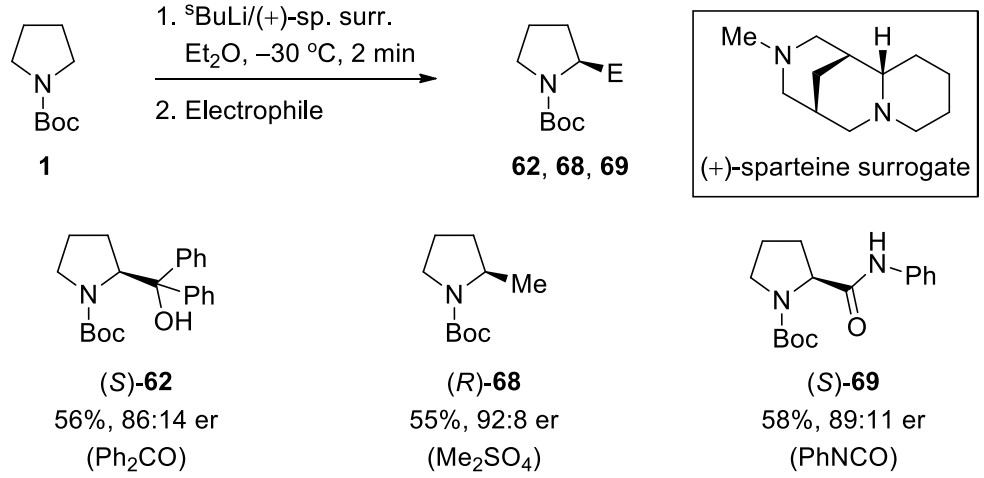
The 20% overall yield represents a very important result since Beak had reported that *n*-BuLi/(–)-sparteine was unreactive towards the lithiation of *N*-Boc pyrrolidine **1** even at –40 °C.[11] However, we have to consider that the 20% total yield plus the 35% yield of recovered **1** are only accountable for about half of the reaction mass. Therefore, it appears that competing reactions are occurring, reducing the amount of **1** available for lithiation, or reducing the quantity of the *n*-BuLi, or both. It is possible that *n*-BuLi could act as a nucleophile and attack the C=O of the Boc group forming amide **63**, which could further react with another *n*-BuLi to ultimately give ketone **67**, or enamine **66** upon acidic quenching (Scheme 2.31). Unfortunately, in the case of our lithiation of *N*-Boc pyrrolidine **1** with *n*-BuLi we were not able to isolate any of the suggested by-products, probably due to their volatility.



Scheme 2.31

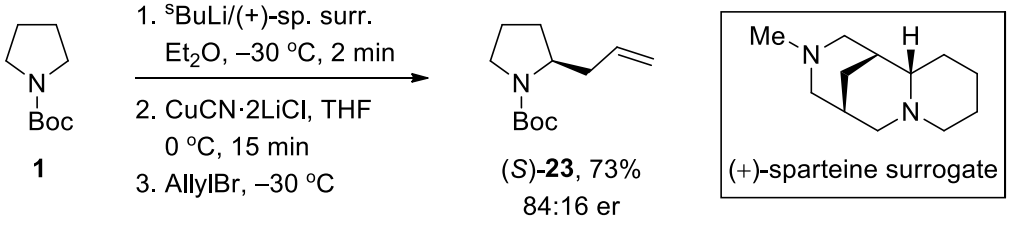
In the optimisation of the high temperature asymmetric α-lithiation-trapping of *N*-Boc pyrrolidine **1**, the aim was to find the highest temperature which would give the best yield of the products with the highest enantioselectivity. Such requirements were met

using a 2 minute lithiation with *s*-BuLi/(+)-sparteine surrogate in Et_2O (94% overall yield and 90:10 er). Hence, using these optimised conditions, the trapping with other electrophiles was explored focussing on C-C bond-forming reactions: benzophenone, Me_2SO_4, PhNCO, allyl bromide and bromobenzene were chosen. The results using benzophenone, Me_2SO_4 and PhNCO are shown in Scheme 2.32. Trapping with benzophenone gave alcohol (*S*)-**62** in 56% yield and 86:14 er, the use of Me_2SO_4 afforded methylated pyrrolidine (*R*)-**68** (55% yield) in a high 92:8 er, while (*S*)-**69** was obtained in 58% yield and 89:11 er with PhNCO.



Scheme 2.32

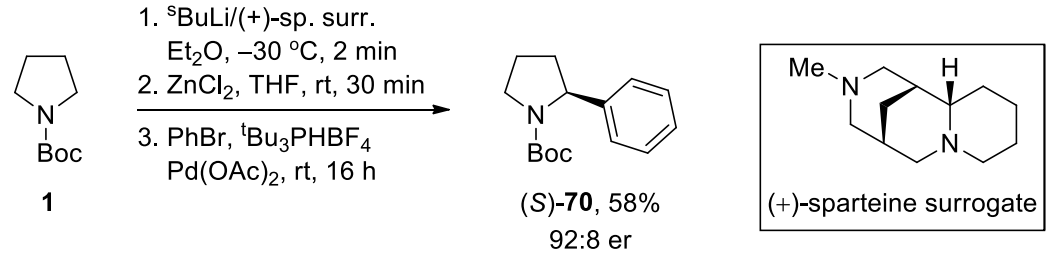
The allylation of *N*-Boc pyrrolidine **1** was performed following the conditions reported by Dieter.[39] Thus, the lithiated intermediate was first transmetallated to a *N*-Boc organocuprate using the CuCN·2LiCl complex. The organocuprate was then reacted with allyl bromide to give allyl pyrrolidine (*S*)-**23** (73% yield) in 84:16 er (Scheme 2.33). The lower er observed in this reaction was not surprising since lithium-copper transmetallation and allylation usually give slightly reduced er.[13,39]



Scheme 2.33

Finally, the arylation of *N*-Boc pyrrolidine **1** was achieved using the Campos procedure.[29,30,56] Lithium-zinc transmetallation with $ZnCl_2$ in THF was followed by a

Negishi coupling reaction with bromobenzene using *t*-Bu_3PHBF_4 and $Pd(OAc)_2$ as catalyst (details of this transformation will be given in section 4.2.1). As shown in Scheme 2.34, phenyl pyrrolidine (*S*)-**70** (58% yield) was obtained in a high 92:8 er.



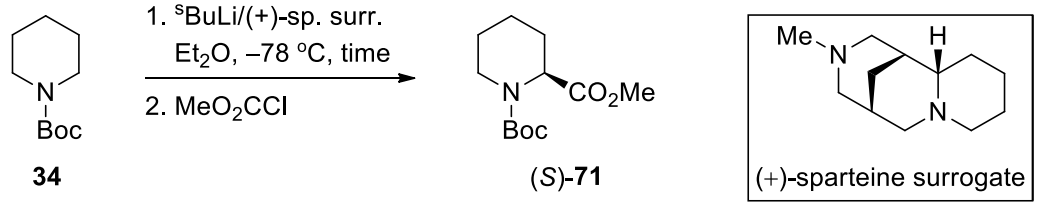
Scheme 2.34

Moderate yields (55-58%) were observed with these electrophiles, except for the allylation which gave a good 73% yield. In addition, high enantioselectivities were observed with PhNCO (89:11 er), Me_2SO_4 (92:8 er) and bromobenzene *via* the lithiation-Negishi coupling reaction (92:8 er) and were of the same level as those achieved with PhCHO. Noticeably, with benzophenone and allyl bromide the enantioselectivity was lower. This may be due to a competing radical-mediated trapping from a radical intermediate. A single electron transfer (SET) mechanism has been reported by Gawley when benzophenone was used as electrophile,[57] or the lithiated intermediate was transmetallated to form an organocuprate.[58]

2.3 High Temperature Asymmetric Lithiation-Trapping of *N*-Boc Piperidine 34 and *N*-Boc Piperazine 35

2.3.1 High Temperature Asymmetric Lithiation-Trapping of *N*-Boc Piperidine 34

N-Boc piperidine **34** can be successfully lithiated using *s*-BuLi/TMEDA in a racemic protocol.[4,6,7] However, the asymmetric lithiation-trapping of **34** was shown to be problematic using several chiral ligands, including (–)-sparteine.[59,60] Recently, our group reported that the asymmetric lithiation-trapping of *N*-Boc piperidine **34** with *s*-BuLi and (+)-sparteine surrogate at –78 °C gave products in high yield and enantioselectivity (Scheme 2.35 and Table 2.8).[61] When the lithiation of **34** was performed for 6 hours, trapping with methyl chloroformate gave ester (*S*)-**71** in 78% yield and 88:12 er (Entry 1). A 3 hour lithiation afforded (*S*)-**71** in a similar yield and er (83%, 87:13 er, Entry 2), whereas 1 hour was not enough to complete the lithiation of **71** and (*S*)-**71** was isolated in a low 24% yield (Entry 3).



Scheme 2.35

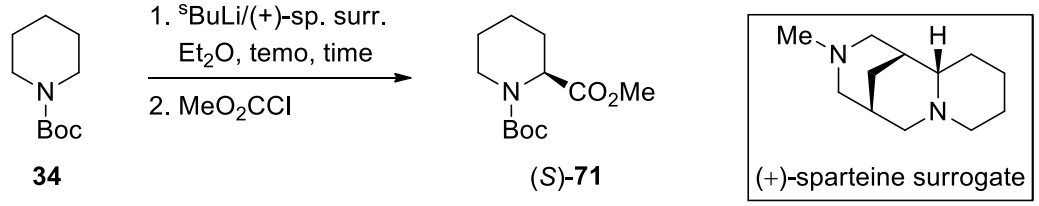
Table 2.8: Optimisation of the Asymmetric Lithiation-Trapping of *N*-Boc Piperidine **34** at –78 °C

Entry	Time (h)	Yield of (*S*)-71 (%)	er
1	6	78	88:12
2	3	83	87:13
3	1	24	86:14

The enantioselectivity obtained with *N*-Boc piperidine **34**, ~88:12 er, was lower than with *N*-Boc pyrrolidine **1** (95:5 er). In addition, at least a 3 hour lithiation time was needed at –78 °C to lithiate **34**. The configurational stability of the lithiated intermediate was also investigated by incubating the lithiated complex at –40 °C for 2 hours before trapping with MeO_2CCl at –78 °C. In this case, (*S*)-**71** was isolated in 83%

yield and 79:21 er, showing a partial configurational instability of the lithiated intermediate at –40 °C. Moreover, the lithiated intermediate was configurationally unstable at –20 °C over 2 hours: ester (*S*)-**71** was obtained in 59:41 er.

The result obtained by incubating the lithiated complex at –40 °C for 2 hours was interesting and we wondered whether the lithiation of *N*-Boc piperidine **34** could be performed directly at higher temperatures. Thus, we began our study by carrying out the lithiation of **34** with *s*-BuLi and the (+)-sparteine surrogate at –50 °C, –40 °C and –30 °C (Scheme 2.36 and Table 2.9). At –50 °C, a 30 minute lithiation and trapping with methyl chloroformate gave ester (*S*)-**71** in 46% yield and 79:21 er (Entry 1). A higher 64% yield (80:20 er) was obtained at –40 °C for 20 minutes (Entry 2), while at –30 °C, (*S*)-**71** was isolated (47% yield) in 77:23 er (Entry 3). At each temperature, unreacted starting material was also recovered, as indicated in Table 2.9 (Entries 1-3).



Scheme 2.36

Table 2.9: Asymmetric Lithiation-Trapping of *N*-Boc Piperidine **34** at Temperature ≥ –50 °C

Entry	Temp (°C)	Time (min)	Yield of (*S*)-71 (%)[a]	er[b]	Yield of rec. SM 34 (%)[a]
1	–50	30	46	79:21	21
2	–40	20	64	80:20	15
3	–30	5	47	77:23	26

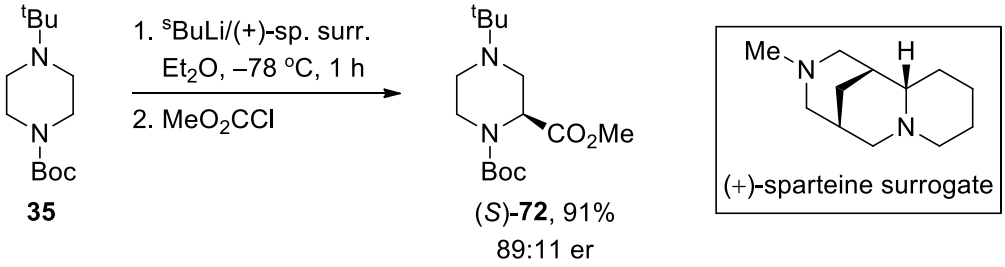
[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Although the best yield (64%) was achieved at –40 °C, good yields were obtained at –50 °C and at –30 °C. These results also showed a similar level of enantioselectivity at each temperature (77:23-80:20 er). As expected, these values were lower than that observed at –78 °C (~88:12 er). Unfortunately, we were unable to establish if the lower enantioselectivity was due to a lower kinetic selectivity of the *s*-BuLi/(+)-sparteine

surrogate complex with *N*-Boc piperidine **34**, or to configurational stability of the lithiated intermediate. In addition, the recovery of **34** was probably due to incomplete lithiation of the substrate.

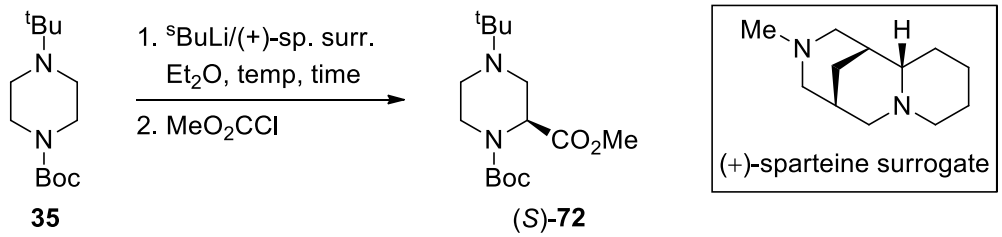
2.3.2 High Temperature Asymmetric Lithiation-Trapping of *N*-Boc Piperazine 35

The high temperature asymmetric lithiation-trapping of *N*-Boc piperazine **35** was also briefly investigated. McDermott reported the only published asymmetric lithiation-trapping of a *N*-Boc piperazine with *s*-BuLi and (–)-sparteine. However, extensive research on the asymmetric lithiation-trapping of *N*-Boc piperazines has recently been carried out in our group. Among those results, it was discovered that lithiation of **35** with *s*-BuLi and the (+)-sparteine surrogate at –78 °C for 1 hour and reaction with methyl chloroformate afforded ester (*S*)-**72** in 91% yield and 89:11 er (Scheme 2.37).[62]



Scheme 2.37

Our results on the "high" temperature lithiation of *N*-Boc piperazine **35** are shown in Scheme 2.38 and Table 2.10. First, **35** was lithiated with *s*-BuLi and the (+)-sparteine surrogate at –50 °C for 3 minutes and trapped with methyl chloroformate to give (*S*)-**72** in 71% yield and 82:18 er (Entry 1). Then, the lithiation-trapping was performed at –30 °C for 2 minutes and (*S*)-**72** was isolated in 88% yield and 78:22 er (Entry 2). Not surprisingly, the use of temperatures ≥ –50 °C resulted in a decreased enantioselectivity compared to the result at –78 °C. However, good yields were achieved even though short lithiation times were employed.



Scheme 2.38

Table 2.10: Asymmetric Lithiation-Trapping of *N*-Boc Piperazine **35** at –50 °C and –30 °C

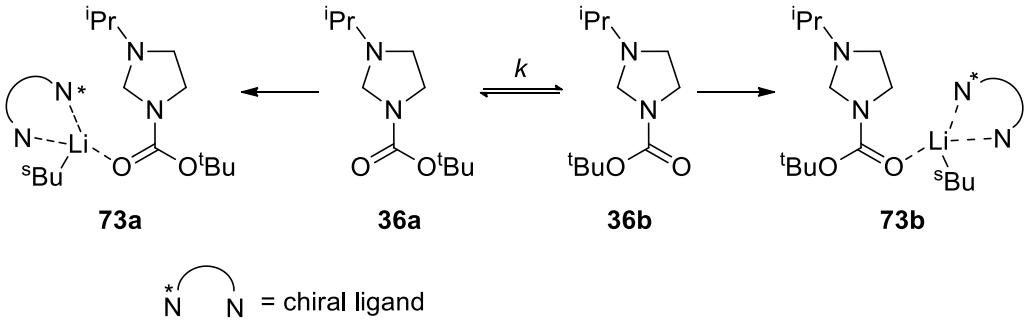
Entry	Temp (°C)	Time (min)	Yield of (*S*)-72 (%)[a]	er[b]
1	–50	3	71	82:18
2	–30	2	88	78:22

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

In conclusion, the "high" temperature asymmetric lithiation-trapping of six-membered heterocycles such as *N*-Boc piperidine **34** and *N*-Boc piperazine **35**, resulted in a reduction of the enantioselectivity. The values of er observed with both substrates were ~80:20 er in each of the conditions explored. Thus, we concluded that 80:20 er is the highest value which can be reached with the lithiation at "high" temperature of these two six-membered *N*-Boc heterocycles.

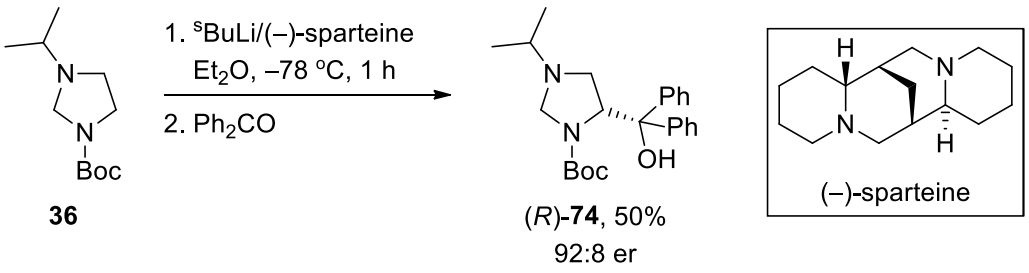
2.4 High Temperature Asymmetric Lithiation-Trapping of *N*-Boc Imidazolidine 36

Next, we decided to investigate a different five-membered ring substrate for the high temperature lithiation-trapping, namely *N*-Boc imidazolidine **36**. The asymmetric lithiation and electrophilic trapping of *N*-Boc imidazolidine **36** has a major limitation: yields above 50% cannot be obtained at –78 °C.[43,44] The reason is the low rate of interconversion of the two *N*-Boc rotamers **36a** and **36b** (Scheme 2.39) and the observation that the deprotonation does not occur on the aminal carbon. Therefore, since the lithiation is directed by the C=O of the Boc group, only pre-lithiation complex **73b**, generated from rotamer **36b**, could be α-lithiated, whereas pre-lithiation complex **73a** will be unreactive as the carbonyl is pointing towards the aminal carbon. The low rate of interconversion of **36a** and **36b** was proven by variable temperature (VT) ^{13}C NMR spectroscopy studies carried out in DMSO-d_6 by Coldham.[43] The half-life ($t_{1/2}$) for rotation about the C-N bond at –78 °C was calculated to be $t_{1/2}$ >100 hours; in contrast, $t_{1/2}$ is ~10 minutes at –40 °C.



Scheme 2.39

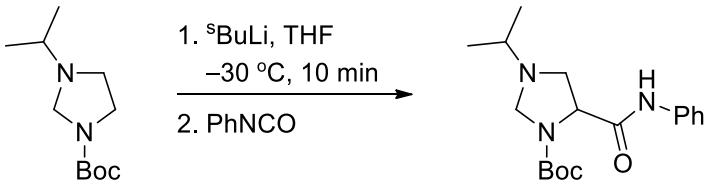
Coldham's experimental results at –78 °C were in accordance with these calculations. Lithiation of **36** with *s*-BuLi and (–)-sparteine in Et_2O at –78 °C for 1 hour followed by trapping with benzophenone gave alcohol (*S*)-**74** in 50% yield and 92:8 er (Scheme 2.40). Trapping with other electrophiles such as Bu_3SnCl, Me_3SiCl, and MeI gave products in 40-50% yield and high enantioselectivity (>92:8 er). The absolute configuration of the products was confirmed by X-ray crystallography of alcohol (*R*)-**74**.



36 (*R*)-**74**, 50%, 92:8 er

Scheme 2.40

In 2010, our group reported the racemic lithiation-trapping of *N*-Boc imidazolidine **36** at –30 °C, using a diamine-free methodology.[5] Lithiation of **36** with *s*-BuLi in THF at –30 °C for 10 minutes and then trapping gave products in 50-74% yield. For example, trapping with PhNCO afforded amide *rac*-**75** in 74% yield (Scheme 2.41). These results showed that it was possible to obtain good yields in the lithiation-trapping of *N*-Boc imidazolidine **36** if a reaction temperature of –30 °C was used. Therefore, these results were evidence that at –30 °C the rotamers **36a** and **36b** could interconvert. In addition, at this temperature the lithiated intermediate was chemically stable for at least 10 minutes.



36 *rac*-**75**, 74%

Scheme 2.41

2.4.1 Investigating the Rotational Barrier for Interconversion of *N*-Boc Rotamers of *N*-Boc Imidazolidine 36

Before investigating the "high" temperature asymmetric lithiation-trapping of *N*-Boc imidazolidine **36**, we carried out our own VT NMR spectroscopic studies. We decided that THF-d_8 was a suitable solvent for these experiments and this is important since THF could also be a potential solvent for the lithiation methodology as has been shown for *N*-Boc pyrrolidine **1**. The equilibrium between **36a** and **36b** shown in Scheme 2.39, is related to rate constant, *k*, which can be calculated using the Eyring equation (1).

$$k = (k_B \cdot T/h) \cdot e^{(-\Delta G‡/RT)} \quad (1)$$

where k_B is Boltzmann's constant, h is Planck's constant, R is the gas constant and $\Delta G^{\ddagger}$ is the Gibbs free energy of activation. It is known that, when the exchange rate between **36a** and **36b** is slow, two different sets of signals are observed in the NMR spectrum, one for each rotamer. In contrast, with a fast rate of interconversion, only the average signal is present. Between these two limits a broad and flat peak should appear. The temperature when this happens is called the coalescence temperature, T_c. At T_c, the rate constant *k* is given by equation (2).

$$k = (\pi \cdot \Delta\nu_0)/\sqrt{2} \quad (2)$$

In this equation, $\Delta\nu_0$ is the separation in Hertz between the peaks of **36a** and **36b** at a slow rate of interconversion. At this point, $\Delta G^{\ddagger}$ can be calculated using equation (3).

$$\Delta G^{\ddagger} = RT[\ln(k_B \cdot T/h) - \ln k] \quad (3)$$

Knowing $\Delta G^{\ddagger}$, it possible to calculate the rate constant *k* at different temperatures using the Eyring equation (1), assuming that the change in entropy is zero on changing the temperature. Finally, the half-life for rotation is given by equation (4).

$$t_{1/2} = \ln 2/k \quad (4)$$

Thus, we started our ^{1}H NMR spectroscopy experiments with a sample of *N*-Boc imidazolidine **36** in THF-d_8. The methylene signals at δ_H 3.87 and δ_H 3.86 were selected and at –20 °C we measured $\Delta\nu_0$ = 6.11 Hz (Figure 2.1, a). This value gives a rate constant k = 13.6 s^{-1} and a half-life $t_{1/2}$ = 0.05 s at the T_c. The two signals coalesced at about 38 °C (311 K) (Figure 2.1, e) and therefore, the barrier for rotation, $\Delta G^{\ddagger}$, was calculated to be 69.5 kJ mol^{-1}. Then, the use of these data in the Eyring equation gives a half-life $t_{1/2}$ ~200 hours at –78 °C (195 K). At –40 °C (233 K), the value is $t_{1/2}$ ~10 minutes, while at –30 °C the half-life ($t_{1/2}$) is ~2 minutes. These results in THF-d_8 were fully comparable with those obtained by Coldham in DMSO-d_6.

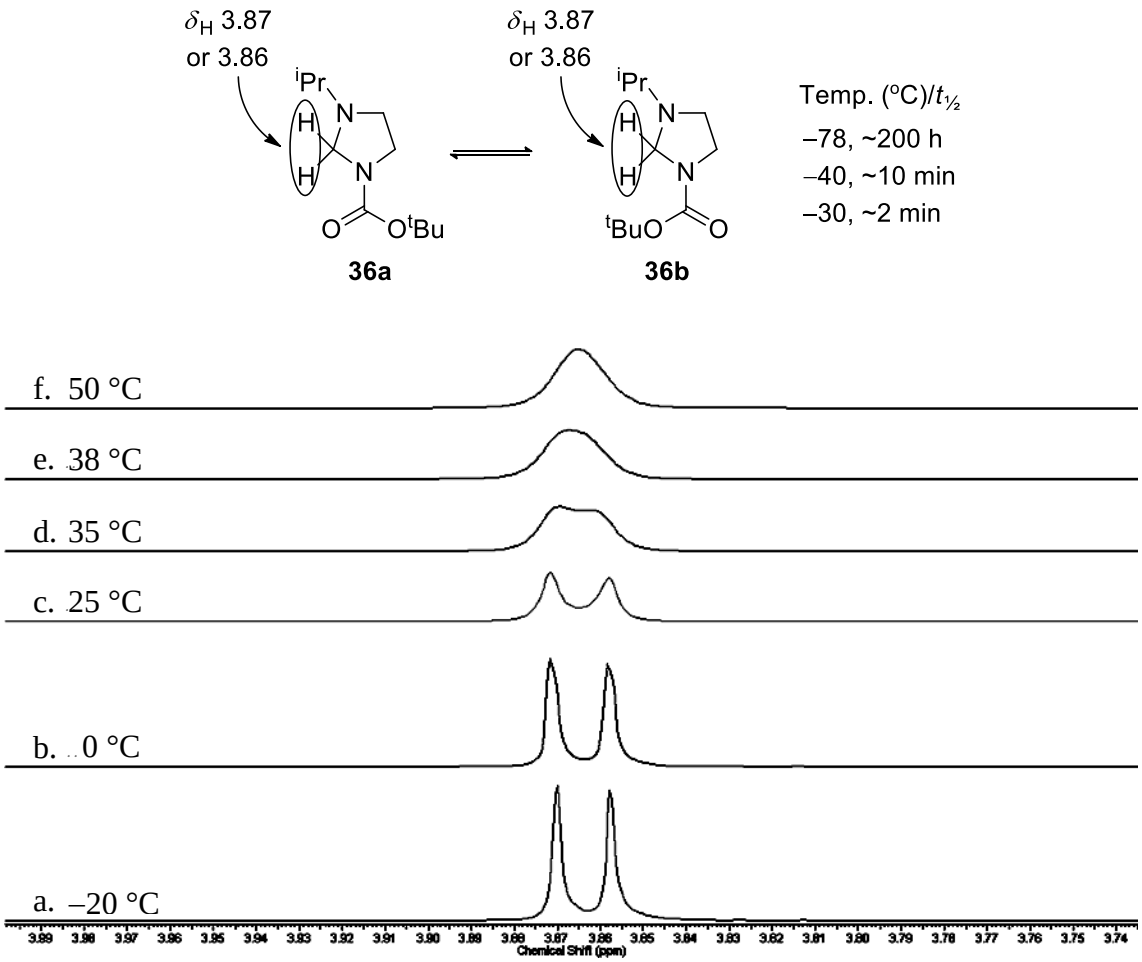
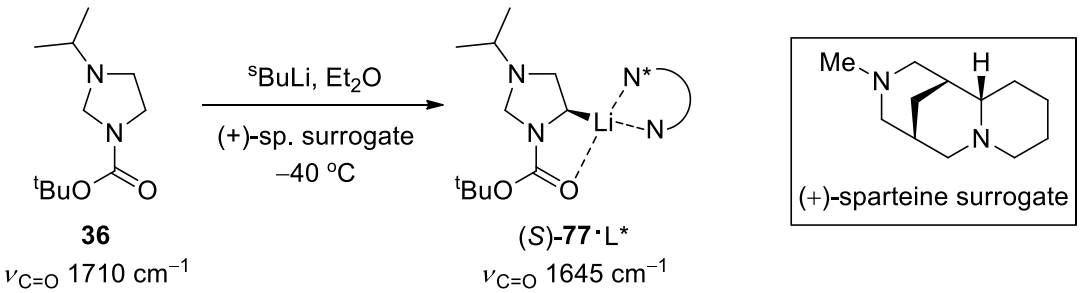


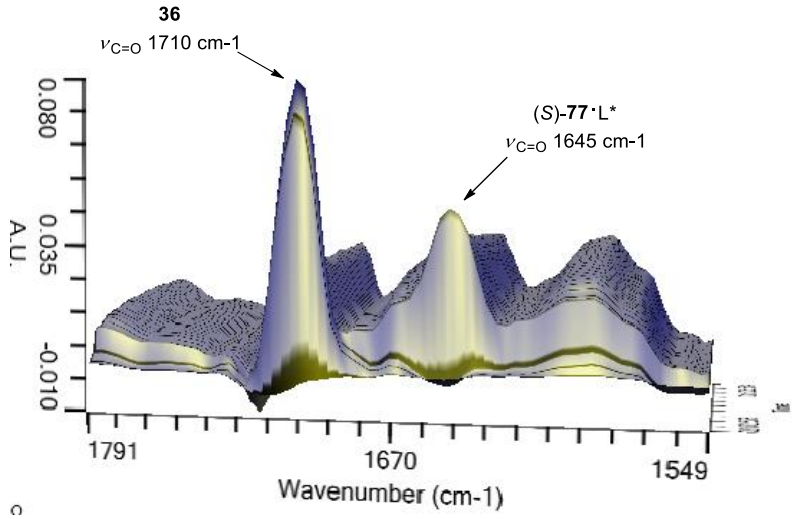
Figure 2.1: VT ^{1}H NMR spectra of *N*-Boc imidazolidine **36** in THF-d_8

In order to have a deeper insight into the lithiation process of *N*-Boc imidazolidine **36**, we decided to use *in situ* infra-red (ReactIR™) spectroscopy which is a useful method to monitor the course of the lithiation, as recently demonstrated by our group.[61,63] These studies monitor the decrease in absorbance of the C=O peak of the Boc group after the addition of *s*-BuLi. The lithiated intermediate that forms has a C=O peak at a different frequency. In Scheme 2.42, the results of the lithiation of *N*-Boc imidazolidine **36** in the presence of *s*-BuLi and the (+)-sparteine surrogate in Et_2O at –40 °C are presented. The reaction progress can be evaluated by the disappearance and appearance of new signals in the 3-D plot (a), or by a 2-D plot of the peak intensity of specific peaks (1710 cm^{-1} and 1645 cm^{-1} in this case) as a function of time (b). In this example, the addition of *s*-BuLi caused a decrease in the $\nu_{C=O}$ of *N*-Boc imidazolidine **36** (1710 cm^{-1}) and an increase in the 1645 cm^{-1} peak, corresponding to the $\nu_{C=O}$ of the lithiated intermediate (*S*)-**77**·L*.

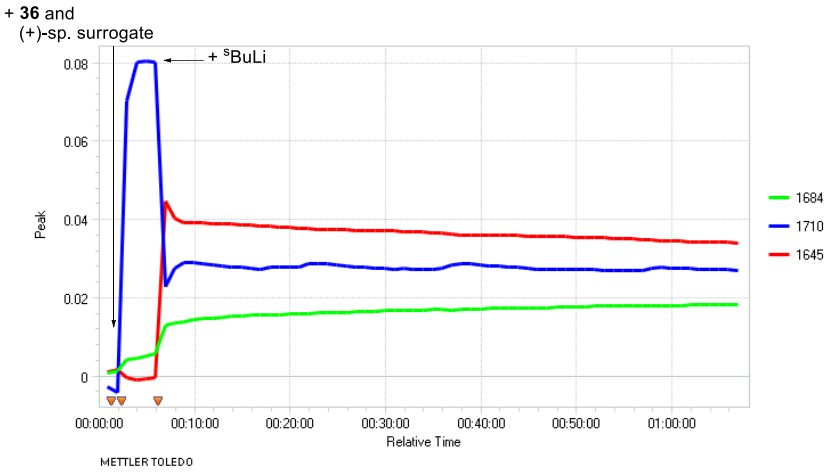


36
$\nu_{C=O}$ 1710 cm^{-1}

(*S*)-**77**·L*
$\nu_{C=O}$ 1645 cm^{-1}



(a)



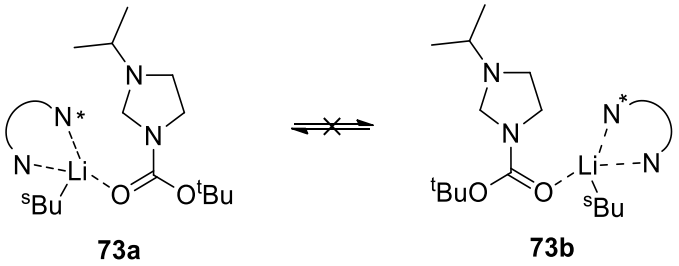
(b)

Scheme 2.42

Interestingly, these plots showed a fast initial lithiation of a part of *N*-Boc imidazolidine **36** in about 2 minutes. However, the lithiation was incomplete and no further change in the concentration of the lithiated species and *N*-Boc imidazolidine **36** was observed over 1 hour. This could be explained by a slow rate of interconversion of the two rotamers even at –40 °C. The peak at 1684 cm^{-1} was also noteworthy. After an initial formation, the intensity of the peak remained constant over 1 hour and we believe that this peak

(1684 cm^{-1}) could be assigned to the pre-lithiation complex of the unreactive rotamer **73a**. This may represent additional evidence for the non-interconversion of the rotamers. On the other hand, the ReactIR™ data did not fit with the calculation of the half-life for rotation obtained by VT ^{1}H NMR spectroscopy studies ($t_{1/2}$ ~10 minutes).

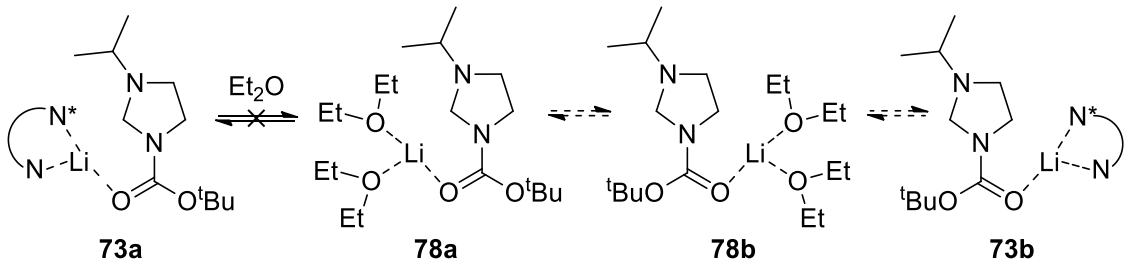
A reason for the difference between the ReactIR™ data and VT ^{1}H NMR spectroscopy results could be due to the formation of the pre-lithiation complexes, between the substrate and (+)-sparteine surrogate, **73a** and **73b** which are equally formed under the lithiation conditions (Scheme 2.43). It might be possible that the rotation of the rotamers is blocked by the increased steric hindrance, once **73a** and **73b** are formed.



73a **73b**

Scheme 2.43

Therefore, in order to allow the rotamers to interconvert, it is necessary that the formation of **73a** and **73b** is reversible. With Et_2O as lithiation solvent, the formation of the pre-lithiation complexes **73a** and **73b** could be an irreversible process (Scheme 2.44). This may be due to the incapacity of the Et_2O to displace the chiral ligand from the pre-lithiation complex. Thus, only pre-lithiation complex **73b** would be lithiated. This would lead to a highest theoretical yield of 50%. For clarity, *s*-butyl group of *s*-BuLi is omitted in Schemes 2.44 and 2.45.

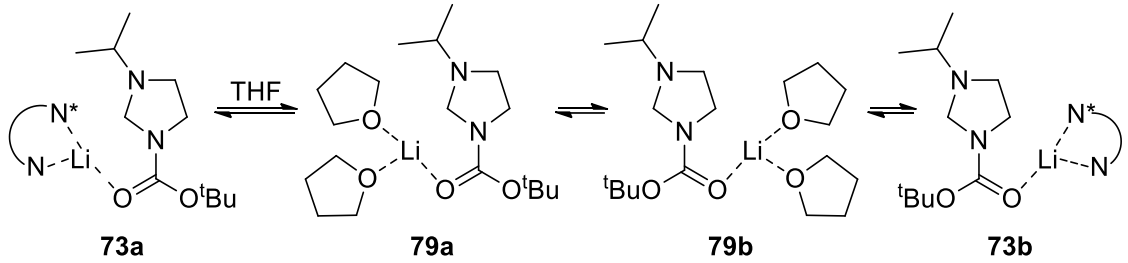


73a **78a** **78b** **73b**

Scheme 2.44

In contrast, we reasoned that THF, which is a good coordinating solvent, could displace the chiral ligand on **73a** and coordinate to the organolithium to form **79a** (Scheme 2.45).

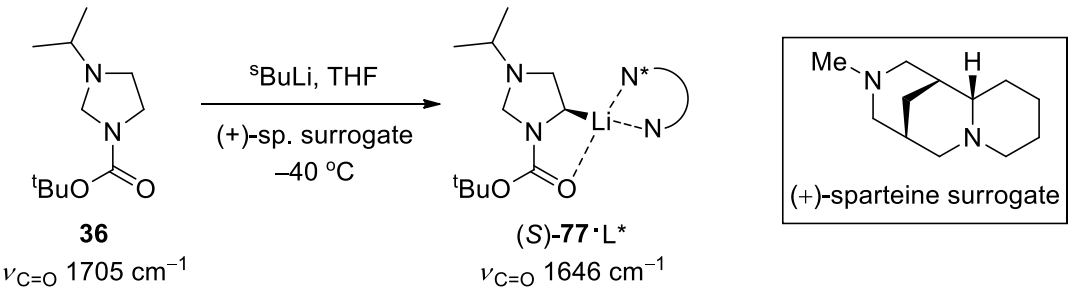
At this point, the rotamers could eventually interconvert due to reduced steric hindrance. Finally, the chiral ligand should form the reactive pre-lithiation complex **73b** and lead to the lithiation of **36**.



Scheme 2.45

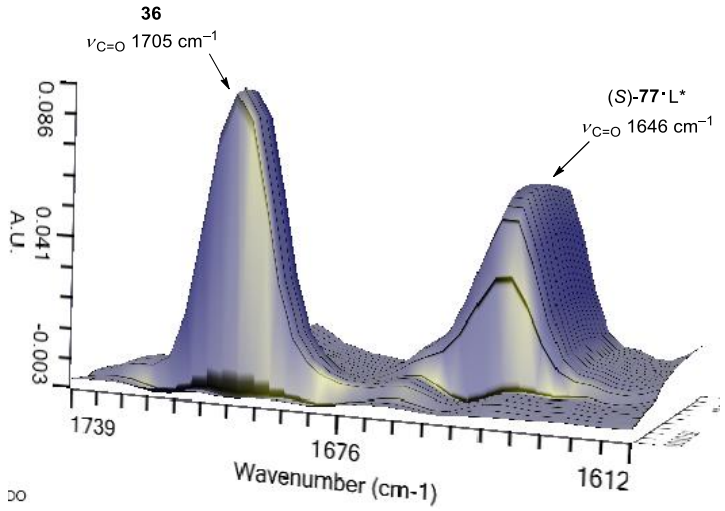
In addition to these considerations, previous work in our group had shown that THF could give high enantioselectivity in the asymmetric lithiation-trapping protocol, as long as the (+)-sparteine surrogate was used as the chiral ligand (see Scheme 2.9). Therefore, we decided to study the effect of THF with *N*-Boc imidazolidine **36**. First, the progress of the lithiation of *N*-Boc imidazolidine **36** with *s*-BuLi and the (+)-sparteine surrogate in THF at –40 °C was monitored using ReactIR™ spectroscopy (Scheme 2.46).

Surprisingly, complete disappearance of the 1705 cm^{-1} peak corresponding to the $\nu_{C=O}$ of **36** was observed in ~10 minutes, with a parallel formation of the lithiated intermediate (*S*)-**77**·L* peak (at 1646 cm^{-1}). The traces obtained in THF were substantially different from those with Et_2O (see Scheme 2.42). In particular, from the 2-D plot (b), the formation of the lithiated intermediate appeared to proceed more in THF than in Et_2O. In addition, the 2-D plot (b) showed an initial fast lithiation in ~1 minute, followed by a slower lithiation. This was presumably due to the interconversion of unreactive rotamer **73a** to rotamer **73b**, which was then lithiated.

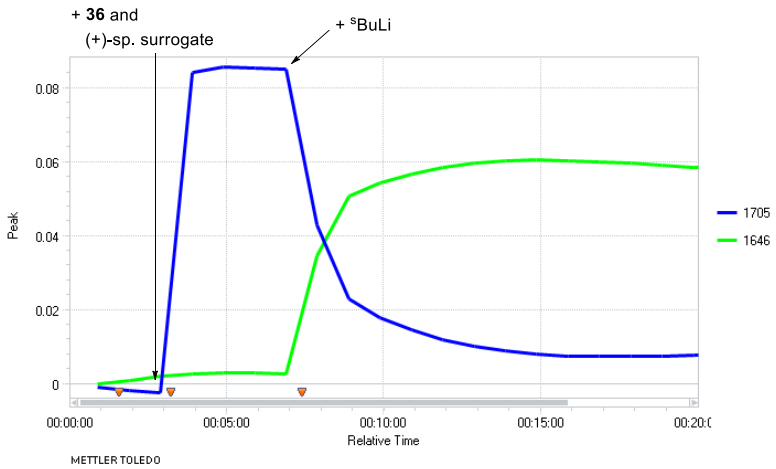


36
$\nu_{C=O}$ 1705 cm^{-1}

(*S*)-**77**·L*
$\nu_{C=O}$ 1646 cm^{-1}



(a)



(b)

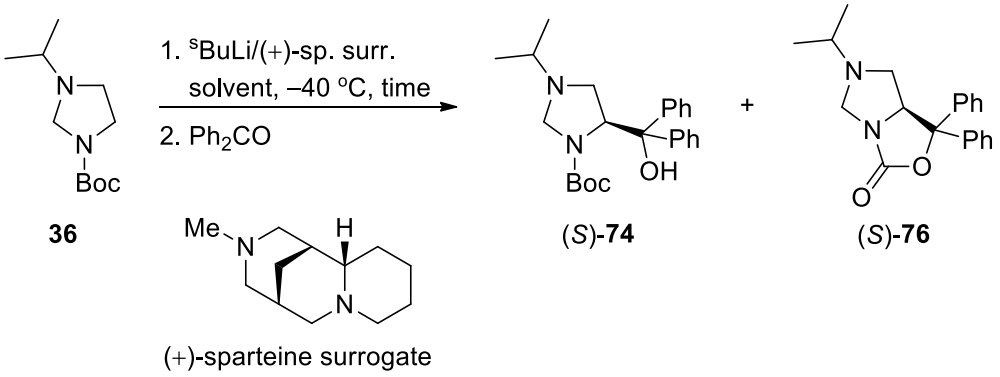
Scheme 2.46

Thus, the ReactIR™ results suggested that higher yields of trapped products should be obtained in THF than in Et_2O. Therefore, a range of synthetic experiments were carried out to providing supporting results.

2.4.2 Asymmetric Lithiation-Trapping of *N*-Boc Imidazolidine 36

We decided to investigate the solvent effect by comparing the lithiation-trapping of **36** in Et_2O and in THF. First, **36** was lithiated with *s*-BuLi and (+)-sparteine surrogate at –40 °C and trapped with benzophenone (Scheme 2.47 and Table 2.11). The use of benzophenone presented a complication due to the formation of both the desired alcohol (*S*)-**74** and cyclised (*S*)-**76**, which was not always isolated. Lithiation for 1 hour in Et_2O gave (*S*)-**74** (40% yield) in 93:7 er (Entry 1) and 17% of recovered starting material. Despite the low isolated yield of (*S*)-**74**, the ^{1}H NMR spectrum of the crude product showed 74% conversion of **36** into the products.

The lithiation of *N*-Boc imidazolidine **36** was performed in Et_2O for 30 minutes. Alcohol (*S*)-**74** and cyclised (*S*)-**76** were obtained in 36% yield (92:8 er) and 10% yield (77:23 er) respectively (Entry 2); starting **36** was recovered in 26% yield. It is clear that the er of alcohol (*S*)-**74** and cyclised (*S*)-**76** were considerably different. Specifically, the er of (*S*)-**74** derived from direct trapping by benzophenone, whereas the er of oxazolidinone (*S*)-**76** originated from a kinetic cyclisation of one lithium alkoxide over the other. We can assume that the (+)-sparteine surrogate would be coordinated to the lithium alkoxide generating a diastereomeric lithiated species, where one diastereoisomer would cyclise faster than the other. Using the er and yields of (*S*)-**74** and (*S*)-**76**, it is possible to calculate the er of the combined products. For Entry 2 this value was 89:11 er. Next, lithiation for 30 minutes in THF gave (*S*)-**74** (90:10 er) in 52% yield together with cyclised (*S*)-**76** in 24% yield (70:30 er) (Entry 3); starting **36** (20% yield) was also recovered. The combined er was 86:14 er in this case. The total isolated yield of the lithiation in Et_2O (46%) was lower than the one in THF (76%), but the er was slightly higher for the reaction in Et_2O (89:11 er versus 84:16 er). Interestingly, the ^{1}H NMR spectra of the crude product from both Entries 2 and 3 showed similar amounts of products:starting material and thus, a yield higher than 46% was expected from the reaction in Et_2O (Entry 2).



Scheme 2.47

Table 2.11: Asymmetric Lithiation-Trapping of *N*-Boc Imidazolidine **36** at –40 °C with Ph_2CO in Et_2O and THF

Entry	Solvent	Time (min)	Yield (%), er of (*S*)-74[a]	Yield (%), er of (*S*)-76[a]	Yield of rec. SM 36 (%)[a]	Total yield (%)[b]	P : SM 36[c]
1	Et_2O	60	40, 93:7	-	17	40	74:26
2	Et_2O	30	36, 92:8	10, 77:23	26	46	73:27
3	THF	30	52, 90:10	24, 70:30	20	76	78:22
4	Et_2O	20	43, 91:9	6, 75:25	34	49	64:36
5	THF	20	50, 93:7	20, 71:29	26	70	69:31
6	THF	10	45, 91:9	-	21	45	74:26

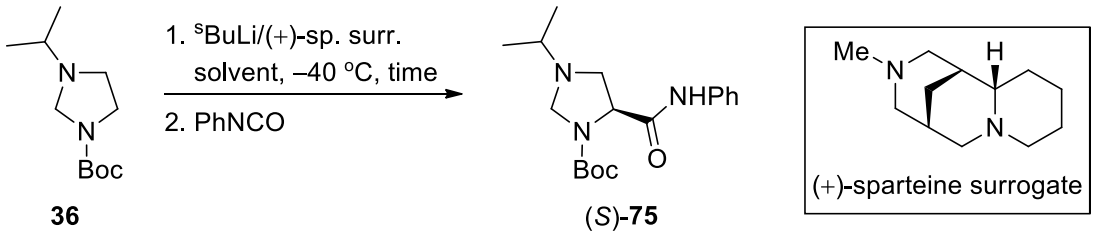
[a]Yield after purification by chromatography; er determined by CSP-HPLC. [b]Total yield of (*S*)-**74** + (*S*)-**76**. [c]P : SM **36** is the ratio of (*S*)-**74** + (*S*)-**76** : **36**, which determined by ^{1}H NMR spectroscopy of the crude product.

A 20 minute lithiation time was also investigated. In Et_2O, (*S*)-**74** was isolated in 43% yield (91:9 er) and (*S*)-**76** in 6% yield (75:25 er) (Entry 4), from which an 89:11 er was calculated; there was also recovered starting **36** (34% yield). In THF, the lithiation-trapping of *N*-Boc imidazolidine **36** afforded (*S*)-**74** in 50% yield (93:7 er) and cyclised (*S*)-**76** in 20% yield (71:29 er) (Entry 5), with an 87:13 er of combined products; starting **36** (26% yield) was also recovered. As was observed with the 30 minute lithiations, ~65-70% conversion of **36** for the lithiation in THF and Et_2O was noticed. In addition, the higher value of recovered starting material **36** (~30-35%) is consistent with the shorter lithiation time compared to the 30 minute lithiations. The reaction in THF gave a better total yield (70%), but a slightly lower er (87:13 er) (Entry 5) than the one

in Et_2O (49% overall yield and 89:11 er, Entry 4). Finally, a 10 minute lithiation in THF gave (*S*)-**74** in 45% yield and 91:9 er and recovered starting **36** (21% yield, Entry 6).

Analysing the products:starting material ratios obtained from the ^1H NMR spectra of the crude reaction mixture, it was clear that conversions of ≥64% were achieved both in Et_2O and THF. These values appeared to be in contrast with the ReactIR™ observations and did not provide any evidence for a solvent effect.

Hence, other electrophiles such as phenyl isocyanate and methyl iodide were explored. The results with phenyl isocyanate are shown in Scheme 2.48 and Table 2.12. Lithiation-trapping of *N*-Boc imidazolidine **36** at –40 °C for 30 minutes in THF or Et_2O gave (*S*)-**75** in 58% (85:15 er) and 48% yield (88:12 er) respectively (Entries 1 and 2). Starting **36** was recovered in 18% yield in THF and 26% yield in Et_2O. When the lithiation was performed for 20 minutes, (*S*)-**75** was isolated in 71% yield and 85:15 er in THF (Entry 3) and in 30% yield (89:11 er) in Et_2O (Entry 4). **36** was recovered in 25% and 11% yield respectively.



36 (*S*)-**75**

Scheme 2.48

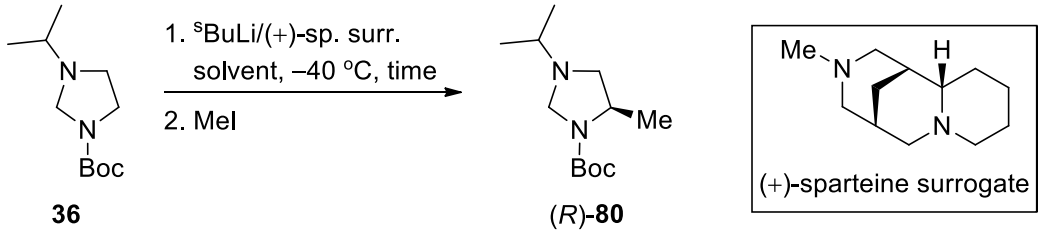
Table 2.12: Asymmetric Lithiation-Trapping of *N*-Boc Imidazolidine **36** at –40 °C with PhNCO in Et_2O and THF

Entry	Solvent	Time (min)	Yield of (*S*)-75 (%)[a]	er[b]	Yield of rec. SM 36 (%)[a]
1	THF	30	58	85:15	18
2	Et_2O	30	48	88:12	26
3	THF	20	71	85:15	25
4	Et_2O	20	30	89:11	11

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Finally, the electrophilic trapping was carried out with methyl iodide (Scheme 2.49 and Table 2.13). Methylated product (*R*)-**80** was obtained in 56% yield (THF) and 39%

yield (Et_2O) from the 30 minute lithiations (Entries 1 and 2), whereas the 20 minute reactions gave (*R*)-**80** in 52% yield (THF) and 37% yield (Et_2O) (Entries 3 and 4). As for the other electrophiles, recovered **36** was also isolated (19-32% yield). Unfortunately, with methylated (*R*)-**80** it was not possible to develop a CSP-HPLC or GC method to determine the er. In addition, we assumed that the use of chiral shift NMR spectroscopy experiments would be ineffective due to the presence of *N*-Boc rotamers. Hence, chiral shift NMR spectroscopy studies were not attempted.



36 (*R*)-**80**

Scheme 2.49

Table 2.13: Asymmetric Lithiation-Trapping of *N*-Boc Imidazolidine **36** at –40 °C with MeI in Et_2O and THF

Entry	Solvent	Time (min)	Yield of (*R*)-80 (%)[a]	Yield of rec. SM 36 (%)[a]
1	THF	30	56	19
2	Et_2O	30	39	22
3	THF	20	52	38
4	Et_2O	20	37	32

[a]Yield after purification by chromatography.

With phenyl isocyanate and methyl iodide it was not possible to determine the conversion of **36** due to the complexity of the ^1H NMR spectra of the crude products. However, the isolated yields in THF were both >50%, whereas 49% yield was the highest yield achieved in Et_2O. Therefore, the observation based on the isolated yields would suggest a solvent effect. Nevertheless, the low starting material recovery showed that more than 50% of **36** was probably lithiated both in Et_2O and THF. Hence, these results could not represent a conclusive evidence for the solvent effect observed in the ReactIR™ spectroscopy experiments.

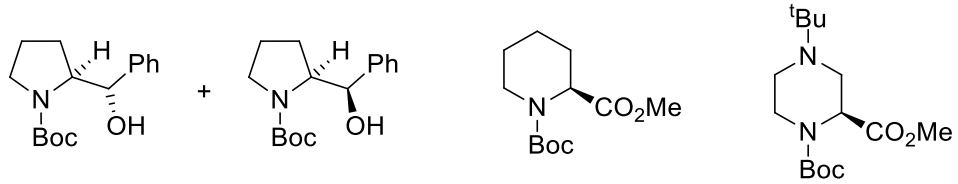
Considering the enantioselectivities, it was noticed that in THF ~85:15 er were obtained with both benzophenone and phenyl isocyanate, whereas in Et_2O these electrophiles

gave ~89:11 er. Hence, the enantioselectivity of the asymmetric lithiation-trapping of *N*-Boc imidazolidine **36** in THF is lower than in Et_2O, as already observed with *N*-Boc pyrrolidine **1** (see Scheme 2.29, Table 2.7).

To conclude this section, we were unable to prove the solvent effect apparently observed in the ReactIR™ spectroscopy studies using synthetic experiments. However, we were very pleased to be able to achieve yields of >50% in the asymmetric lithiation-trapping of *N*-Boc imidazolidine **36**.

2.5 Conclusions and Future Work

In this chapter, it was demonstrated that the asymmetric lithiation and electrophilic trapping of *N*-Boc heterocycles with *s*-BuLi and chiral diamines could be successfully performed at temperatures between –50 and –20 °C, giving good yields (47-95%) and synthetically useful enantioselectivities (77:23-93:7 er). It was also shown that at these temperatures high yields could be achieved even using very short reaction times (2-20 min) (Scheme 2.50). Clearly, the application of this high temperature methodology to process-scale lithiations would potentially reduce the energy cost in using this chemistry.

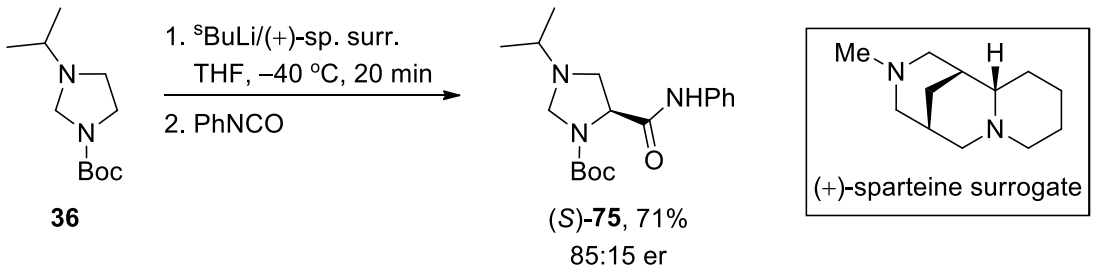


(1*S*,2*S*)-**29**, 67% (1*R*,2*S*)-**30**, 27% (*S*)-**71**, 64% (*S*)-**72**, 71%
90:10 er 90:10 er 80:20 er 82:18 er
(–30 °C, 2 min) (–40 °C, 20 min) (–50 °C, 3 min)

Scheme 2.50

It was also illustrated that the reduction of er observed at high temperatures compared to the results at –78 °C was due to a lower kinetic selectivity and not due to the configurational instability of the lithiated intermediate. However, at temperatures > –20 °C, the lithiated intermediate was considerably configurationally unstable and the loss of er was larger.

Ultimately, we studied the lithiation and electrophilic trapping of *N*-Boc imidazolidine **36**. A solvent effect was highlighted with ReactIR™ spectroscopy studies. Unfortunately, synthetic results were not sufficient to support this observation. However, with the use of THF, we showed that high yields could be obtained (52-76%). For example, lithiation in THF and trapping with phenyl isocyanate gave amide (*S*)-**75** (85:15 er) in 71% yield (Scheme 2.51).



Scheme 2.51

Having developed the asymmetric lithiation-trapping methodology with these *N*-Boc heterocycles, our future plan would be to apply this chemistry in the total synthesis of natural products and pharmaceutically active compounds. Suitable targets could include eletriptan (Relpax®), marketed by Pfizer for the acute treatment of migraine,[2] and (–)-kainic acid as suitable targets (Figure 2.2).

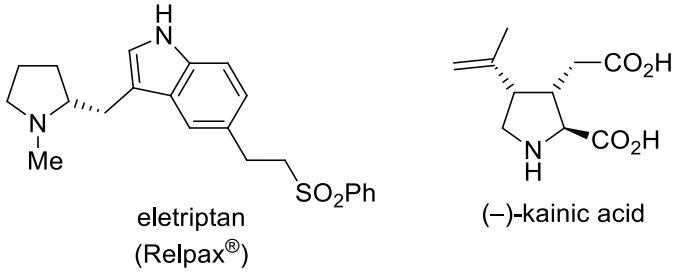
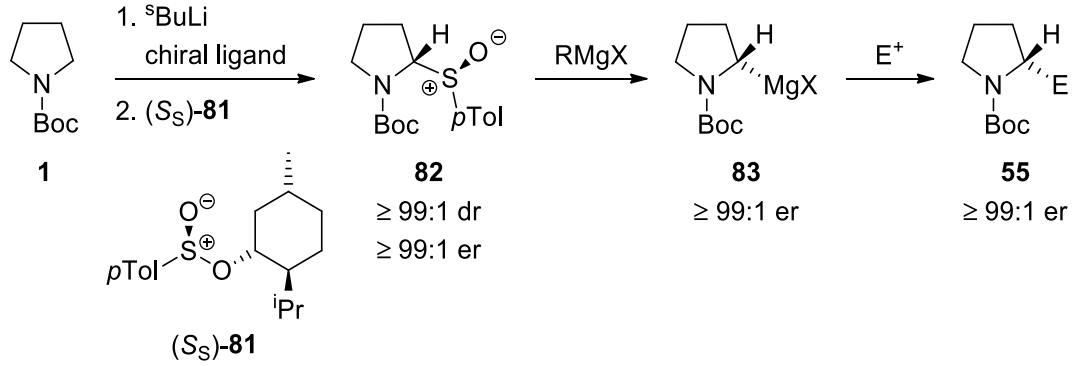


Figure 2.2

Chapter Three: Studies Towards the Synthesis of Stable α-Amino Sulfoxides

One of the main areas of research in our group for the past few years has been the exploration of the synthesis of enantiopure *N*-Boc α-amino sulfoxides such as **82**. These substrates could be used as stable and storable precursors to enantiopure α-substituted *N*-Boc heterocycles. It was hoped that the use of enantiopure *N*-Boc α-amino sulfoxides would address the major limitations related to asymmetric lithiation chemistry: the requirement for low temperatures (−78 °C), long reaction times (1-6 hours) for the lithiations and a typical highest er of the products of ~95:5 er.

The approach proposed in our group to achieve the synthesis of α-amino sulfoxide **82** in ≥99:1 er and ≥99:1 dr was by asymmetric lithiation of *N*-Boc pyrrolidine **1** and trapping with Andersen's sulfinate (S_S)-**81**.[64,65] This would be followed by sulfoxide-magnesium exchange to give Grignard intermediate **83** in ≥99:1 er.[65-67] Finally, electrophilic trapping of the organomagnesium **83** should allow access to α-substituted pyrrolidines **55** in ≥99:1 er (Scheme 3.1).

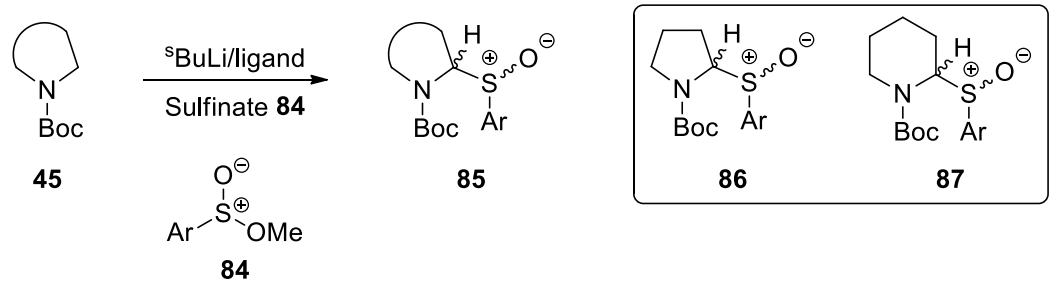


Scheme 3.1

This chapter describes our attempts at synthesising *N*-Boc α-amino sulfoxides such as **82**, including an overview of previous work in the group.

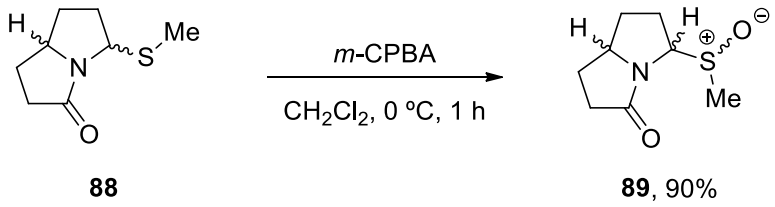
3.1 Overview of Synthetic Approaches to α-Amino Sulfoxides

Although our interest was to access *N*-Boc α-amino sulfoxides such as pyrrolidine sulfoxides **86** and piperidine sulfoxides **87** *via* asymmetric lithiation-trapping of *N*-Boc heterocycles **45** (Scheme 3.2), the lack of literature reporting such a transformation urged us to consider the different methods which have been used to synthesise α-amino sulfoxides.



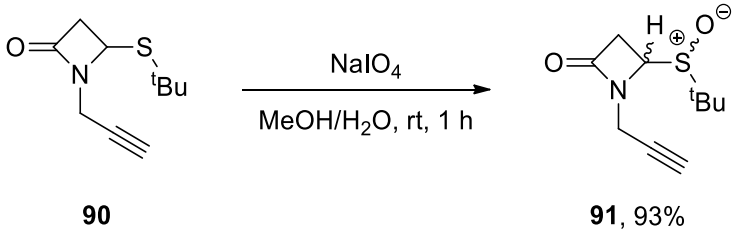
Scheme 3.2

The principal synthetic strategy to α-amino sulfoxides was oxidation of lactam-containing α-amino sulfides. For example, Thomas in 1989, used oxidation of sulfides **88** with *m*-CPBA to prepare a diastereomeric mixture of sulfoxides **89** in 90% yield (Scheme 3.3).[68]



Scheme 3.3

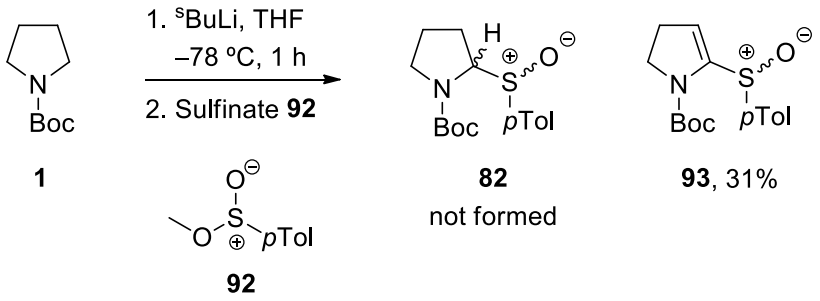
Similarly, a diastereomeric mixture of sulfoxide azetidones **91** was synthesised from sulfide **90** in a high 93% yield using sodium periodate as the oxidising agent (Scheme 3.4).[69] An analogous stable azetidone sulfoxide was used as a precursor for the synthesis of β-lactam antibiotics.[70]



90 **91**, 93%

Scheme 3.4

More recently, research in our group was focused on the synthesis of α-amino *N*-Boc sulfoxides **82**.[71] The use of lithiation-trapping methodology[5] would arguably be the most step efficient route for the synthesis of sulfoxides **82**. Hence, *N*-Boc pyrrolidine **1** was lithiated with *s*-BuLi in THF at −78 °C for 1 hour and then trapped with sulfinate **92**. Under these conditions, instead of the desired sulfoxides **82**, the only product isolated was vinyl sulfoxide **93** (31% yield) (Scheme 3.5). Attempts to synthesise α-amino *N*-Boc sulfoxides **82** *via* oxidation of the corresponding sulfide were also unsuccessful. It is also worth mentioning that the same elimination process was reported for the analogous lithiation-trapping of *N*-Boc piperidine and the corresponding vinyl sulfoxide was the only product isolated.

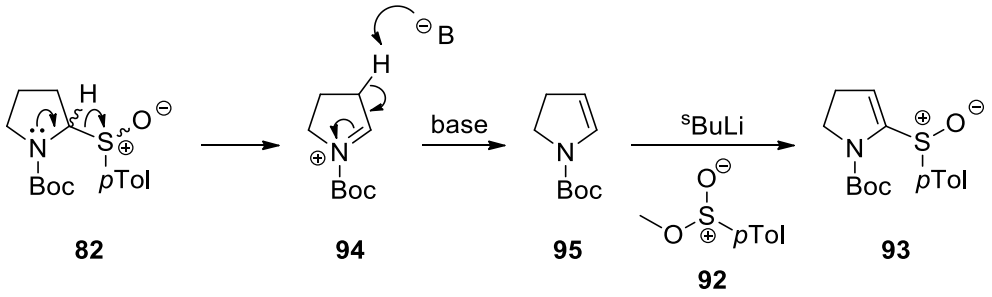


1 **92** **82** not formed **93**, 31%

Scheme 3.5

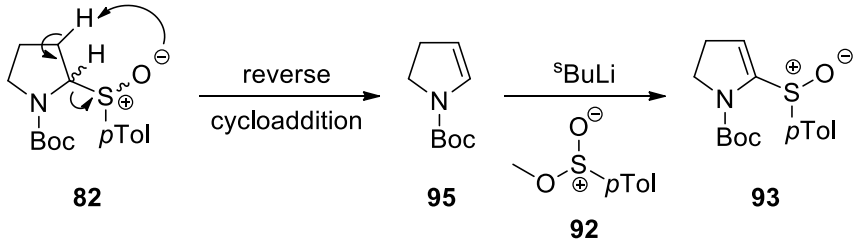
In order to explain these disappointing results, two possible mechanisms which could lead to the formation of the undesired vinyl sulfoxide **93** were proposed: both mechanisms arise from the elimination of the α-sulfoxide group from **82**.[71] First, it was envisaged that an elimination mechanism triggered by the nitrogen lone pair could occur. According to this, the elimination of α-sulfoxide would form iminium ion **94**, which could be subsequently deprotonated by removal of the β-proton to give dihydropyrrole **95**. Finally, **95** could be subjected to vinylic lithiation, as reported by Beak in related systems,[7] and trapped with sulfinate **92** to give vinyl sulfoxide **93** (Scheme 3.6). Notably, the formation of dihydropyrrole **95** was previously reported

from an α-sulfonyl pyrrolidine in the presence of a Lewis acid under ultrasonication conditions.[72]



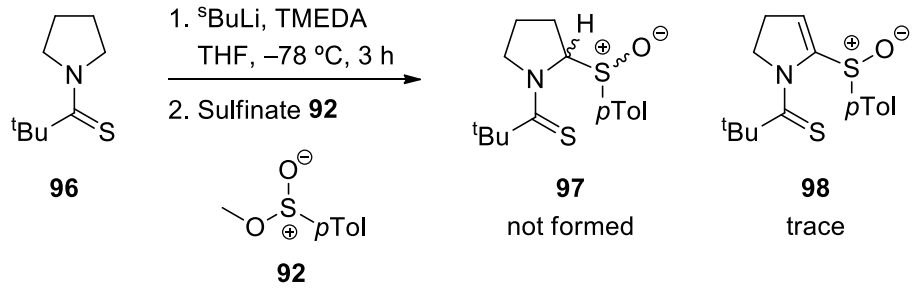
Scheme 3.6

The second mechanism which was hypothesised follows a pericyclic pathway. In this case, sulfoxide **82** would undergo a reverse cycloaddition to give dihydropyrrole **95**, which would be lithiated[7] and trapped with sulfinate **92** to afford vinyl sulfoxide **93** (Scheme 3.7). This mechanism was based on the well-known elimination of sulfoxides.[73] As has been reported, aryl sulfoxides can undergo β-elimination at room temperature, although higher temperatures are usually needed to facilitate the process.[74-76]



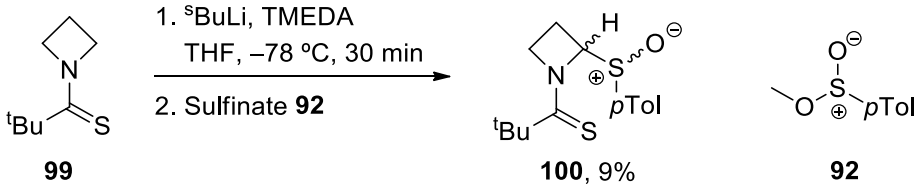
Scheme 3.7

Hence, to understand which elimination mechanism was prevailing, a range of *N*-amido and *N*-thioamido heterocycles were used as substrates in the lithiation-trapping methodology.[77,78] It was suggested that the increased electron withdrawing effect of amide and thioamide groups could make the nitrogen lone pair less available for the α-elimination. However, the lithiation-trapping of *N*-thiopivaloyl pyrrolidine **96** with *s*-BuLi/TMEDA in THF at −78 °C for 3 hours and trapping with sulfinate **92** gave traces of eliminated sulfoxide **98** and no α-amino sulfoxide **97** was formed (Scheme 3.8). Amides were also used, but the lithiation-trapping of these substrates was unsuccessful.



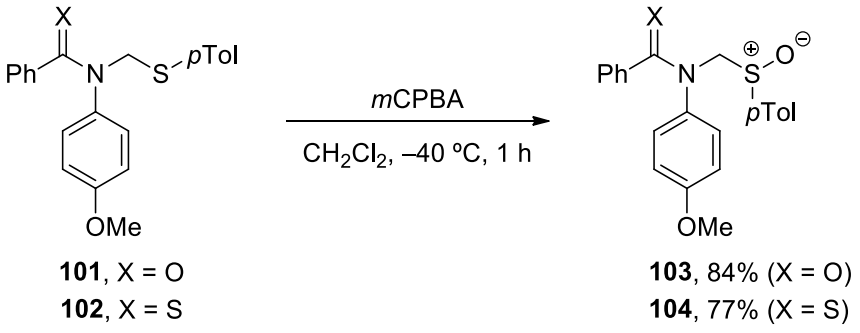
Scheme 3.8

Slightly better results were achieved when *N*-thiopivaloyl azetidine **99** was lithiated. In this case, sulfoxides **100** were isolated in 9% yield (Scheme 3.9). It was suggested that the four-membered ring strain could disfavour both the reverse cycloaddition and the α-elimination. Unfortunately, the use of *s*-BuLi/(–)-sparteine in Et_2O with **99** gave only recovered starting material.



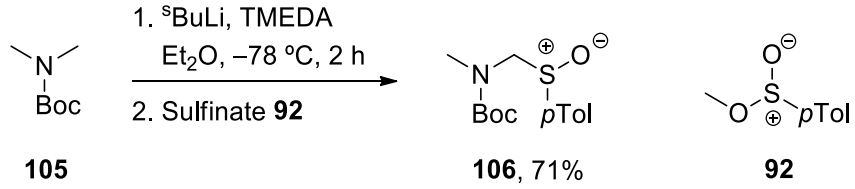
Scheme 3.9

Due to the problems encountered caused by the presumed instability of α-amino sulfoxides, the synthesis of acyclic α-amino sulfoxide was also explored. It was hoped that the absence of β-protons would provide some evidence for which elimination pathway was occurring. Interestingly, the oxidation of benzamide **101** and thiobenzamide **102** with *m*-CPBA gave stable sulfoxides **103** and **104** in high yields, 84% and 77% yield respectively (Scheme 3.10).



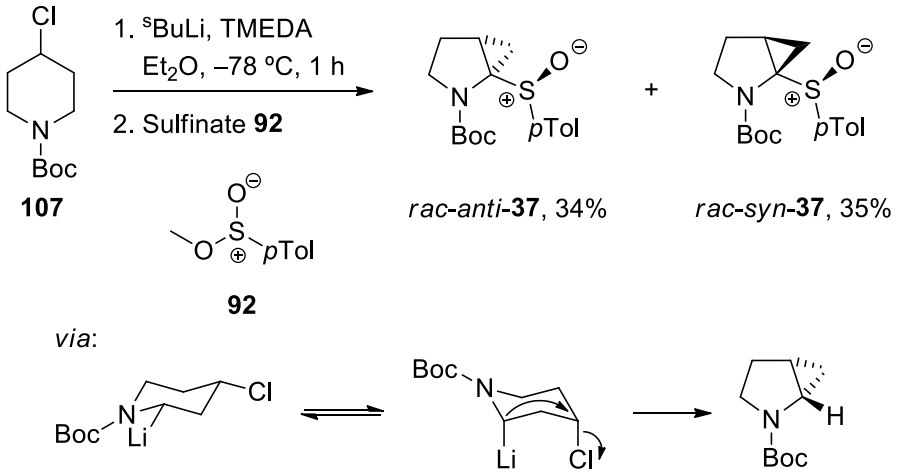
Scheme 3.10

As an acyclic *N*-Boc example, *N*-Boc dimethylamine **105** was lithiated and trapped with sulfinate **92** to give sulfoxide **106** in 71% yield (Scheme 3.11). The stability of acyclic sulfoxides such as **103**, **104** and **106** seemed to support the hypothesis of a reverse cycloaddition pathway. However, the partial instability of **106** on silica (presumably due to α-elimination) prevented our group from having absolute certainty on the elimination process which was occurring.



Scheme 3.11

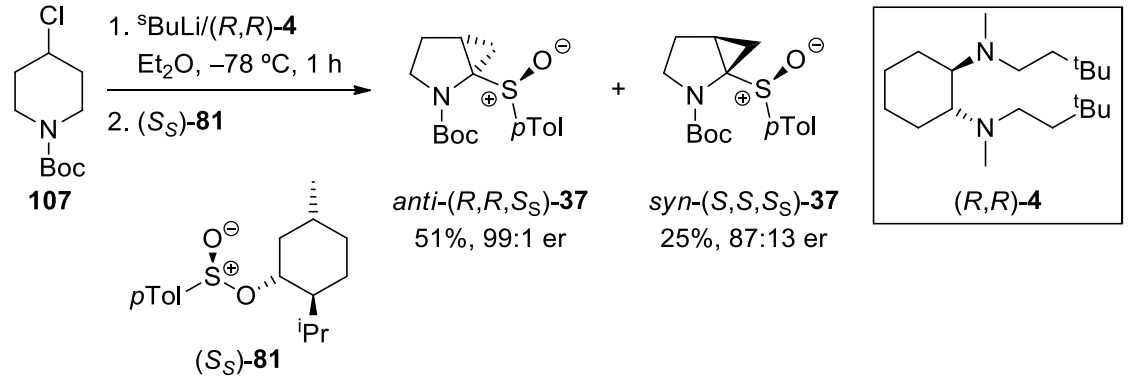
Finally, the problem of the sulfoxide stability was elegantly bypassed using azabicyclo[3.1.0]hexanes.[31] In these substrates, the elimination of the sulfoxide is not allowed by Bredt's rule.[79,80] Azabicyclo[3.1.0]hexanes were synthesised from 4-chloro piperidine **107**, as previously reported by Beak.[81,82] Thus, treatment of 4-chloro *N*-Boc piperidine **107** with *s*-BuLi and TMEDA at –78 °C for 1 hour and subsequent trapping with sulfinate **92** gave diastereoisomers *rac*-*anti*-**37** and *rac*-*syn*-**37** in 51% and 25% yields respectively (Scheme 3.12).



Scheme 3.12

Remarkably, the asymmetric version of the lithiation-trapping of 4-chloro *N*-Boc piperidine **107** performed with *s*-BuLi/diamine (*R*,*R*)-**4** and Andersen's sulfinate (S_S)-**81** led to sulfoxides *anti*-(*R*,*R*,S_S)-**37** (51% yield) in high 99:1 er and *syn*-(*S*,*S*,S_S)-**37** (25% yield) in 87:13 er (Scheme 3.13). The low er observed for *syn*-(*S*,*S*,S_S)-**37** was ascribed

to a competitive sulfoxide-lithium exchange process which could cause an inversion of configuration at the sulfur. Several chiral ligands were explored in order to obtain *syn*-(*S*,*S*,S_S)-**37** in ≥99:1 er, but without any success.



Scheme 3.13

To summarise, from the background knowledge on α-amino sulfoxides in the literature and in our group, we could place the sulfoxides in two principal categories: stable α-amino sulfoxides and unstable α-amino sulfoxides. Stable sulfoxides were both cyclic, such as lactams **89** and **91**, *N*-thiopivaloyl azetidine **100** and *N*-Boc azabicyclo[3.1.0]hexanes **37**, and acyclic such as amide **103**, thioamide **104** and *N*-Boc dimethylamine **106** (Figure 3.1).

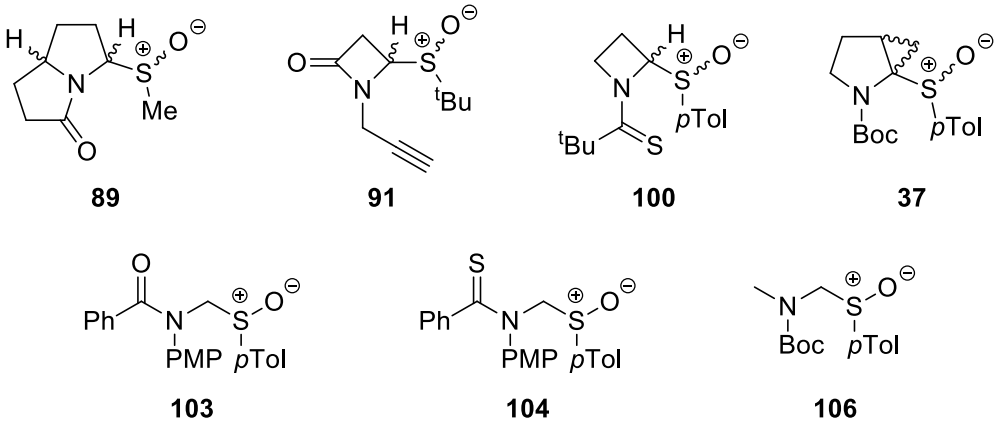
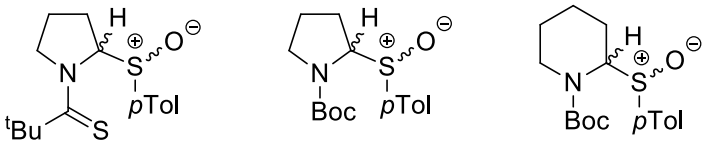


Figure 3.1

In contrast, sulfoxides of amide **96**, *N*-Boc pyrrolidine **82** and *N*-Boc piperidine **108** were unstable and only the corresponding vinyl sulfoxides were isolated from their attempted synthesis *via* lithiation-trapping (Figure 3.2). It can also be concluded that both stable and unstable sulfoxides presented chemical features which made the understanding of the elimination mechanism unclear.



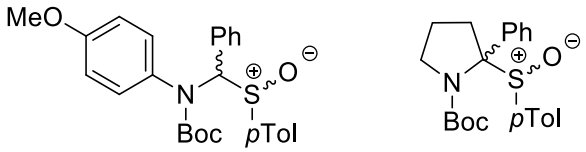
96 **82** **108**

Figure 3.2

3.2 Project Outline

Considering α-amino sulfoxides in Figures 3.1 and 3.2 in relation to the proposed elimination mechanisms, it is possible to notice that the stability could be equally due to a lack of β-protons, or to a delocalisation of the nitrogen lone pair. Therefore, these compounds had not provided a conclusive explanation on the potential pathway for the elimination of the α-sulfoxide group. For this reason, we decided to explore different strategies which could hopefully clarify the elimination process and open the way to the synthesis of stable α-amino sulfoxides.

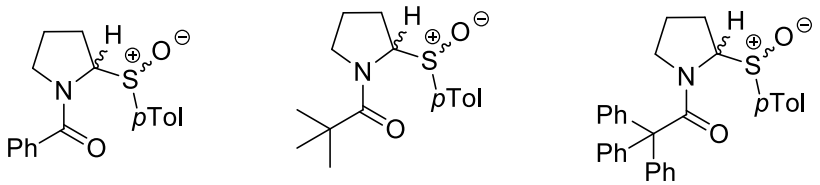
We envisaged three main areas that could help in understanding the elimination mechanism. First, the presence of β-hydrogens that could favour the reverse cycloaddition mechanism would be investigated. For example, comparison of *N*-Boc *p*-anisidine sulfoxide **40**, which has no β-hydrogens, and 2-phenyl 2-sulfoxide *N*-Boc pyrrolidine **41**, having β-hydrogens, could give an insight into the reverse cycloaddition mechanism (Figure 3.3).



40 **41**

Figure 3.3

The second strategy would be to make the nitrogen lone pair less available, so that it would not promote the α-elimination of the sulfoxide. For this, due to the more electron-withdrawing character of amides, *N*-acyl pyrrolidine sulfoxides **109**-**111** were chosen as potential targets to be synthesised (Figure 3.4).



109 **110** **111**

Figure 3.4

Finally, we developed a conformational hypothesis. In the two previous series (*N*-Boc or *N*-acyl), the nitrogen is sp^2 hybridised and thus it is planar. In those molecules, $A_{1,3}$ strain will force the α-sulfoxide substituent to occupy a *pseudo*-axial position.[18] This is suitably aligned with the nitrogen lone pair and thus the elimination would be favoured (Figure 3.5, **A**). In contrast, a pyrrolidine ring with a pyramidal sp^3 nitrogen would prefer to place the substituent in a *pseudo*-equatorial position, which would hopefully make the α-elimination less favourable (**B**). This could be achieved with a *N*-sulfonyl or *N*-alkyl group.

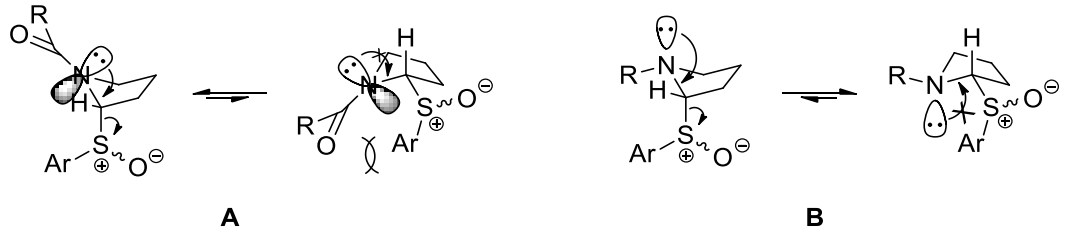


Figure 3.5

However, the possibility for the pyrrolidine ring with sp^3 hybridised nitrogen (**B**) to ring-flip and generate the conformation which leads to α-elimination, could result in unstable and non-isolable α-amino sulfoxides. For this reason, we proposed the exploration of more conformationally locked substrates such as 4-substituted piperidines *rac-syn*-**112** and *rac-syn*-**113** (Figure 3.6). Our efforts in exploring these three approaches are described in the following sections.

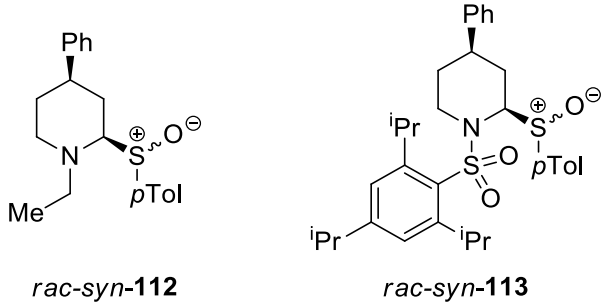
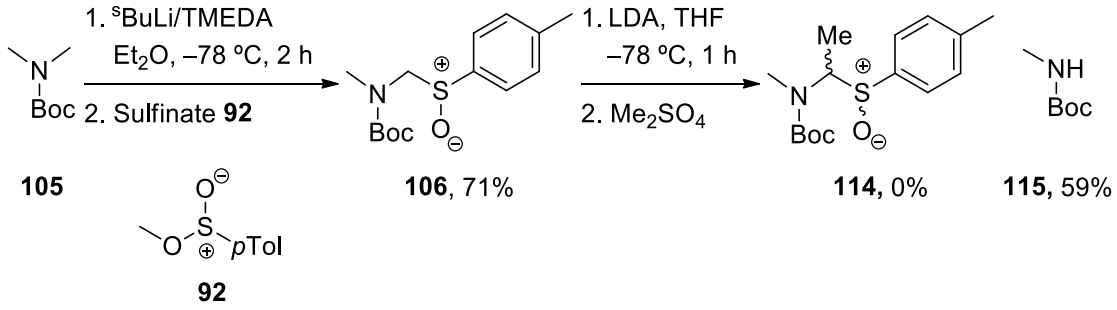


Figure 3.6

3.3 Attempted Synthesis of Acyclic and Cyclic α-Amino Sulfoxides

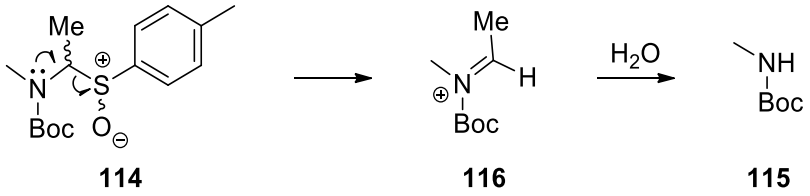
3.3.1 Attempted Synthesis of Acyclic *N*-Boc α-Amino Sulfoxides

We decided to start the exploration by comparing substrates with and without β-protons. Previous results in our group had shown that sulfoxide **106** was stable and could be easily synthesised *via* α-lithiation-trapping of *N*-Boc dimethylamine **105**. Thus, treatment of **105** with *s*-BuLi/TMEDA in Et_2O and trapping with sulfinate **92** gave **106** in 71% yield. Further substitution of **106** was considered *via* deprotonation and trapping. First, the lithiation of sulfoxide **106** was attempted using LDA in THF at –78 °C. A 10 minute reaction time followed by electrophilic trapping with Me_2SO_4 showed only unreacted starting material **106** by ^{1}H NMR spectroscopy of the crude product. Thus, the lithiation time was increased to 1 hour. Unfortunately, under these conditions the product obtained was not the expected sulfoxide **114**. Instead, *N*-Boc methylamine **115** was the only product isolated after flash column chromatography in 59% yield (Scheme 3.14).



Scheme 3.14

Analysing the ^{1}H NMR spectrum of the crude product, it was not possible to identify any trace of *N*-Boc methylamine **115**. Therefore, we hypothesised that **115** was formed during purification on silica. A probable mechanism proceeds *via* the formation of the desired sulfoxide **114**, which can then eliminate the sulfoxide to give iminium ion **116** and its hydrolysis can then give *N*-Boc methylamine **115** (Scheme 3.15). It is worth noticing that, in sulfoxide **114**, elimination *via* β deprotonation could also be occurring. Trapping with Me_3SiCl was also attempted, but the ^{1}H NMR spectrum of the crude product showed only decomposition of the starting sulfoxide **106**.

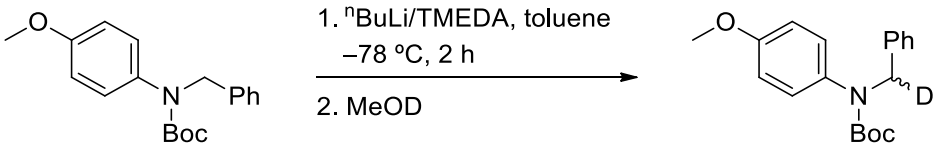


114 **116** **115**

Scheme 3.15

Despite the simple structure of sulfoxide **106**, its α-lithiation-trapping was more difficult than expected and the inability to isolate the desired sulfoxide **114** discouraged us from using **106** as a substrate for further exploration.

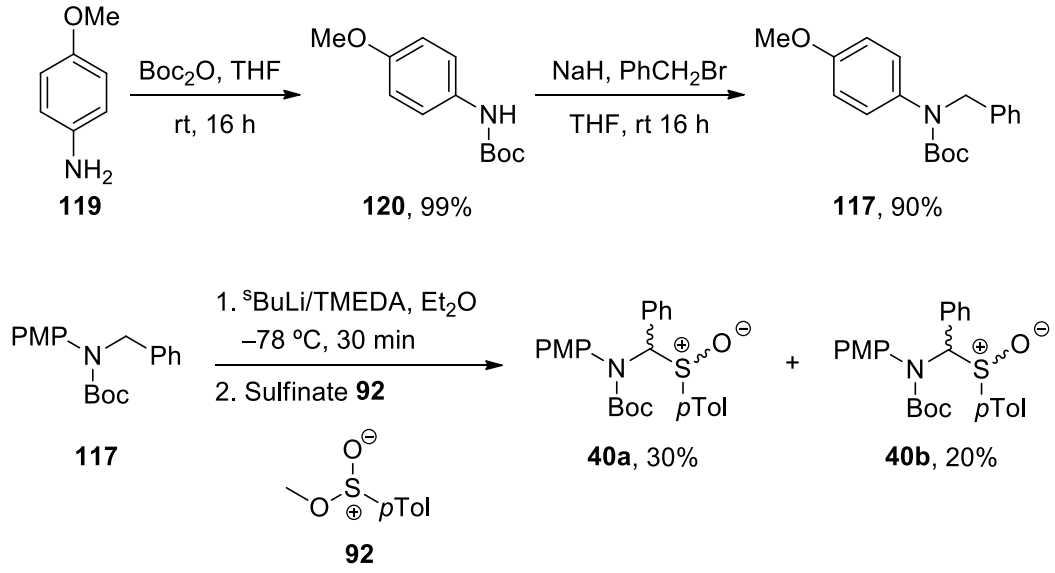
Our interest was then attracted by the stability of sulfoxide amide **103** and thioamide **104** (see Scheme 3.10). We wondered whether the *N*-Boc *p*-anisidine analogue **117** could give stable sulfoxides upon lithiation-trapping. The racemic benzylic lithiation of **117** was reported by Beak in 1997.[83] In 2008, Clayden used *n*-BuLi and TMEDA to lithiate **117** at −78 °C in toluene for 2 hours. After quenching with MeOD, deuterated **118** was formed in 99% yield (Scheme 3.16).[84,85] In addition, our experience on the benzylic lithiation-trapping of 2-phenyl pyrrolidine (*vide infra*) suggested that a lithiation time of 2 hours was not required if *s*-BuLi/TMEDA was used and we proposed a 30 minute reaction time in Et_2O at −78 °C.



117 **118**, 99%

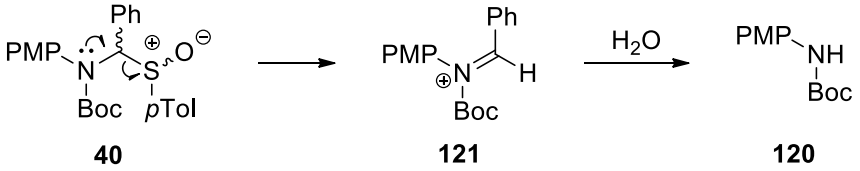
Scheme 3.16

Thus, *N*-Boc *N*-benzyl *p*-anisidine **117** was synthesised from *p*-anisidine **119** in 89% yield over two steps, according to the procedure reported by Beak *et al.*[86,87] *N*-Boc *p*-anisidine **117** was then lithiated using *s*-BuLi and TMEDA in Et_2O at −78 °C for 30 minutes. To our initial delight, the trapping with sulfinate **92** gave two diastereomeric sulfoxides **40a** and **40b** in 30% and 20% yield respectively, which were isolated after flash column chromatography (Scheme 3.17).



Scheme 3.17

Unluckily, it was noticed that sulfoxides **40a** and **40b** decomposed on standing. Subsequent attempts to repeat the lithiation-trapping reaction in Scheme 3.17 were unsuccessful and none of the products were isolated. Instead, *N*-Boc *p*-anisidine **120** was isolated in quantitative yield. In contrast to sulfoxide **114**, in sulfoxides **40a** and **40b**, the mechanism for the elimination of the sulfoxide must be due to the nitrogen lone pair as there are no β-protons in the molecule. We believe that the stabilised iminium ion **121** is formed and then hydrolysed to give **120** (Scheme 3.18).



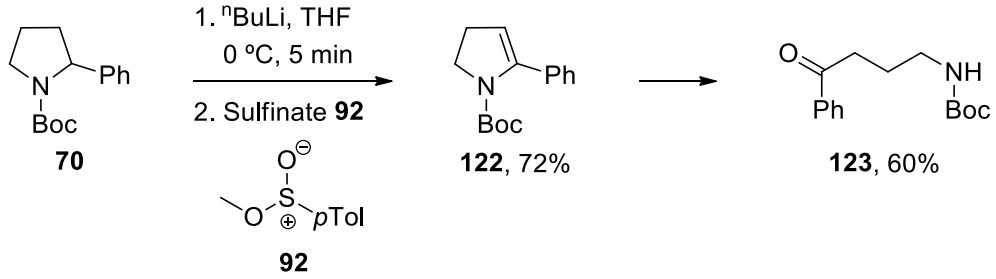
Scheme 3.18

From the above reactions, the only clear result was that both *N*-Boc dimethylamine sulfoxide **114** and *N*-Boc *p*-anisidine sulfoxide **40** were unstable. As shown in Scheme 3.15 and Scheme 3.18, the mechanisms proposed for their instability could proceed *via* the nitrogen lone pair elimination. Indeed, with **40** this is the only mechanism which could happen, although with **114** both the reverse cycloaddition and the α-elimination pathways are possible. Therefore, these results are not conclusive and add only partial support for the mechanism triggered by the nitrogen lone pair. Finally, due to the lack of

success with these substrates, we decided not to explore other acyclic substrates and our interest shifted to cyclic compounds.

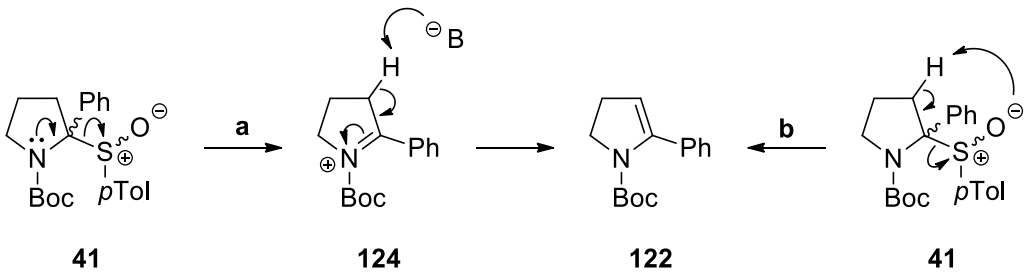
3.3.2 Attempted Synthesis of 2-Phenyl 2-Sulfoxide *N*-Boc Pyrrolidine 41

To start the investigation on cyclic substrates, we considered *N*-Boc 2-phenyl pyrrolidine **70** which has been proven to be a versatile substrate for benzylic lithiation-trapping methodology, as discussed in section 4.2.2 (*vide infra*). We hypothesised that a bulky substituent like a phenyl group could force the sulfoxide substituent into a conformation that would reduce the chances of elimination. Thus, following the reported procedure, *N*-Boc 2-phenyl pyrrolidine **70** was lithiated and trapped with sulfinate **92**. Purification by flash column chromatography gave only 2-phenyl dihydropyrrole **122** in 72% yield. This compound was found to be unstable and, on standing, **122** was completely hydrolysed to amino butyrophenone **123** (Scheme 3.19). The same instability of compound **122** was also observed by Tomooka.[88]



Scheme 3.19

The formation of **122** presumably proceeds *via* the desired phenyl sulfoxides **41**, which then α-eliminates the sulfoxide following pathway **a** or **b** to give **122**. The lack of an α proton in **122** does not allow vinylic lithiation as in the previous substrates (see Scheme 3.6) and thus, dihydropyrrole **122** was isolated (Scheme 3.20).

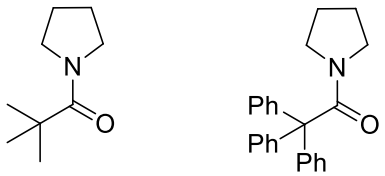


Scheme 3.20

Although the outcome of the lithiation reaction was completely unexpected, this result provides an interesting route to synthesise dihydropyrrole **122**, which could be used for further transformations. In addition, there is only one report on this compound in the literature.[88] However, the results obtained with *N*-Boc *p*-anisidine **117** and *N*-Boc 2-phenyl pyrrolidine **70** provided inconclusive evidence on the elimination mechanism.

3.3.3 Attempted Synthesis of Cyclic *N*-Amido and *N*-Sulfonamido Pyrrolidine Sulfoxides *via* Tin-Lithium Exchange

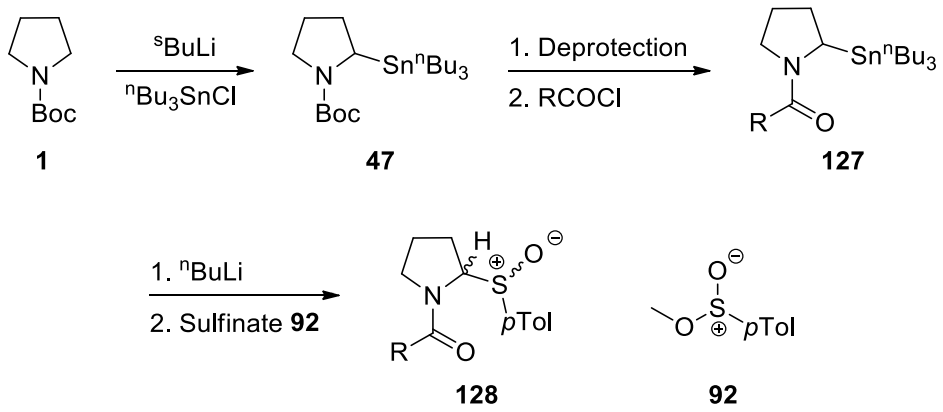
Some of the stable, isolated sulfoxides had an amide or a thioamide group, such as **103** and **104** (see Figure 3.1), and it was believed that the higher electron-withdrawing property of the amide group could improve the stability of these sulfoxides. In an amide group, the nitrogen lone pair can be easily delocalised through the amidic bond and thus it will be less available to trigger the α-elimination of the sulfoxide. Therefore, the idea was to attempt the synthesis of amide sulfoxides. Previous attempts in our group showed that the α-lithiation of pyrrolidine amides **125** and **126** (Figure 3.7) was not successful, due to nucleophilic addition of the organolithium base to the amide carbonyl group.[71]



125 **126**

Figure 3.7

Therefore, a different synthetic pathway which could lead to the desired *N*-amido α-sulfoxides **128** was planned. As shown in scheme 3.21, the designed route requires initial formation of *N*-Boc tributyltin pyrrolidines **47** which would then be Boc-deprotected and acylated to form amides **127** as key intermediates. Tin-lithium exchange[89] of **127**, followed by trapping with aryl sulfinate **92** could eventually give the desired *N*-amido α-sulfoxides **128**. Tributyltin amides **129**-**131** (Figure 3.8) were selected as candidates for the tin-lithium exchange in our exploration.



Scheme 3.21

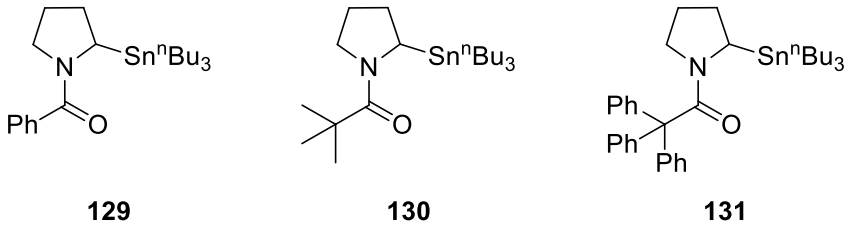
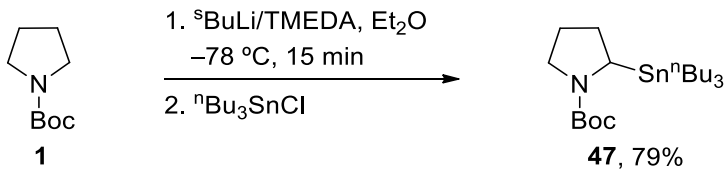


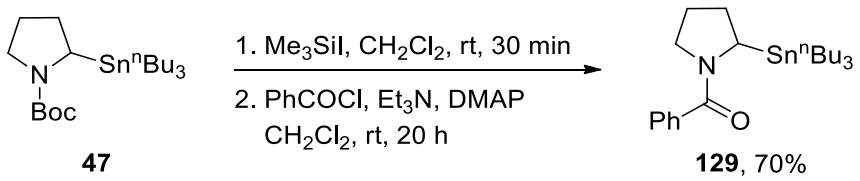
Figure 3.8

The lithiation of *N*-Boc pyrrolidine **1** (10 mmol) was performed with *s*-BuLi and TMEDA in Et_2O at −78 °C for 15 minutes. Trapping with Bu_3SnCl gave *N*-Boc 2-stannyl pyrrolidine **47** in 79% yield (Scheme 3.22). Unfortunately, subsequent Boc deprotection using TFA resulted in decomposition when isolation of the amine was attempted.



Scheme 3.22

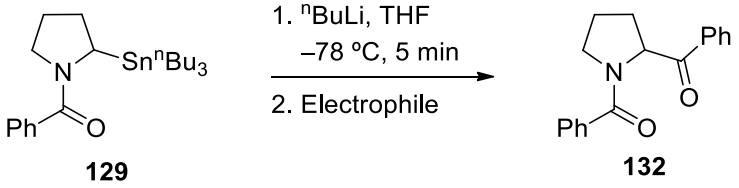
However, treatment of the crude stannyl amine with benzoyl chloride afforded the desired *N*-acylated pyrrolidine. First, Boc deprotection was carried out with TFA in CH_2Cl_2 and then the crude product was reacted with benzoyl chloride in a $NaOH_{(aq)}$ and CH_2Cl_2 system to give *N*-benzyl pyrrolidine **129** in a low 7% yield. Luckily, performing the deprotection with Me_3SiI as reported by Gawley,[90] and then reacting with benzoyl chloride, Et_3N and DMAP in CH_2Cl_2 gave **129** in 70% yield (Scheme 3.23).



47 **129**, 70%

Scheme 3.23

The next step was the tin-lithium exchange of **129**. Thus, *N*-benzoyl pyrrolidine **129** was treated with *n*-BuLi in THF at −78 °C for 5 minutes followed by the addition of the electrophile (Scheme 3.24 and Table 3.1). Interestingly, when MeOH or sulfinate **92** were used, ketone **132** was the only product isolated in 48% yield (Entry 1) and 62% yield (Entry 2) respectively. Trapping with PhCHO resulted in a complex mixture of products which was not purified (Entry 3).



129 **132**

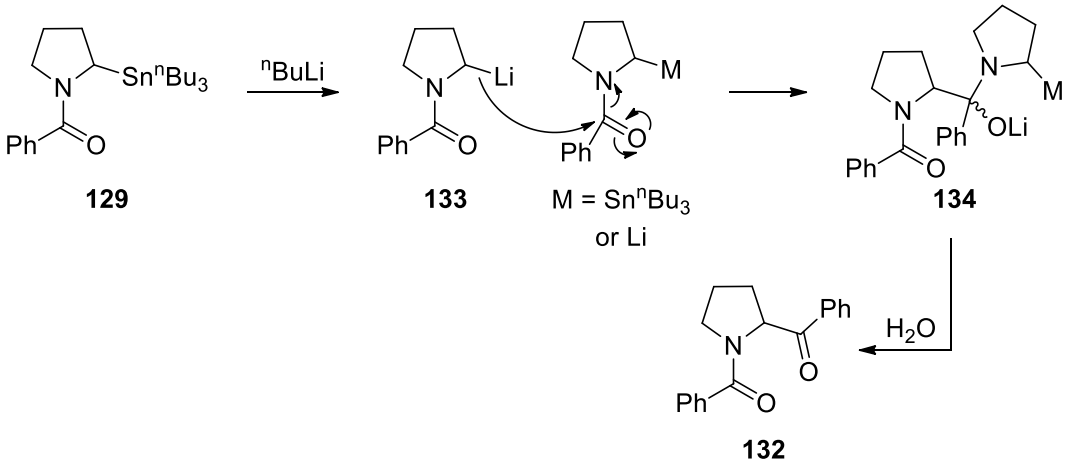
Scheme 3.24

Table 3.1: Tin-lithium Exchange of *N*-Benzoyl Pyrrolidine **129**

Entry	Electrophile	Yield of 132 (%)[a]
1	MeOH	48
2	Sulfinate **92**	62
3	PhCHO	-

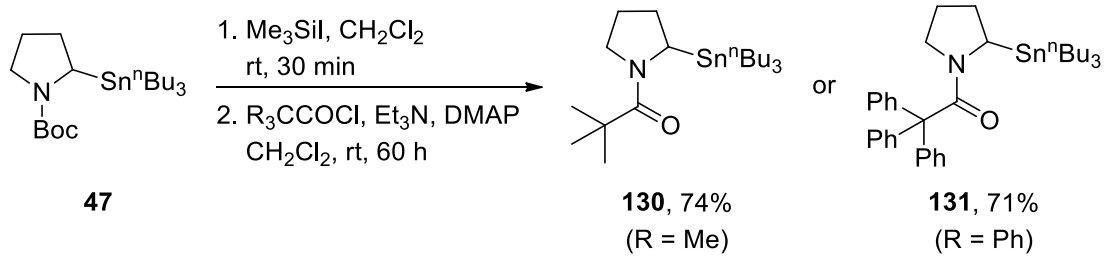
[a]Yield after purification by chromatography.

A proposed mechanism for the formation of ketone **132** is shown in Scheme 3.25. First, tin-lithium transmetallation of *N*-benzoyl pyrrolidine **129** would form lithiated intermediate **133**, which could subsequently act as a nucleophile on the amide C=O of another molecule of **129** or **133**. Aqueous work-up would then cause hemi-aminal **134** to collapse to ketone **132**.



Scheme 3.25

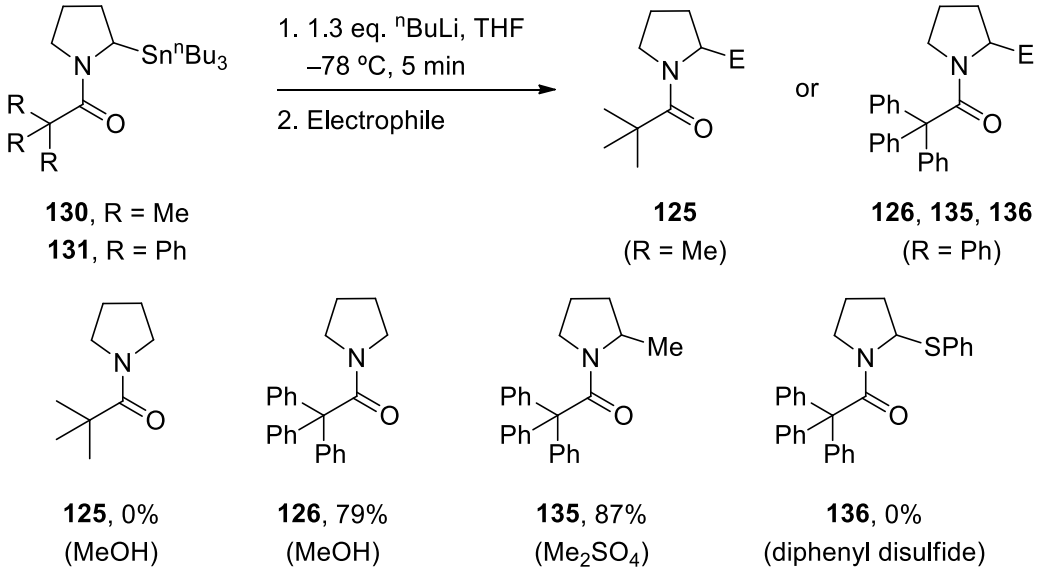
We envisaged that the formation of ketone **132** could be due to the ability of the nucleophile to approach the C=O group. Thus, we thought that by increasing the steric hindrance of the substituents on the amide moiety the nucleophilic attack on the C=O group could be prevented. For this purpose, pivaloyl pyrrolidine **130** and triphenylacetyl pyrrolidine **131** (see Figure 3.8) were synthesised from *N*-Boc stannyl pyrrolidine **47** using Me_3SiI deprotection followed by amide formation as shown in Scheme 3.26. For **131**, triphenylacetic acid was activated with oxalyl chloride and DMF before use in the acylation step.



Scheme 3.26

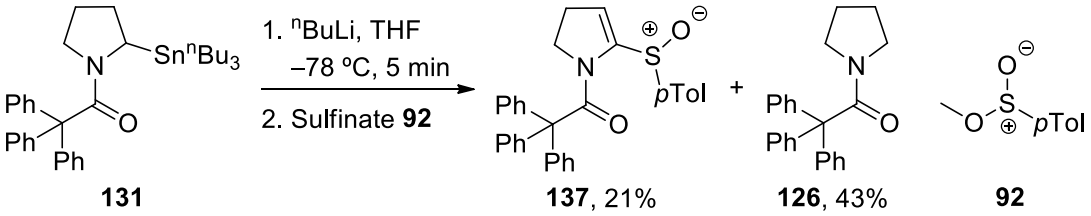
Tin-lithium exchange of amide **130** and **131** was attempted using the procedure employed for *N*-benzoyl pyrrolidine **129**: *n*-BuLi, THF at –78 °C for 5 minutes (Scheme 3.27). To probe whether the transmetallation was occurring, MeOH was used as the electrophile. With pivaloyl amide **130**, the tin-lithium exchange and MeOH trapping did not work and gave an unidentified mixture of products, where the desired amide **125** was not present. Using **131** as the substrate, transmetallation followed by

electrophilic trapping afforded **126** (MeOH) and **135** (Me_2SO_4) in 79% and 87% yields respectively; in contrast, trapping with diphenyl disulfide was unsuccessful.



Scheme 3.27

Encouraged by the result obtained with triphenylacetyl amide **131**, we decided to attempt the trapping with sulfinate **92**. Unfortunately, in this case, the only product isolated after flash column chromatography was dihydropyrrole sulfoxide **137** in low 21% yield (Scheme 3.28), resulting from the elimination of the sulfoxide group.

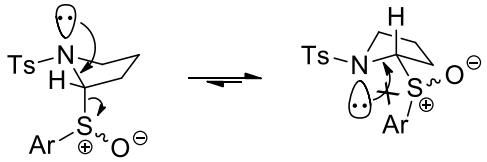


Scheme 3.28

To our disappointment, the tin-lithium transmetallation and electrophilic trapping of amides **129**, **130** and **131** was unsuccessful either because the substrate was not stable to the reaction conditions (**129** and **130**), or because the sulfoxide group was eliminated as had happened with *N*-Boc protected amines.

We therefore decided to try an sp^3 hybridised nitrogen and it has been reported that the nitrogen in *N*-tosyl pyrrolidine **141** is pyramidalised in the crystalline state.[91] Therefore, if *N*-tosyl sulfoxide **138** was formed, then it would prefer a conformation with all the

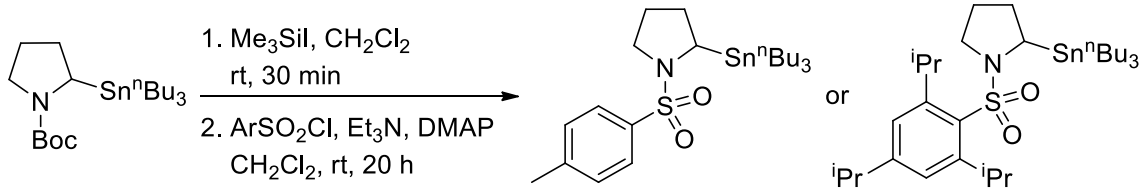
substituents in *pseudo*-equatorial positions as in **138b** (Scheme 3.29). This conformation should disfavour the α-elimination of the sulfoxide because the nitrogen lone pair is not suitably aligned with the leaving group.



138a **138b**

Scheme 3.29

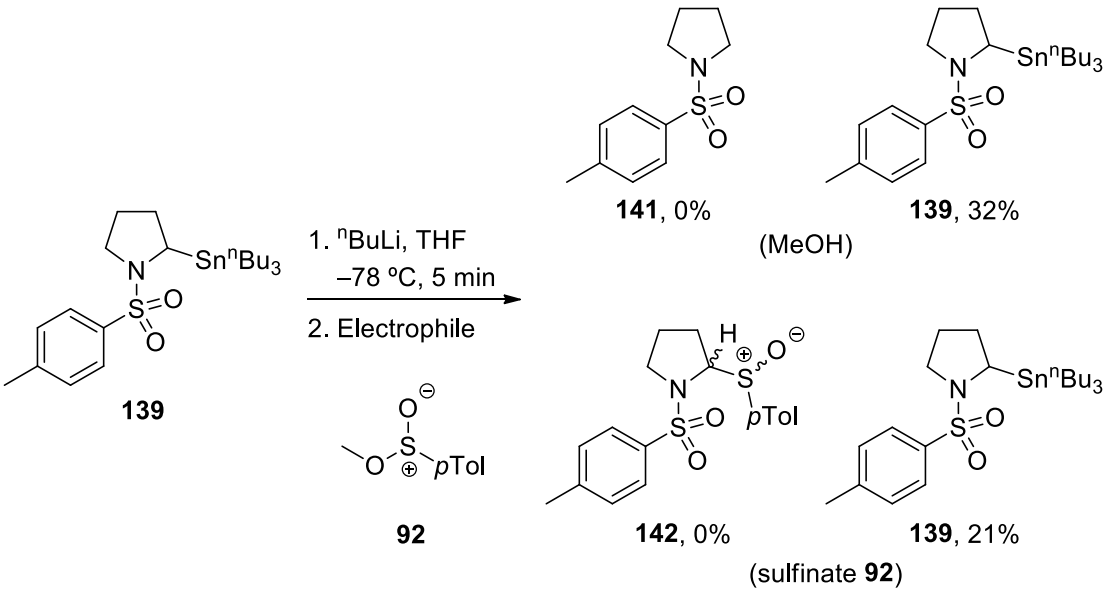
Hence, *N*-tosyl stannyl pyrrolidine **139** and *N*-2,4,6-tri-*i*-Pr-phenyl sulfonyl stannyl pyrrolidine **140** were prepared from *N*-Boc stannyl pyrrolidine **47**. Deprotection with Me_3SiI followed by treatment with tosyl chloride or 2,4,6-tri-*i*-Pr-aryl sulfonyl chloride afforded **139** (57% yield) and **140** (50% yield) respectively (Scheme 3.30).



47 **139**, 57% Ar = *p*-tolyl **140,** 50% Ar = 2,4,6-$^{i}Pr_3$-phenyl

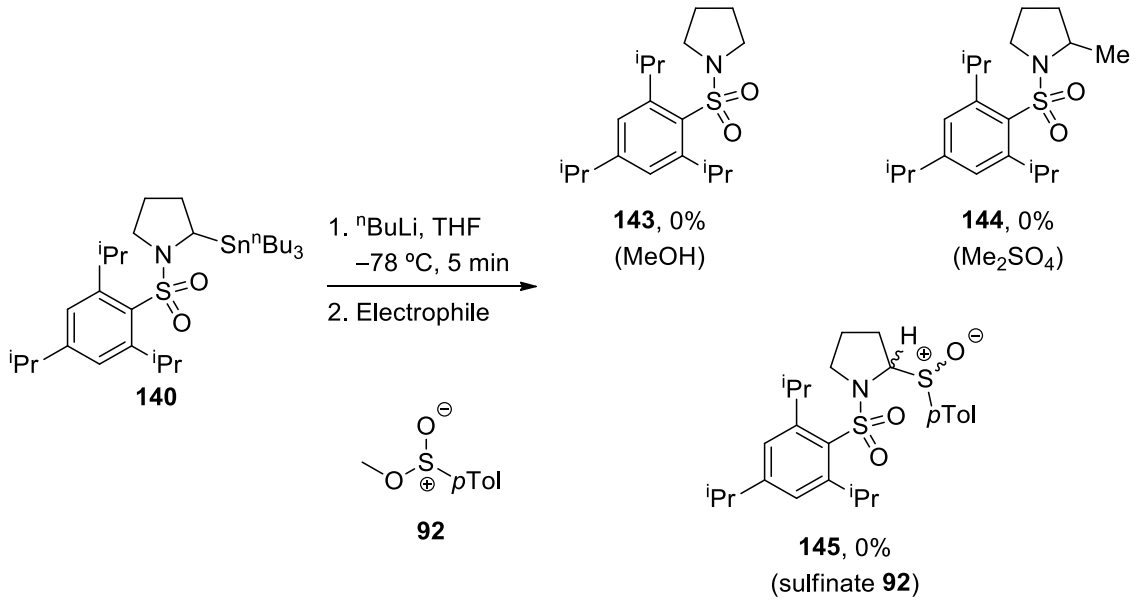
Scheme 3.30

The tin-lithium transmetallation was initially attempted on tosyl pyrrolidine **139**. Electrophilic trapping with MeOH gave only recovered starting **139** in 32% yield. With addition of sulfinate **92**, the desired sulfoxide was not formed and, after purification, starting material **139** was isolated in 21% yield (Scheme 3.31). Due to the low yields of recovered **139** in both reactions, we can assume that the tin-lithium exchange process could happen, but this could be followed by further reactivity of the intermediate. Unfortunately, we were unable to isolate any other products to validate this theory.



Scheme 3.31

No better results were obtained with the tin-lithium exchange of 2,4,6-tri-*i*-Pr-aryl sulfonyl pyrrolidine **140**. A complex mixture of products was observed in the ^{1}H NMR spectra of the crude products when MeOH or sulfinate **92** were used as electrophiles, whereas starting material **140** was the sole product after attempted trapping with Me_2SO_4 (Scheme 3.32). Frustratingly, despite our efforts, we were not able to isolate stable amino sulfoxides *via* tin-lithium exchange of pyrrolidine amides and sulfonamides.

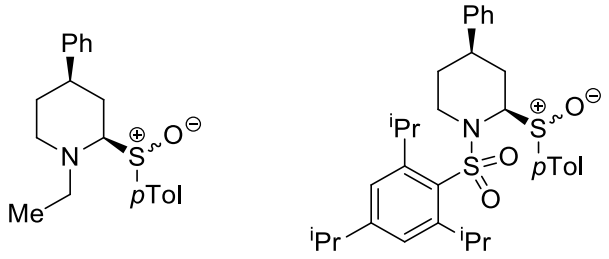


Scheme 3.32

The use of *N*-amido and *N*-sulfonamido pyrrolidines in the lithiation chemistry presented reactivity issues other than the stability of the α-amino sulfoxides, which were never detected anyway. This represented a major problem with these substrates and did not allow any development of understanding the elimination mechanism. For these reasons, we decided to abandon the line of research with pyrrolidine substrates.

3.4 Attempted Synthesis of 4-Phenyl Piperidine Sulfoxides

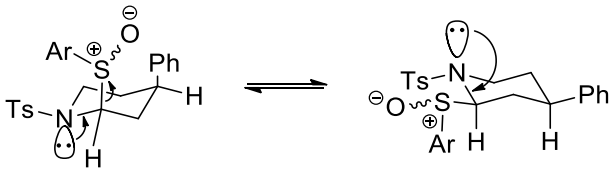
Irrespective of the results with the pyrrolidines series, we moved our interest to the exploration of six-membered ring substrates such as 4-phenyl *N*-ethyl piperidine sulfoxide *rac-syn*-**112** and 4-phenyl *N*-sulfonamido piperidine sulfoxide *rac-syn*-**113** (Figure 3.9).



rac-syn-**112** *rac-syn*-**113**

Figure 3.9

At first, we assumed that, by analogy with *N*-tosyl pyrrolidines **141**, *rac-syn*-**112** and *rac-syn*-**113** have the nitrogen with sp^3 hybridisation. In addition, it is known that the lithiation of 4-phenyl *N*-Boc piperidines tend to give *syn* diastereoisomers as the sole products.[4,92] Combining these two factors, it possible to predict that between the two possible conformations which can be adopted, the favoured one is that with the substituents in the equatorial position **146b** (Scheme 3.33). As shown for **138b**, in this conformation the α-elimination of sulfoxide should be disfavoured.



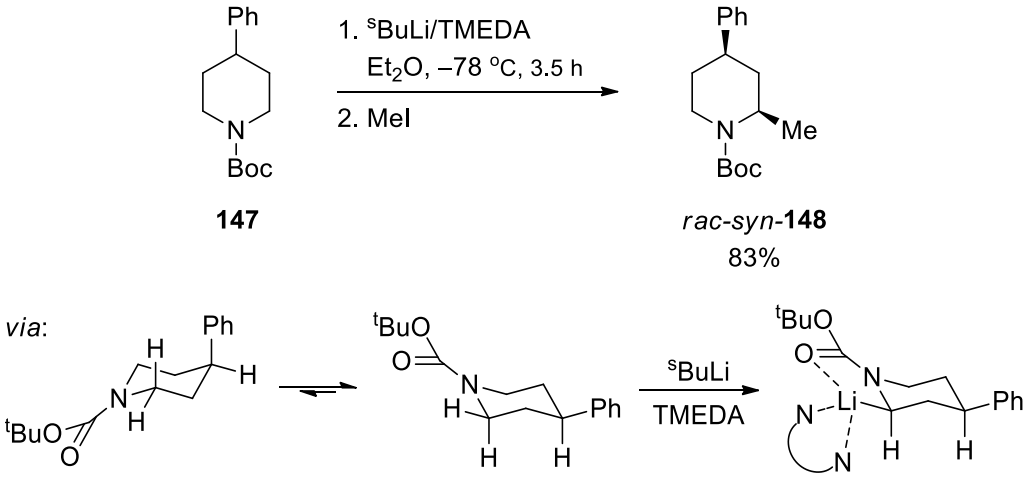
146a **146b**

Scheme 3.33

3.4.1 Lithiation-Trapping of 4-Phenyl *N*-Boc Piperidine 147

The racemic lithiation-trapping of 4-phenyl *N*-Boc piperidine **147** was first reported by Beak and Lee in 1989.[4] Lithiation of **147** with *s*-BuLi and TMEDA in Et_2O at –78 °C for 3.5 hours, followed by trapping with methyl iodide gave methyl piperidine *rac-syn*-**148** in 83% yield (Scheme 3.34). Subsequently, it was demonstrated that the

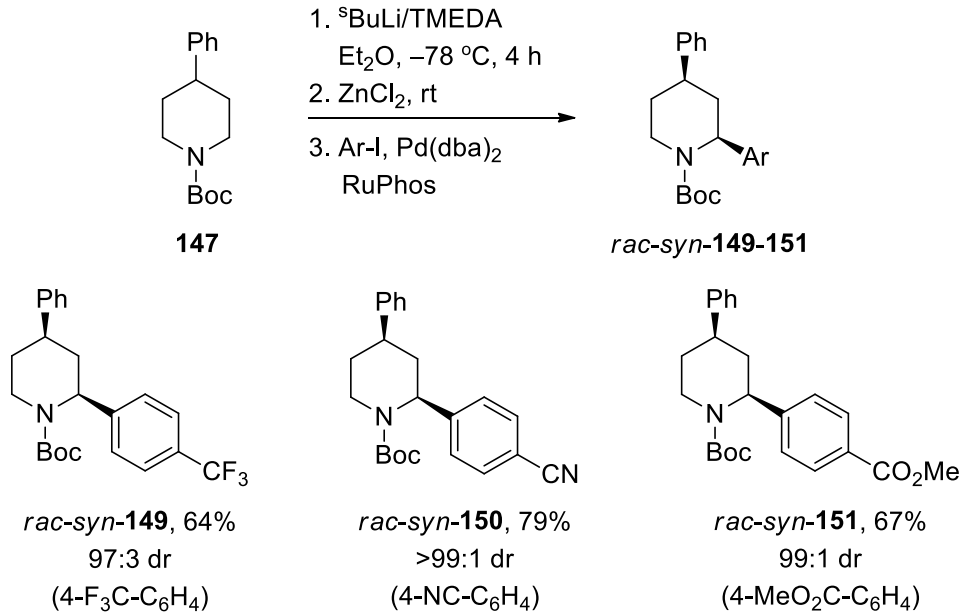
stereochemical outcome of these reactions follows the removal of an equatorial α-proton from a chair-like conformation with the 4-substituent also in the equatorial position. Then, the electrophilic trapping proceeds with retention of configuration to give 2,4-*syn* disubstituted products.[6,7]



Scheme 3.34

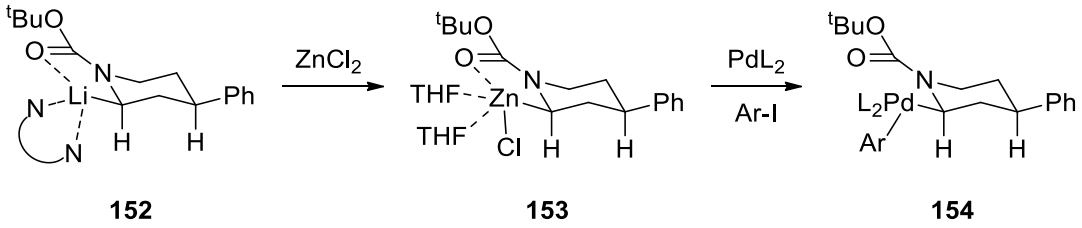
It is worth noticing that this procedure, *s*-BuLi and TMEDA in Et_2O at −78 °C for 3.5 hours, was also applied to 4-methyl piperidine which was trapped with methyl iodide to give 41% yield of the methylated product.[4]

More recently, Knochel reported the Negishi cross-coupling of 4-aryl *N*-Boc piperidines.[92] Lithiation of **147** with *s*-BuLi and TMEDA in Et_2O at −78 °C was followed by transmetallation with $ZnCl_2$. Then, the organozinc was reacted with a mixture of aryl iodide, $Pd(dba)_2$ and RuPhos to give α-arylated products *rac-syn*-**149**-**151** in good yields (64-79% yield) and high diastereoselectivities (97:3 to >99:1 dr) (Scheme 3.35). Full details of the lithiation-Negishi coupling reaction will be discussed in section 4.2.1.



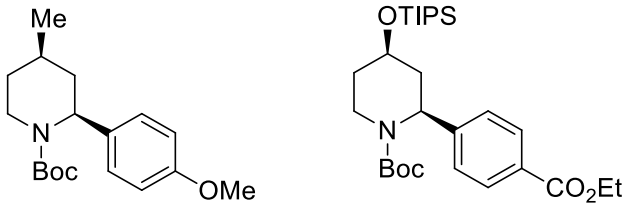
Scheme 3.35

The zincated intermediate **153** was stabilised by the C=O oxygen in the equatorial position (Scheme 3.36), as shown by DFT calculations. The relative stereochemistry was then maintained in the organopalladium intermediate **154** and then was imparted to the cross-coupling step to give the high diastereoselectivities observed.



Scheme 3.36

This methodology was also used to synthesise 4-substitued piperidines with substituents at C-4 other than the phenyl group. Products were obtained in 64-84% yield and >95:5 dr. As examples, 4-methyl *rac-syn*-**155** (78%, >99:1 dr) and 4-triisopropyl silyloxy piperidine *rac-syn*-**156** (84%, 97:3 dr) were prepared (Figure 3.10).

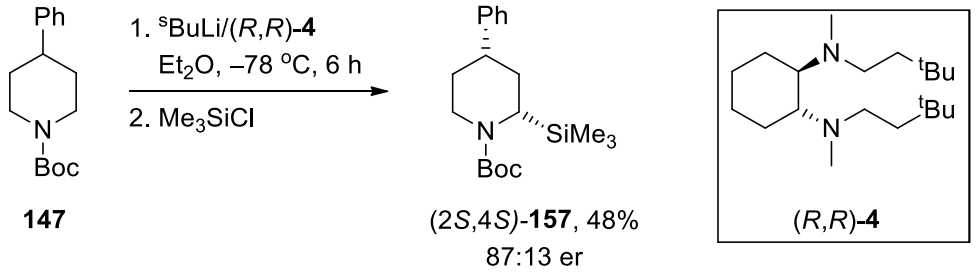


rac-syn-**155**, 78%
>99:1 dr

rac-syn-**156**, 84%
97:3 dr

Figure 3.10

In another report, the asymmetric lithiation-trapping of 4-phenyl *N*-Boc piperidine **147** was described by our group in collaboration with Coldham's group.[59] Lithiation of **147** with *s*-BuLi and diamine (*R*,*R*)-**4**[34,35] in Et_2O –78 °C for 6 hours and then trapping with Me_3SiCl gave silyl product (2*S*,4*S*)-**157** in 48% yield and 87:13 er (Scheme 3.37). The absolute configuration was not proven, but assigned by analogy to the asymmetric deprotonation of *N*-Boc piperidine using *s*-BuLi/(–)-sparteine.[60] Other chiral diamine ligands were screened, but gave lower levels of enantioselectivity (<58:42 er) and variable yields (24-68%).



147

(2*S*,4*S*)-**157**, 48%
87:13 er

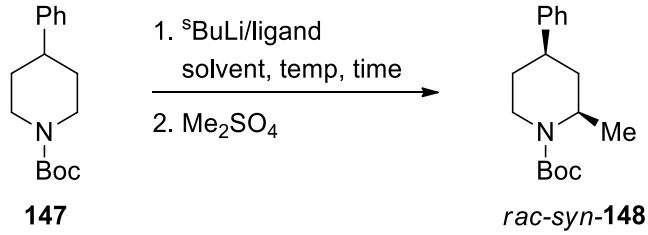
(*R*,*R*)-**4**

Scheme 3.37

3.4.2 Exploration of the Lithiation-Trapping of 4-Phenyl *N*-Boc Piperidine 147

Before investigating the attempted synthesis of α-amino sulfoxides *rac-syn*-**112** and *rac-syn*-**113**, a short exploration of the lithiation-trapping of 4-phenyl *N*-Boc piperidine **147** was carried out. We started our study with racemic methodology. Thus, lithiation of **147** was explored using *s*-BuLi in the presence of TMEDA in Et_2O at –78 °C or in THF without ligand at –78 °C or at –30 °C (Scheme 3.38 and Table 3.2). When the lithiation was performed with *s*-BuLi/TMEDA in Et_2O at –78 °C, trapping with Me_2SO_4 gave α-methylated piperidine *rac-syn*-**148** in 67% yield after a 1 hour lithiation (Entry 1) and 60% yield after 3 hours lithiation time (Entry 2). In THF without ligand, the lithiation at

–78 °C for 3 hours afforded *rac-syn*-**148** in 38% yield (Entry 3), whereas at –30 °C for 10 minutes *rac-syn*-**148** was isolated in 20% yield (Entry 4).



147 *rac-syn*-**148**

Scheme 3.38

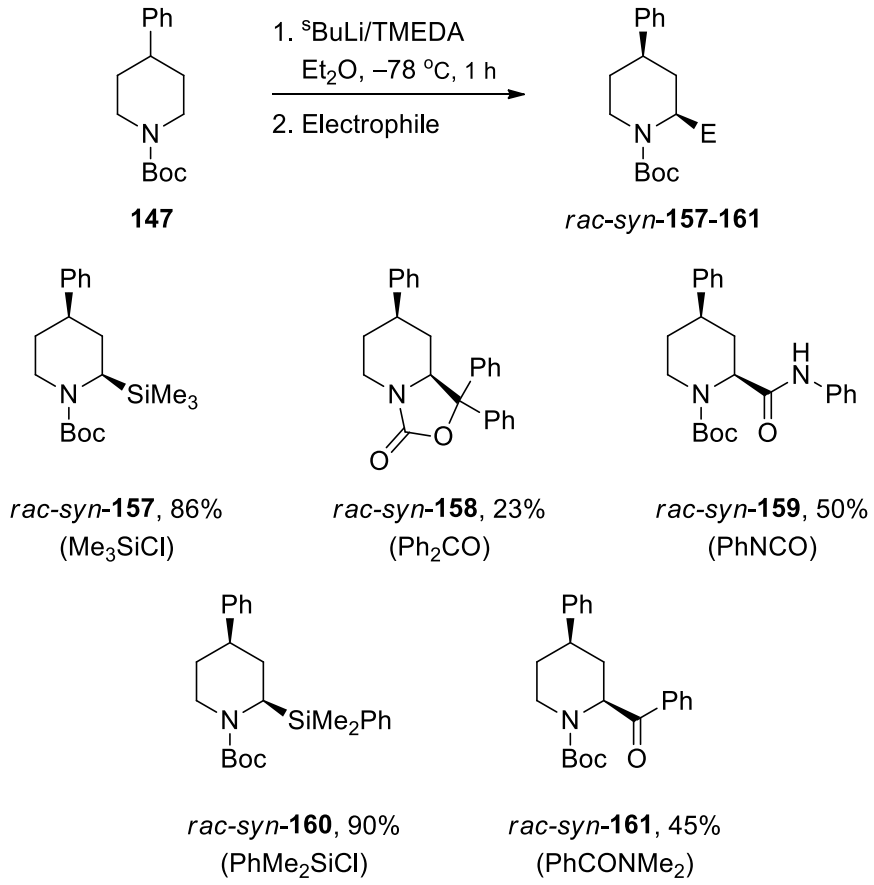
Table 3.2: Optimisation of the Lithiation-Trapping of 4-Phenyl *N*-Boc Piperidine **147**

Entry	Ligand	Solvent	Temp. (°C)	Time (h)	Yield of 148 (%)[a]
1	TMEDA	Et_2O	–78	1	67
2	TMEDA	Et_2O	–78	3	60
3	-	THF	–78	3	38
4	-	THF	–30	10 min	20

[a]Yield after purification by chromatography.

In each case, only one diastereoisomer was obtained (based on the ^{1}H NMR spectra of the crude product) and the relative stereochemistry was assigned by analogy with previous examples.[4,92] The result obtained using THF without TMEDA were rather surprising. Although the isolated yields were moderate at –78 °C and –30 °C, 38% and 20% yield respectively, these were important results since it was previously reported that *s*-BuLi in THF at –30 °C did not lithiate *N*-Boc piperidine **34**.[5] Possibly, the presence of the phenyl group could increase the reactivity of 4-phenyl *N*-Boc piperidine **147**.

Using the lithiation conditions which gave the highest yield, *s*-BuLi, TMEDA in Et_2O at –78 °C for 1 hour, the trapping was explored with other electrophiles. Trapped products *rac-syn*-**157**-**161** were isolated in 23-90% yields (Scheme 3.39).



Scheme 3.39

As was observed for the methylated product *rac-syn*-**148**, in all these examples, only one diastereoisomer of the product was isolated. The relative stereochemistry of the products was assumed to be *syn* based on the ^{1}H NMR spectroscopic data of *rac-syn*-**158** and *rac-syn*-**161**. Key spectroscopic data, which allowed the *syn* diequatorial configuration to be identified, include the signal corresponding to the benzylic proton of *rac-syn*-**158** and *rac-syn*-**161** (δ_H 2.77 ppm and 2.87 ppm respectively) (Figure 3.11). This signal is a dddd with *J* values of 12.0, 12.0, 3.0, 3.0 Hz (*rac-syn*-**158**) and 11.5, 4.0 Hz (*rac-syn*-**161**). These values indicate an axial-axial and axial-equatorial relationship. Hence, the 4-phenyl substituent should occupy an equatorial orientation. The other key spectroscopic data are the signals for the proton α to nitrogen. In oxazolidinone *rac-syn*-**158** (δ_H 4.45 ppm) and in ketone *rac-syn*-**161** (δ_H 4.80 ppm), this signal is a double doublet with *J* values of 12.0, 3.5 Hz and 11.0, 4.5 Hz respectively, indicating the axial position of this proton. The *syn* configuration of *rac-syn*-**157**, *rac-syn*-**159**-**160** was assigned by analogy with *rac-syn*-**158** and *rac-syn*-**161**.

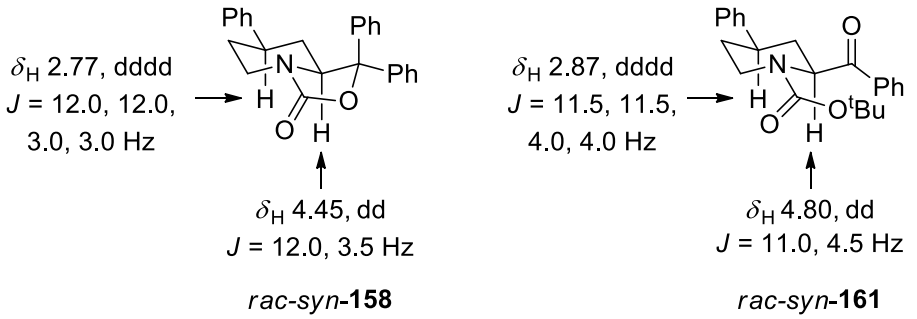
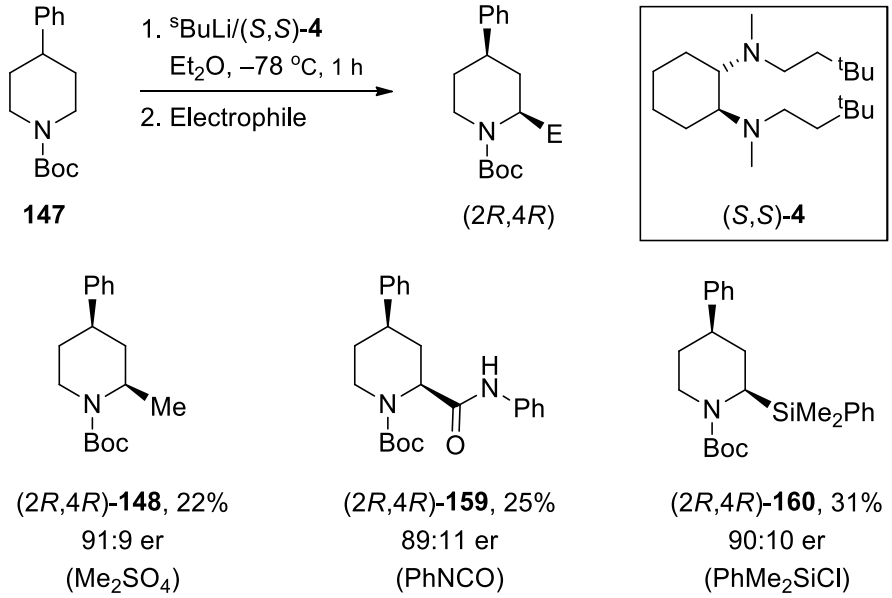


Figure 3.11

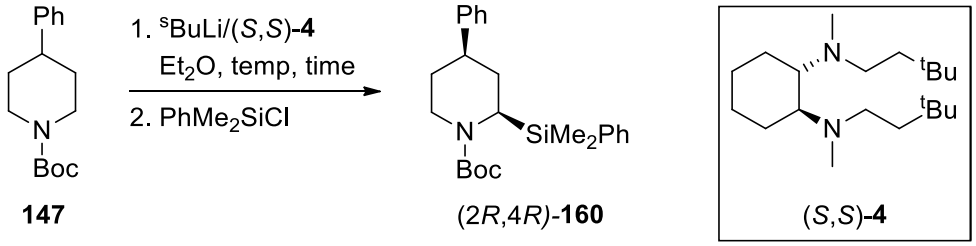
Next, the asymmetric lithiation and electrophilic trapping of 4-phenyl *N*-Boc piperidine **147** was explored. Our group has reported that better enantioselectivities were obtained using diamine (*R*,*R*)-**4** as ligand and a lithiation time of 6 hours (see Scheme 3.34). We thought that such a long reaction time was not necessary and thus, the deprotonation with *s*-BuLi and (*S*,*S*)-**4** was carried out for 1 hour. Electrophilic trapping with Me_2SO_4, PhNCO and $PhMe_2SiCl$ gave trapped products in low yields (22-31%) and >89:11 er (Scheme 3.40).



Scheme 3.40

These results showed that high enantioselectivity could be achieved with the asymmetric lithiation-trapping of 4-phenyl *N*-Boc piperidine **147**. However, the yields were very unsatisfactory. In all these cases, starting material **147** was also recovered after flash column chromatography in 49-51% yield. This could probably indicate an incomplete lithiation of the substrate under the reaction conditions (*s*-BuLi/Alexakis

diamine (*S*,*S*)-**4**, 1 hour). Thus, a longer lithiation time (3 hours) was used (Scheme 3.42 and Table 3.3). Trapping with $PhMe_2SiCl$ gave (2*R*,4*R*)-**160** (92:8 er) in a higher 43% yield (Entry 2). Although this was an improved result, we were interested in yields ≥60%. Therefore, the role of the temperature was also investigated and **147** was lithiated at −40 °C for 1 hour. In this case, (2*R*,4*R*)-**160** was isolated in only 9% yield and with a lower enantioselectivity (80:20 er); starting **147** was also recovered in 64% yield (Entry 3).



Scheme 3.41

Table 3.3: Optimisation of the Asymmetric Lithiation-Trapping of 4-Phenyl *N*-Boc piperidine **147**

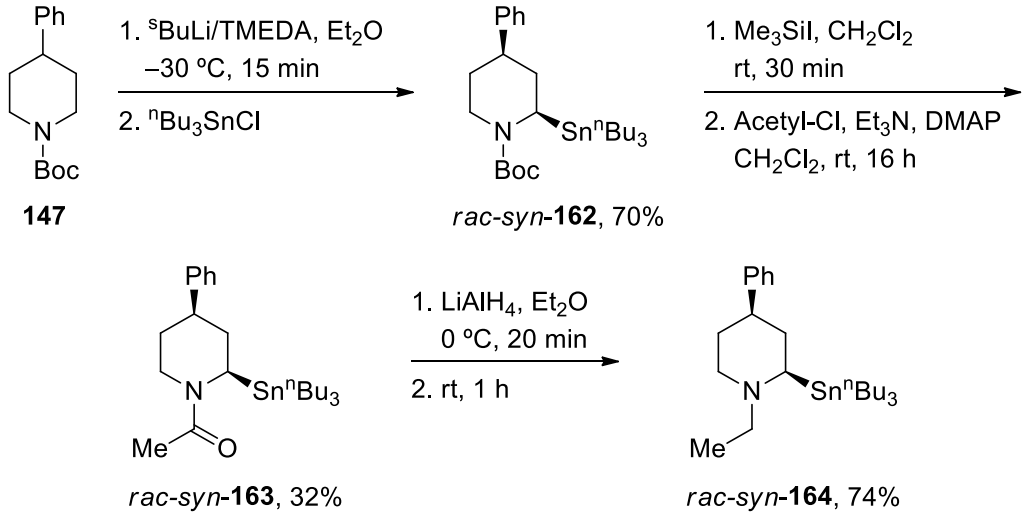
Entry	Temp. (°C)	Time (h)	Yield of 160 (%)[a]	er[b]	Yield of rec. SM 147 (%)[a]
1	−78	1	31	90:10	51
2	−78	3	43	92:8	-
3	−40	1	9	80:20	64

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

The low yields observed were possibly due to a slow rate of lithiation even at −40 °C. In addition, the 9% yield at −40 °C could indicate chemical instability of the lithiated intermediate. Moreover, a decrease in the kinetic selectivity of the deprotonation was observed with the increase of the temperature. Due to the lack of success in the asymmetric lithiation-trapping of 4-phenyl *N*-Boc piperidine **147**, no further asymmetric reactions were explored.

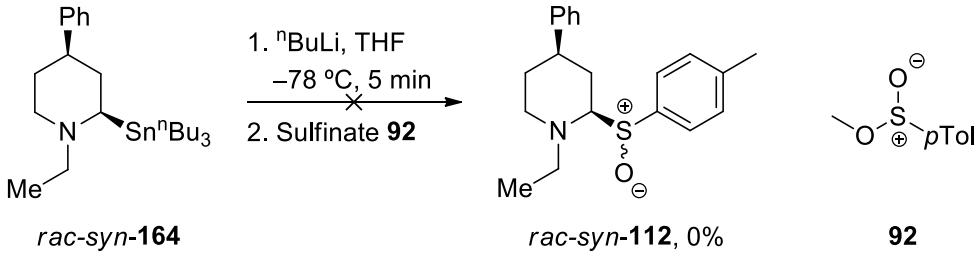
3.4.3 Attempted Synthesis of *N*-Ethyl and *N*-Sulfonamido Piperidine Sulfoxides *via* Tin-Lithium Exchange

Next, our attention was directed to the synthesis of α-amino sulfoxides and the planned route was *via* tin-lithium exchange. Hence, 4-phenyl stannyl piperidine *rac-syn*-**162** was synthesised in 70% yield from 4-phenyl piperidine **147** using *s*-BuLi and TMEDA in Et_2O at −30 °C for 15 minutes followed by trapping with Bu_3SnCl. Then, *rac-syn*-**162** was deprotected with Me_3SiI and the crude amine was acylated with acetyl chloride in the presence of Et_3N and DMAP to afford 4-phenyl acetyl piperidine *rac-syn*-**163** (32% yield). Subsequently, *rac-syn*-**163** was reduced with $LiAlH_4$ to give the desired 4-phenyl *N*-ethyl piperidine *rac-syn*-**164** in 74% yield (Scheme 3.42).



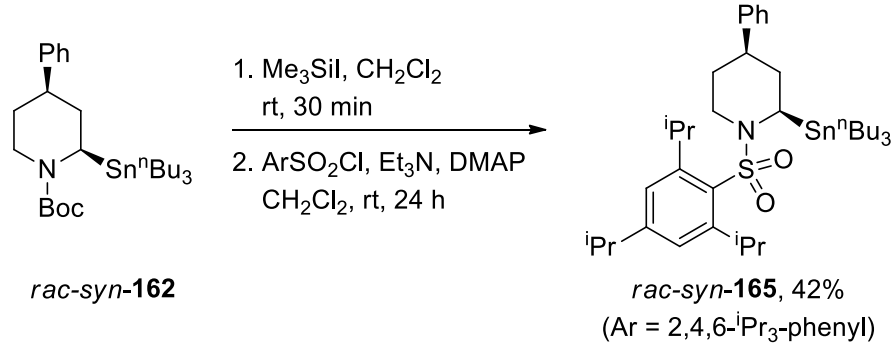
Scheme 3.42

Tin-lithium exchange is known on *N*-ethyl stannyl pyrrolidine,[50] and we assumed that *N*-ethyl piperidine *rac-syn*-**164** could undergo the same process. Therefore, tin-lithium exchange was attempted with *rac-syn*-**164** using *n*-BuLi in THF at −78 °C for 5 minutes. Unfortunately, electrophilic trapping with sulfinate **92** resulted in a mixture of unidentified products by ^1H NMR spectroscopy of the crude product (Scheme 3.43). For this reason, further exploration on this substrate was not carried out.



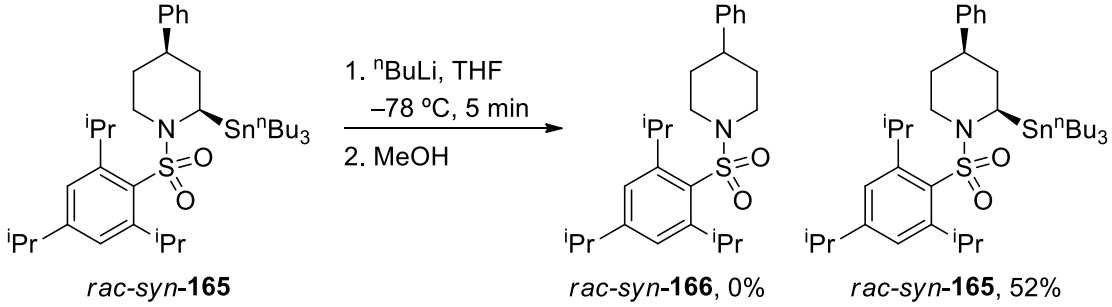
Scheme 3.43

Next, 4-phenyl *N*-sulfonyl piperidine *rac-syn*-**165** was considered. Starting from 4-phenyl stannyl piperidine *rac-syn*-**162**, *rac-syn*-**165** (42% yield) was prepared following the Me_3SiI deprotection and sulfonylation procedure used for the other substrates (Scheme 3.44).



Scheme 3.44

The tin-lithium exchange protocol using *rac-syn*-**165** as substrate was not known and so we decided to perform a test reaction first. Thus, *rac-syn*-**165** was treated with *n*-BuLi in THF at –78 °C for 5 minutes and then MeOH was added. The sole product isolated after flash column chromatography was recovered *rac-syn*-**165** in 52% yield (Scheme 3.45). Unfortunately, we were not able to isolate any other compound to further understand what happened in the reaction. Due to this unsatisfactory result, we decided not to carry on with the exploration using different electrophiles.

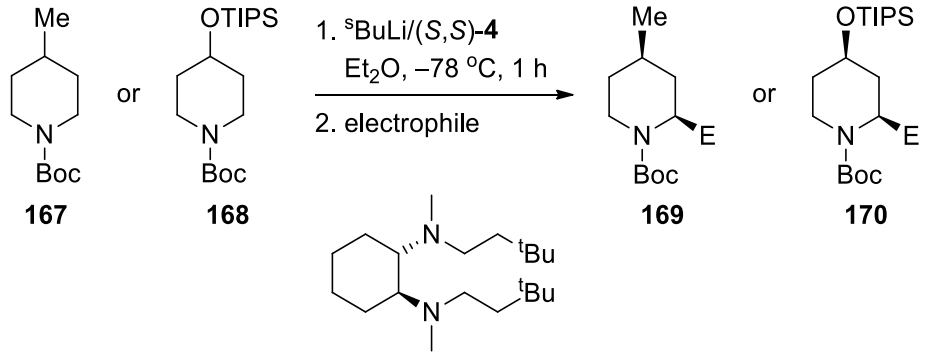


Scheme 3.45

The disappointing results obtained with the 4-substituted piperidines led us to stop the study of the tin-lithium exchange on these substrates.

3.5 Conclusions and Future Work

To our disappointment and frustration, the synthetic strategies planned to understand the elimination mechanism at the basis of the instability of α-amino sulfoxides were unsuccessful. Consequently, we could not confirm the mechanistic pathway for elimination of the sulfoxide group. However, the instability observed during the exploration of acyclic α-amino sulfoxides without β-protons could indicate that the elimination is triggered by the nitrogen lone pair. Unfortunately, tin-lithium exchange experiments with cyclic substrates presented reactivity issues which could not give further evidence. Alongside these negative results, we were successful in developing a racemic and an asymmetric lithiation-trapping methodology of 4-phenyl piperidine **147**. Hence, future work could involve extension of the asymmetric methodology to 4-substituted piperidines such as 4-methyl piperidine **167** and 4-triisopropyl silyloxy piperidine **168** (Scheme 3.46).



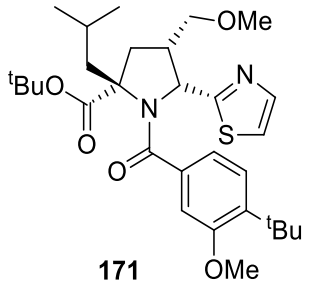
167 **168** **169** **170**

(*S*,*S*)-**4**

Scheme 3.46

Chapter Four: Synthesis of Tetra-Substituted Pyrrolidines

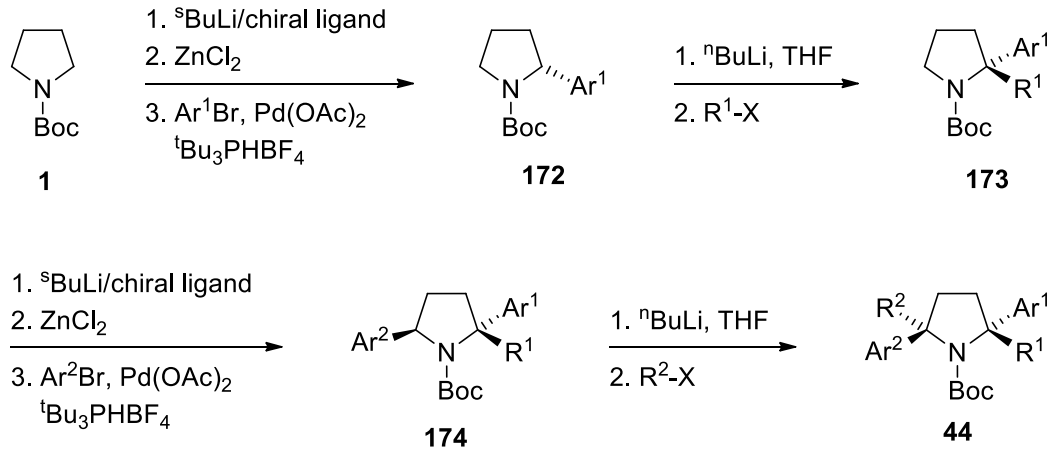
Our attention was attracted by the molecular complexity of tetra-substituted pyrrolidines and the synthesis of such tetra-substituted pyrrolidines would allow the potential exploration of new chemical space. Interestingly, some tetra-substituted pyrrolidines such as **171** have been synthesised and studied as potential hepatitis C virus (HCV) polymerase inhibitors (Figure 4.1).[93,94]



171

Figure 4.1

In particular, we were intrigued by the possibility of substituting each of the four protons next to the nitrogen atom using α-lithiation-trapping chemistry. The proposed synthetic route which could give tetra-substituted pyrrolidines **44** is shown in Scheme 4.1. It was envisaged that tetra-substituted pyrrolidines could be achieved starting from *N*-Boc pyrrolidine **1** *via* two consecutive "high" temperature asymmetric lithiation-Negishi coupling reactions and benzylic lithiation-trapping steps.



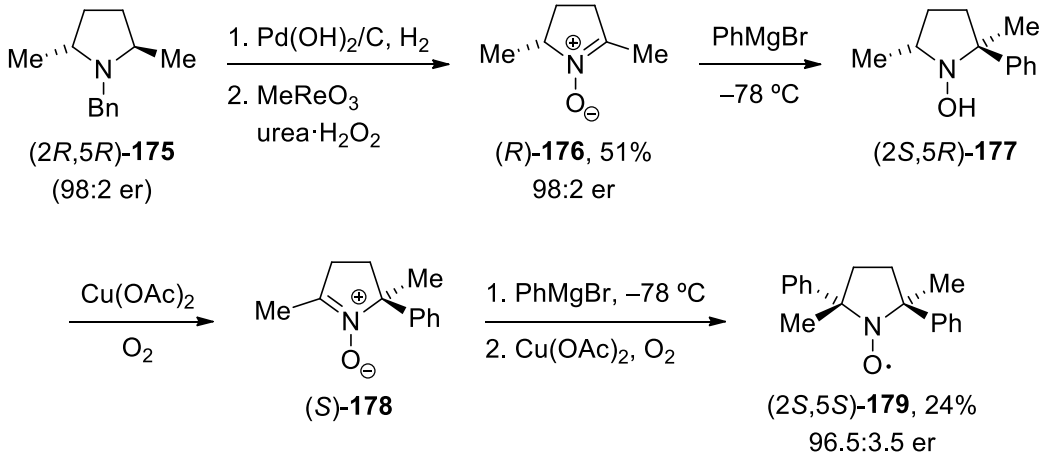
1 **172** **173** **174** **44**

Scheme 4.1

In this sequence, the use of the aryl groups is strategic for the introduction of a second substituent on the same carbon, because of the increased acidity of the benzylic protons in **172** and **174**. In addition, it was envisaged that the stereochemistry of the lithiation-Negishi coupling step could be controlled by using different chiral ligands, such as (−)-sparteine and the (+)-sparteine surrogate. For the lithiation-trapping of unsymmetrical *N*-Boc pyrrolidines **172**, **173** and **174**, the orientation of the C=O of the Boc group in the two rotamers and the ease of rotamer interconversion are key factors to be considered. Furthermore, electrophiles introduced in the benzylic lithiation-trapping step to give **173** have to be compatible with the subsequent lithiation conditions, narrowing the selection down to alkyl groups mainly. Our efforts at implementing this novel strategy to tetra-substituted pyrrolidines **44** are described in this chapter.

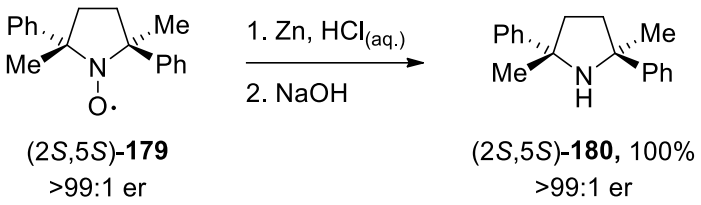
4.1 Previous Syntheses of Tetra-Substituted Pyrrolidines

Our interest was mainly directed at pyrrolidines having *α,α′*-aryl substitution. Surprisingly, there are not many syntheses of tetra-substituted pyrrolidines with such a substitution pattern reported in the literature. The general strategy for the synthesis of 2,5-tetra-substituted pyrrolidines utilises a protocol developed by Keana and co-workers, namely the addition of Grignard reagents to nitrones.[95,96] In a recent example of Keana's approach, the Einhorn group reported the synthesis of tetra-substituted pyrrolidine (2*S*,5*S*)-**179** (Scheme 4.2).[97] The synthetic pathway started with enantioenriched dimethyl *N*-benzyl pyrrolidine (2*R*,5*R*)-**175** (98:2 er), which was deprotected *via* hydrogenolysis and then oxidised with $MeReO_3$ and urea-hydrogen peroxide[98] to give nitrone (*R*)-**176** (51% yield). Nucleophilic addition of PhMgBr to nitrone (*R*)-**176** afforded tri-substituted pyrrolidine (2*S*,5*R*)-**177**, which was oxidised to nitrone (*S*)-**178** using oxygen and copper(II) acetate. Then, (*S*)-**178** was converted into nitroxide (2*S*,5*S*)-**179** (24% yield, 96.5:3.5 er) *via* a second Grignard addition and oxidation sequence.



Scheme 4.2

Finally, as shown in Scheme 4.3, nitroxide (2*S*,5*S*)-**179** was first recrystallized to enantiopurity (>99:1 er) and then quantitatively reduced with zinc in aqueous HCl to afford tetra-substituted amine (2*S*,5*S*)-**180** (>99:1 er).



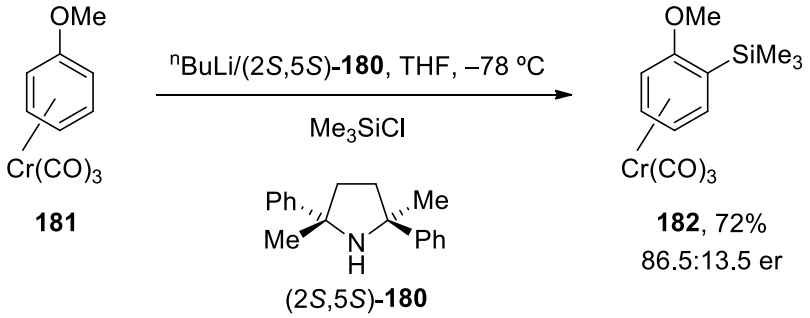
(2*S*,5*S*)-**179**
>99:1 er

(2*S*,5*S*)-**180,** 100%
>99:1 er

Scheme 4.3

The diastereoselectivity of this sequence of reactions is entirely controlled in the Grignard addition to the nitrones. The nucleophile approached the nitrone from the least hindered face and therefore generated a *trans* relationship with the substituent on the stereogenic centre. This effectively created an inversion of configuration of the starting (2*R*,5*R*)-**175** stereocentres.

Kündig showed that amine (2*S*,5*S*)-**180** could be used as precursor to a chiral lithium amide base in the asymmetric *ortho*-lithiation-trapping of tricarbonylchromium-arene **181**.[99] In this procedure, (2*S*,5*S*)-**180** was treated with *n*-BuLi to form the lithium amide and subsequent addition of Me_3SiCl and substrate **181** gave *ortho*-disubstituted arene **182** in 72% yield and 86.5:13.5 er (Scheme 4.4).



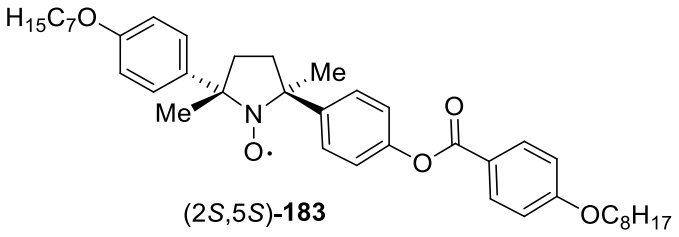
181

(2*S*,5*S*)-**180**

182, 72%
86.5:13.5 er

Scheme 4.4

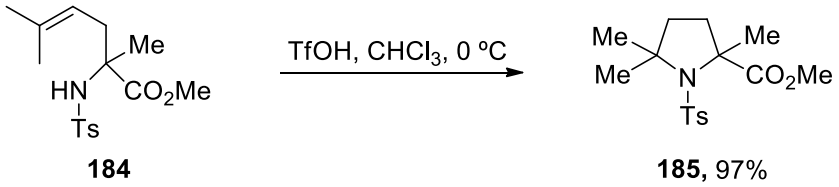
In 2004, the methodology reported by Einhorn was used by the Tamura group to synthesise 2,5-alkoxyphenyl nitroxides such as (2*S*,5*S*)-**183** (Figure 4.2).[100] Such tetra-substituted pyrrolidine nitroxides were used in the development of new liquid crystals.



(2*S*,5*S*)-**183**

Figure 4.2

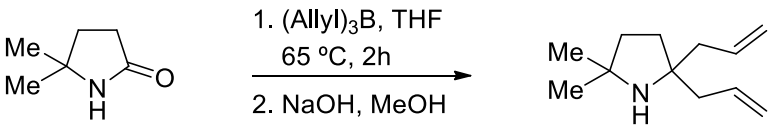
Tetra-substituted pyrrolidines could also be obtained *via* a cyclisation methodology as shown by Knight.[101] In this synthetic route, pyrrolidine **185** was achieved in a high 97% yield by treatment of homoallylic sulfonamide **184** with triflic acid *via* a 5-*endo*-trig cyclisation (Scheme 4.5).



184 **185,** 97%

Scheme 4.5

A different approach for the synthesis of tetra-substituted pyrrolidines was reported by the Bubnov group in 2008.[102] Pyrrolidinone **186** was reacted with tri-allylborane and then NaOH in MeOH to afford 2,2-diallyl-5,5-dimethyl pyrrolidine **187** in 91% yield (Scheme 4.6).



186 **187**, 91%

Scheme 4.6

4.2 Overview of Methodology for the Synthesis of 2-Aryl and 2,2-Di-Substituted Pyrrolidines

As part of the overall strategy towards tetra-substituted pyrrolidines, the synthesis of 2-aryl and 2-di-substituted pyrrolidines was required. The interest in such compounds can be attributed to the fact that α-arylated pyrrolidines represent a common motif in both natural products, such as (*S*)-nicotine and (*R*)-harmicine, and pharmaceuticals, such as the anti-cancer drug Veliparib® (ABT-888) (Figure 4.3).[103] Some synthetic routes to enantioenriched 2-aryl and 2,2-di-substituted pyrrolidines are summarised in this section.

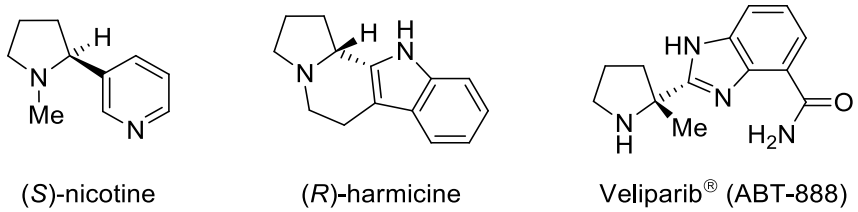
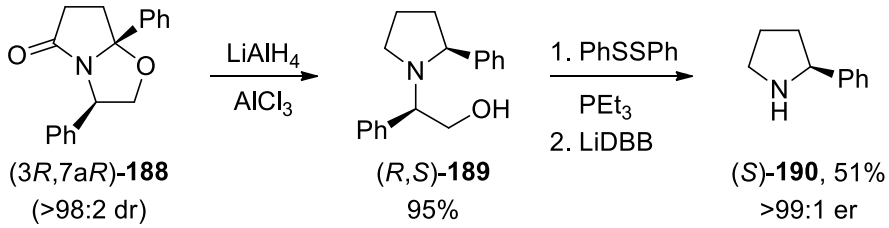


Figure 4.3

4.2.1 Previous Asymmetric Syntheses of 2-Aryl Pyrrolidines

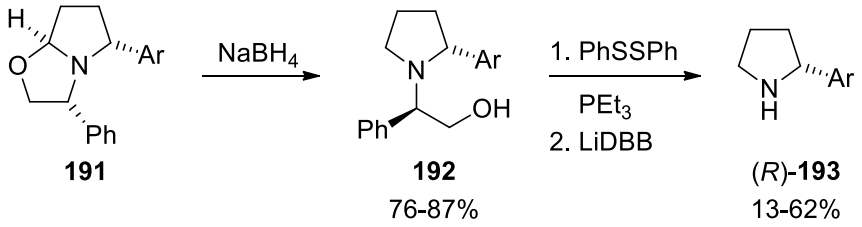
In 1992, Meyers reported the synthesis of 2-phenyl pyrrolidine (*S*)-**190**.[104] This protocol used (*R*)-phenylglycinol as a chiral auxiliary, which was converted into lactam (3*R*,7a*R*)-**188** with high diastereoselectivity in one step. Reduction of (3*R*,7a*R*)-**188** with $LiAlH_4$ and $AlCl_3$ afforded amino alcohol (*R*,*S*)-**189** (95% yield), which was deprotected in two steps using diphenyl disulfide and lithium di-*tert*-butylbiphenylide to give enantiopure 2-phenyl pyrrolidine (*S*)-**190** in 51% yield (Scheme 4.7).



Scheme 4.7

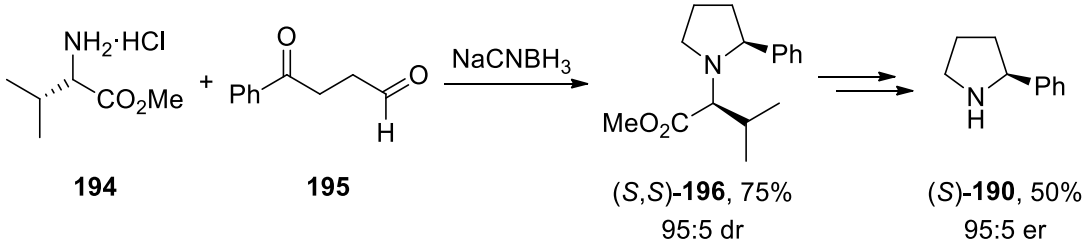
A similar approach was used two years later by Higashiayama and co-workers for the synthesis of three different 2-aryl pyrrolidines **193**.[105] In that methodology, enantiopure

phenylglycinol was converted with moderate yields in three steps into 1,3-oxazolidines **191** claimed to have high diastereomeric ratio. Reduction and deprotection of **191** afforded 2-aryl pyrrolidines **193** in low to moderate yields (13-62%) as shown in Scheme 4.8.



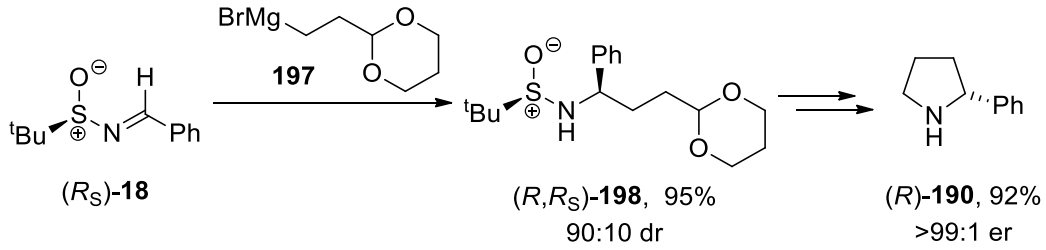
Scheme 4.8

Reductive amination of the iminium ion, formed by reacting (*S*)-valine methyl ester **194** with keto-aldehyde **195**, is an alternative method. This route showed a slightly lower enantioselectivity as reported by the Savoia group (Scheme 4.9).[106]



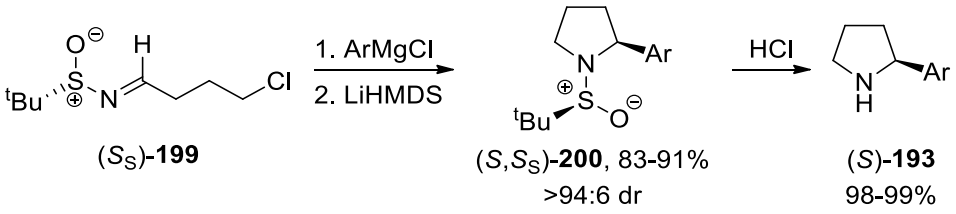
Scheme 4.9

In 2005, Ellman reported the addition of Grignard reagents to *N*-sulfinyl imines as an efficient method for the synthesis of 2-phenyl pyrrolidine (*R*)-**190**.[107] As shown in Scheme 4.10, *N*-sulfinyl imine (R_S)-**18** was reacted with Grignard **197** to afford sulfinamide (R,R_S)-**198** in good yield (95% yield) and 90:10 dr. Acetal deprotection, cyclisation and reduction of the iminium ion, followed by removal of the *N*-sulfinyl group gave (*R*)-**190** in 92% yield.



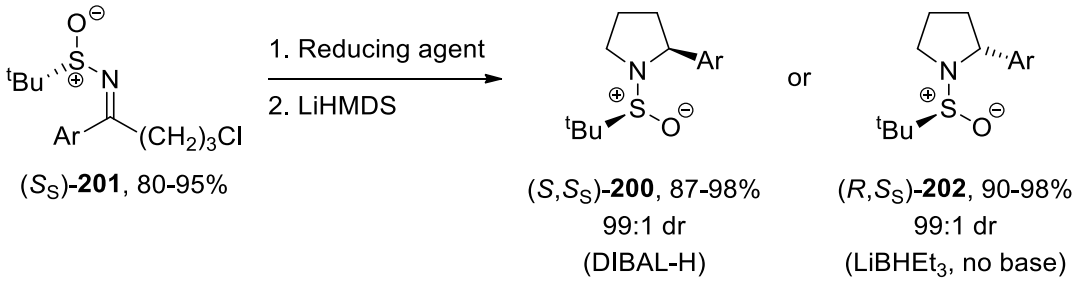
Scheme 4.10

The scope of the aryl group was investigated by the Reddy group.[108] Addition of a range of Grignard reagents to the *N*-sulfinyl imine (S_S)-**199** and subsequent cyclisation with LiHMDS afforded aryl pyrrolidines (*S*,S_S)-**200** in 83-91% yield and >94:6 dr. Simple deprotection of the *N*-sulfinyl group using HCl gave 2-aryl pyrrolidines (*S*)-**193** in 98-99% yields (Scheme 4.11).



Scheme 4.11

Subsequently, the same research group showed that the diastereoselectivity of the products could be controlled by switching the reducing agent.[109] The two diastereomeric series were accessed utilising the same starting *N*-sulfinyl ketimines (S_S)-**201**. Treatment with DIBAL-H gave pyrrolidines (*S*,S_S)-**200** (87-98% yield, 99:1 dr), whereas reaction with $LiBHEt_3$ afforded pyrrolidines (*R*,S_S)-**202** (90-98% yield, 99:1 dr, Scheme 4.12). A similar methodology was also reported by De Kimpe, but diastereoselectivities were lower.[110]

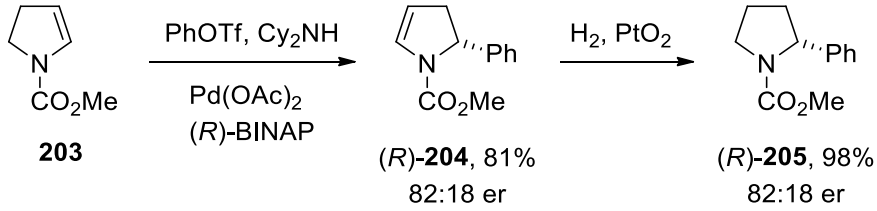


Scheme 4.12

More recently, Guijarro reported that (*R*,R_S)-**202** could also be accessed from *N*-sulfinyl ketimines (R_S)-**201** *via* a hydrogenation approach with a ruthenium catalyst and *i*-PrOH.[111] In this case, 2-aryl pyrrolidines (*R*,R_S)-**202** were obtained in 84-92% yield and >98:2 er.

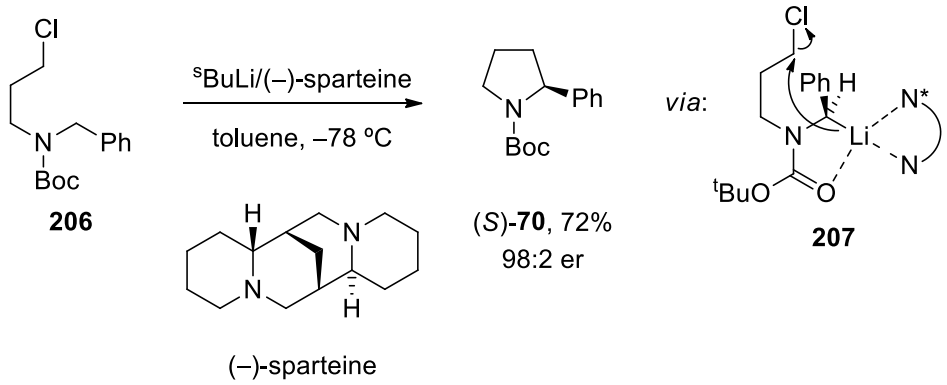
A synthetic protocol based on the Heck coupling reaction was published in 1992 by Ozawa.[112] The preparation of 2-arylated pyrrolidines was accomplished using a coupling reaction between *N*-carbamate pyrrolines and aryl triflates in 45-81% yields

and 82:18-87:13 er. An example is shown in Scheme 4.13. The use of pyrroline **203** and phenyl triflate in the presence of $Pd(OAc)_2$ and (*R*)-BINAP as ligand gave (*R*)-**204** (81% yield, 82:18 er). Hydrogenation of the alkene afforded 2-phenyl pyrrolidine (*R*)-**205**.



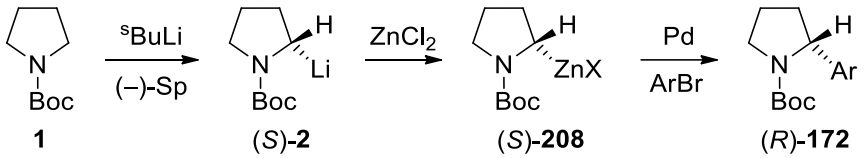
Scheme 4.13

In an alternative strategy, a lithiation-cyclisation protocol was reported by Beak and co-workers in 1996.[113] *N*-Boc chloroamine **206** was lithiated in toluene at –78 °C using *s*-BuLi and (–)-sparteine as chiral ligand. This formed a lithiated intermediate, which cyclised to afford 2-phenyl *N*-Boc pyrrolidine (*S*)-**70** in good yield (72%) and a high 98:2 er (Scheme 4.14). The synthesis of other 2-arylated *N*-Boc pyrrolidines in moderate to good yields and enantioselectivities >92:8 er was also reported using this approach.



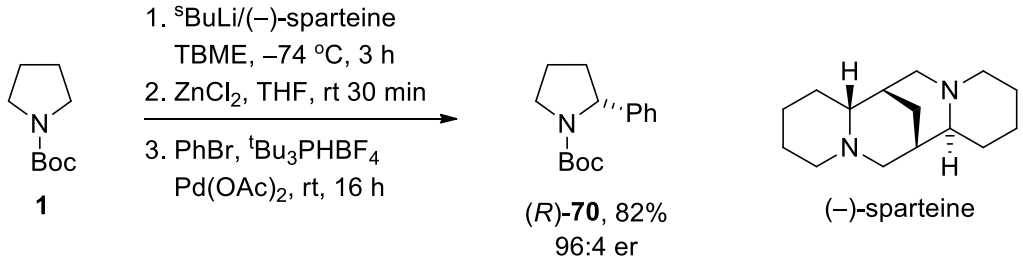
Scheme 4.14

A more convergent synthetic route to 2-aryl pyrrolidines has been reported recently by Campos *et al.*[56] According to the protocol, a broad range of 2-arylated pyrrolidines could be synthesised in one step from *N*-Boc pyrrolidine **1**. Treatment of **1** with *s*-BuLi/(–)-sparteine generated chiral lithiated intermediate (*S*)-**2**, which was transmetallated with $ZnCl_2$ to give organozinc (*S*)-**208**. Then, Pd-catalysed Negishi reaction[114] of (*S*)-**208** with aryl bromides gave 2-phenyl pyrrolidines (*R*)-**172** (Scheme 4.15).



Scheme 4.15

In the optimised procedure, *N*-Boc pyrrolidine **1** was lithiated using *s*-BuLi and (–)-sparteine in TBME for 3 hours at –74 °C, then transmetallated with $ZnCl_2$ and finally coupled with bromobenzene in a Negishi reaction using $Pd(OAc)_2$ and *t*-Bu_3PHBF_4[115] as catalyst. 2-Phenyl pyrrolidine (*R*)-**70** was obtained in 82% yield and 96:4 er (Scheme 4.16).



Scheme 4.16

Interestingly, our group in collaboration with the Campos group studied the whole process by *in situ* ReactIR™ spectroscopy.[30] Monitoring the change in absorbance of the carbonyl peak of the Boc group showed that the lithiation of *N*-Boc pyrrolidine **1** with *s*-BuLi and (–)-sparteine was accomplished within 1 hour. Additionally, it was shown that room temperature was needed for the lithium-zinc transmetallation step to occur. Using this methodology, the synthesis of 2-heteroaryl pyrrolidines (*R*)-**209**-**212** was achieved in good yields (70-76% yield) and enantioselectivities >94:6 er (Figure 4.4).

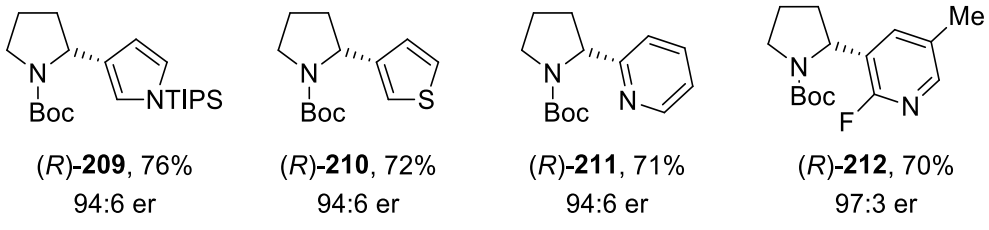


Figure 4.4

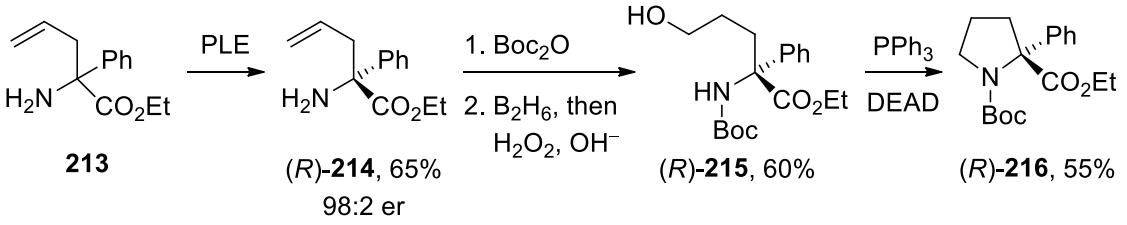
In summary, many of the routes to 2-aryl pyrrolidines generated the products with excellent enantioselectivities. In contrast, high yields were often difficult to achieve

mainly due to the length of the synthetic pathways. It appears that the Campos Pd-catalysed arylation arguably represents the most advantageous and efficient process to 2-aryl pyrrolidines as it combines high yield and good enantioselectivity.

4.2.2 Previous Asymmetric Syntheses of 2,2-Di-Substituted Pyrrolidines

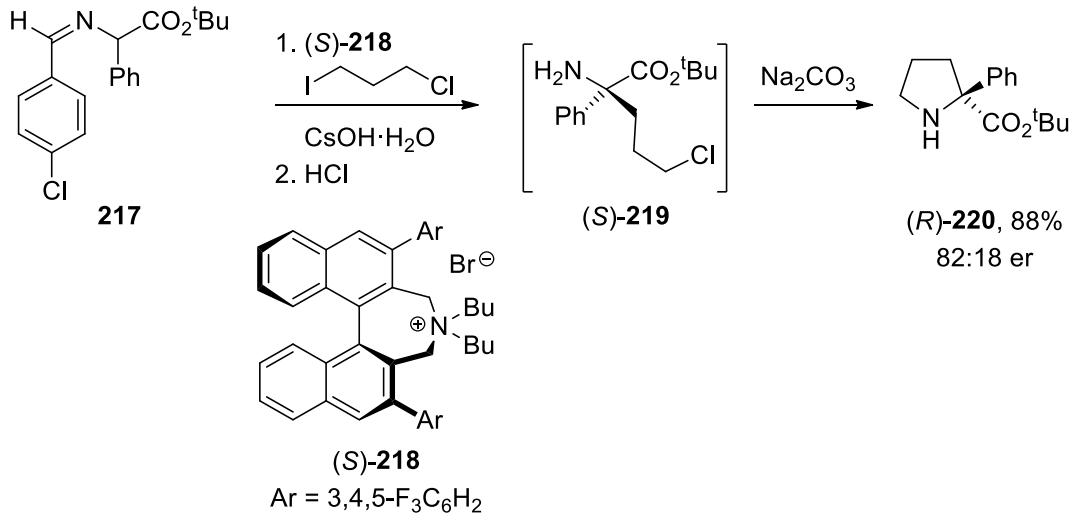
The introduction of a quaternary stereogenic centre with a phenyl substituent in the pyrrolidine ring represents a synthetic challenge which has been tackled using several chemical strategies by different research groups. For example, the possibility of synthesising proline-based non-natural amino acids has attracted some attention.

In 1997, Van Betsbrugge and Tourwe reported the synthesis of 2-phenyl proline ethyl ester (*R*)-**216**.[116] The high level of enantioselectivity arose from enzymatic resolution of allyl-phenyl glycinate **213** using pig liver esterase (PLE). (*R*)-**214** was obtained in 65% yield and 98:2 er. Then, Boc protection and hydroboration afforded amino alcohol (*R*)-**215** (60% yield), which was cyclised using a Mitsunobu reaction with PPh_3 and DEAD to give (*R*)-**216** in 55% yield (Scheme 4.17).



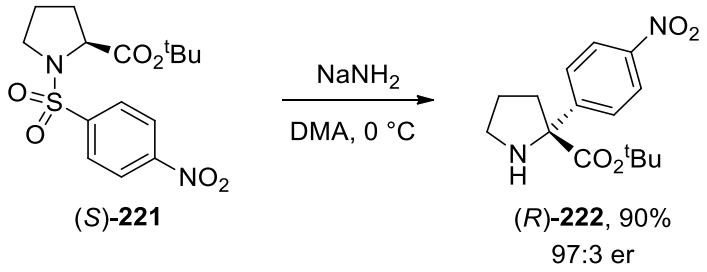
Scheme 4.17

A different cyclisation approach was used by Maruoka (Scheme 4.18).[117] Alkylation of α-phenyl imino acid derivative **217** with iodo-chloropropane in the presence of a chiral phase-transfer catalyst, (*S*)-**218**, and $CsOH{\cdot}H_2O$, followed by hydrolysis with HCl gave the chiral alkylated intermediate (*S*)-**219**. Cyclisation of (*S*)-**219** was performed with Na_2CO_3 and 2-phenyl prolinate (*R*)-**220** was obtained in 88% yield and 82:18 er. The moderate enantioselectivity observed was probably due to the steric hindrance of the phenyl group as higher enantioselectivities (>99:1 er) were obtained with smaller substituents such as methyl or allyl groups.



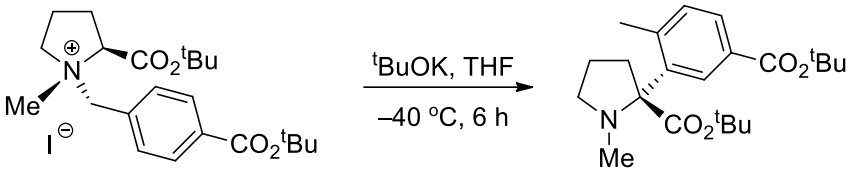
Scheme 4.18

An access to 2-aryl proline-derived amino acids was proposed by Tagliabue and Penso in 2010.[118] Treatment of sulfonamide (*S*)-**221** with $NaNH_2$ at 0 °C initiated a rearrangement of the aryl moiety, with retention of configuration at the stereogenic centre (Scheme 4.19). The process generated di-substituted pyrrolidine (*R*)-**222** in high yield and high enantioselectivity (90%, 97:3 er). Other substituents on the benzene ring led to a reduction in the yields.



Scheme 4.19

In related work, ammonium salt (1*S*,2*S*)-**223** was shown to give 2-aryl proline (*R*)-**224** following a Sommelet-Hauser rearrangement.[119] Deprotonation of (1*S*,2*S*)-**223** with *t*-BuOK at –40 °C triggered the [2,3]-sigmatropic shift which formed enantiopure ester (*R*)-**224** in 96% yield (Scheme 4.20).

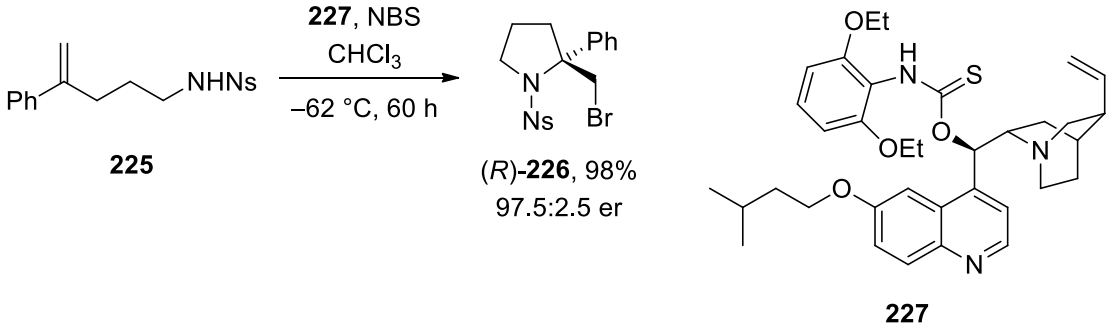


(1*S*,2*S*)-**223** (>99:1 er)

(*R*)-**224**, 96% >99:1 er

Scheme 4.20

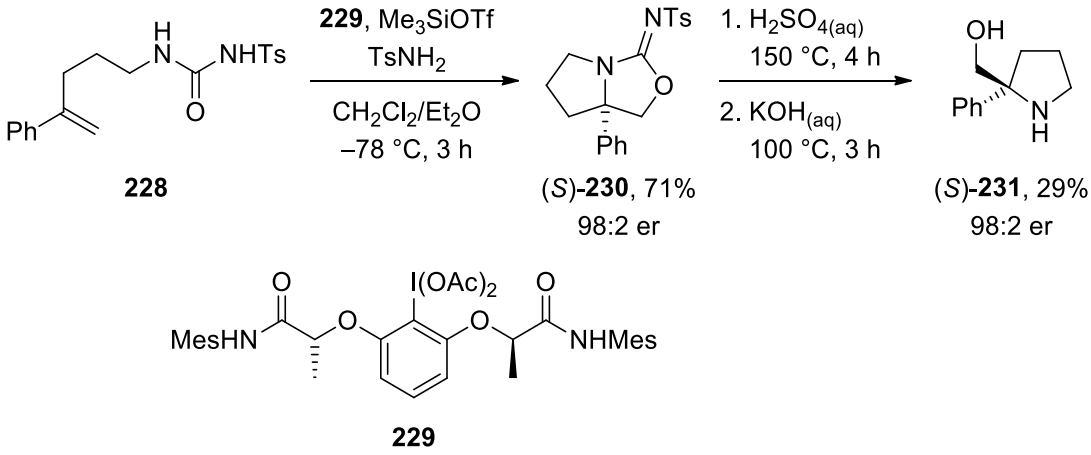
An example of the synthesis of 2,2-di-substituted pyrrolidines with an aryl-alkyl substitution was reported by Yeung *via* the bromo-aminocyclisation of sulfonamides.[120] In the optimised procedure, sulfonamide **225** was treated with NBS in $CHCl_3$ at –62 °C for 60 hours in the presence of a cinchonidine-derived catalyst **227** (Scheme 4.21). (*R*)-**226** was obtained in an excellent 98% yield and high enantioselectivity (97.5:2.5 er). In this case, similar results were obtained using a range of substituents on the aryl group.



(*R*)-**226**, 98% 97.5:2.5 er

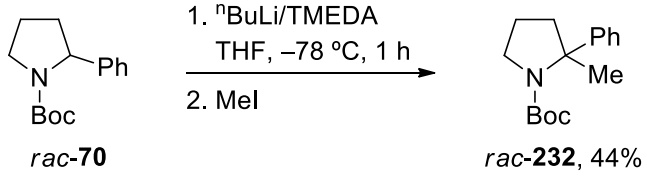
Scheme 4.21

Similarly, Wirth showed that 2,2-di-substituted pyrrolidines could be accessed *via* an asymmetric oxyamination of alkenes catalysed by chiral hypervalent iodine reagents.[121] Reaction of **228** with hypervalent iodine reagent **229** in the presence of Me_3SiOTf and $TsNH_2$ in CH_2Cl_2/Et_2O at –78 °C for 4 hours gave isourea (*S*)-**230** in 71% yield and 98:2 er (Scheme 4.22). Subsequent two-step hydrolysis afforded di-substituted pyrrolidine (*S*)-**231** (29% yield, 98:2 er).



Scheme 4.22

One of the most convergent synthetic pathways to access 2,2-di-substituted pyrrolidines was presented by Xiao and co-workers in 2005.[122] This approach used the increased acidity of the benzylic proton of 2-aryl pyrrolidines. Thus, treatment of 2-phenyl *N*-Boc pyrrolidine *rac*-**70** with *n*-BuLi in the presence of TMEDA in THF at –78 °C, followed by trapping with methyl iodide afforded pyrrolidine *rac*-**232** in 44% yield (Scheme 4.23).

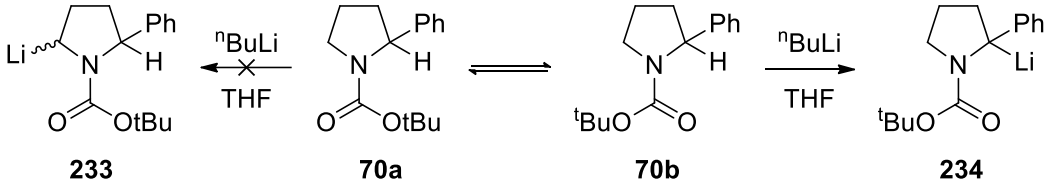


Scheme 4.23

Interestingly, under these conditions, the 2,5-di-substituted pyrrolidine was not obtained, indicating that lithiation using *n*-BuLi as a base proceeded solely towards the benzylic position.

The benzylic lithiation of 2-phenyl *N*-Boc pyrrolidine *rac*-**70** has recently been fully investigated by the O'Brien group in collaboration with the Coldham group.[123] To start with, the lithiation event was monitored using *in situ* ReactIR™ spectroscopy studies. When *rac*-**70** was treated with *n*-BuLi in THF at –78 °C, an initial rapid lithiation was observed, but full conversion to the lithiated intermediate was never achieved. The *n*-BuLi/THF-mediated lithiation of *rac*-**70** was also conducted at 0 °C and under these conditions, complete lithiation took place in 2 minutes or less. It was suggested that the

reason for the difference between the results at –78 °C and 0 °C was due to the rate of interconversion of the Boc rotamers **70a** and **70b** of the substrate (Scheme 4.24).

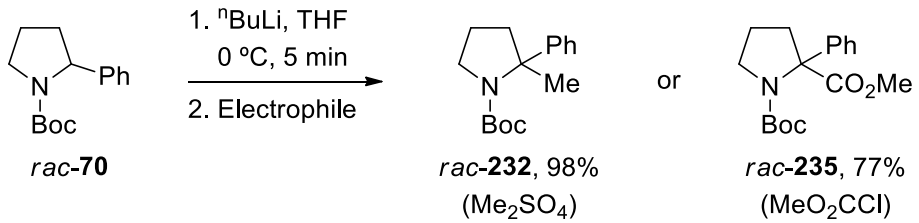


233 **70a** **70b** **234**

Scheme 4.24

It was proposed that at –78 °C rotation of the Boc group about the C-N was significantly slower than the rate of lithiation. In contrast, at 0 °C the interconversion of the rotamers could happen rapidly, leading to full formation of the lithiated species. As expected, *n*-BuLi in THF at –78 °C was not a strong enough base to deprotonate rotamer **70a**. To confirm those observations, variable temperature (VT) ^{1}H NMR spectroscopy studies of *rac*-**70** were performed in THF-d_8. The half-life ($t_{1/2}$) for rotation of the Boc group was calculated and $t_{1/2}$ was ~10 hours at –78 °C, while at 0°C $t_{1/2}$ was ~0.3 seconds.

Additional evidence was shown with synthetic experiments at –78 °C and 0 °C. Lithiation at –78 °C with *n*-BuLi for 3 hours and trapping with methyl chloroformate gave *rac*-**235** in 39% yield with 52% yield of recovered starting material. In contrast, at 0 °C, lithiation with *n*-BuLi in THF for 5 minutes followed by electrophilic quench afforded trapped products in excellent yields. As examples, the trapping with Me_2SO_4 and methyl chloroformate gave *rac*-**232** and *rac*-**235** in 98% and 77% yields respectively (Scheme 4.25).



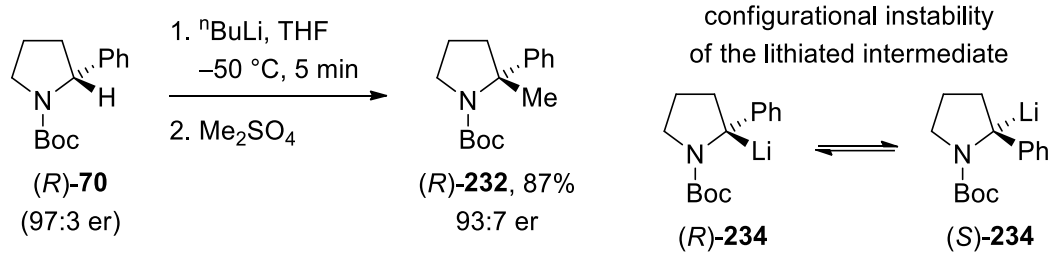
rac-**70** *rac*-**232**, 98% (Me_2SO_4) *rac*-**235**, 77% (MeO_2CCl)

Scheme 4.25

These results showed that the yields were highly affected by interconversion of the *N*-Boc rotamers. Moreover, the use of *in situ* ReactIR™ spectroscopy and VT ^{1}H NMR spectroscopy studies was essential to establish the optimal reaction conditions.

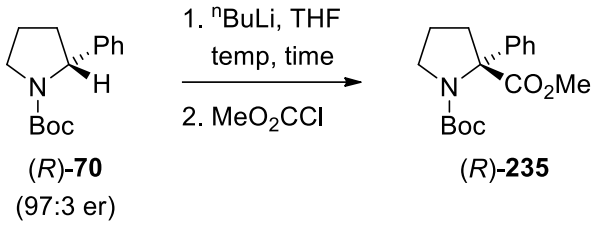
Ultimately, in non-symmetrical substrates, such as *rac*-**70**, understanding the half-life ($t_{1/2}$) for rotation of the Boc group is a fundamental parameter for the success of the lithiation.

The lithiation-trapping of enantioenriched 2-phenyl *N*-Boc pyrrolidine (*R*)-**70** (97:3 er) was also reported. *n*-BuLi was used to lithiate (*R*)-**70** in THF at –50 °C and subsequent electrophilic trapping with Me_2SO_4 afforded 2,2-di-substituted pyrrolidine (*R*)-**232** in 87% yield and 93:7 er (Scheme 4.26).



Scheme 4.26

The slight reduction of er suggested a partial configurational instability of the lithiated intermediate. This observation was supported by the data obtained using MeO_2CCl as electrophile at different temperatures (Scheme 4.27 and Table 4.1). Lithiation of 2-phenyl *N*-Boc pyrrolidine (*R*)-**70** (97:3 er) with *n*-BuLi in THF at –78 °C gave (*R*)-**235** (31% yield) in high 97:3 er (Entry 1). Increasing the temperature to –50 °C resulted in a lower 90:10 er of (*R*)-**235** (74% yield) with a 10 minute reaction (Entry 2), whereas 5 minute lithiation afforded (*R*)-**235** in 94:6 er (Entry 3). At higher temperatures, the enantioselectivity was progressively reduced (Entries 4 and 5).



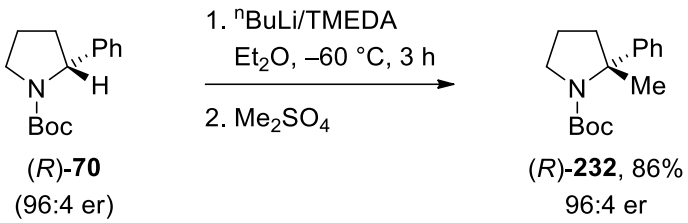
Scheme 4.27

Table 4.1: Optimisation of the Benzylic Lithiation-Trapping of 2-Phenyl *N*-Boc Pyrrolidine (*R*)-**70** in THF

Entry	Temp (°C)	Time (min)	Yield of 235 (%)	er
1	–78	60	31	97:3
2	–50	10	74	90:10
3	–50	5	78	94:6
4	–30	5	79	65:35
5	0	5	82	50:50

These results showed that the configurational stability of the lithiated intermediate was dependent on the temperature and on the lithiation time. Increasing the reaction temperature was detrimental for the configurational stability of the lithiated intermediate. In addition, the results at –50 °C revealed a dependency on the reaction time, as the 10 minute lithiation gave lower er than the 5 minute reaction.

Recently, Gawley reported a protocol for the benzylic lithiation-trapping under similar conditions.[124] Thus, enantioenriched (*R*)-**70** (96:4 er) was lithiated at –60 °C with *n*-BuLi in Et_2O in the presence of TMEDA. Trapping with Me_2SO_4 gave (*R*)-**232** (86% yield) in 96:4 er (Scheme 4.28). The dynamics of racemisation of the lithiated intermediate were investigated in different solvents and calculations showed that the rate of racemisation was faster in THF than in Et_2O. Crucially, the data obtained by Gawley indicated that the lithiated intermediate was configurationally stable in Et_2O/TMEDA and so the er was transferred from the starting material to the product. This result was in agreement with the results obtained by O'Brien and Coldham (see Scheme 4.27).



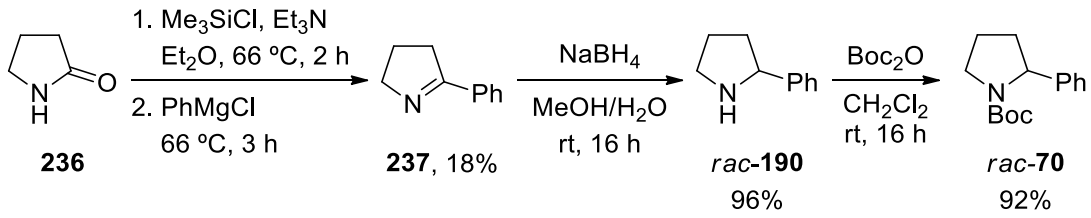
Scheme 4.28

In summary, 2,2-di-substituted pyrrolidines could be accessed in good enantioselectivity *via* several approaches. However, it is clear that the benzylic lithiation-trapping methodology reported by O'Brien, Coldham and Gawley is the shortest route which could afford high yields and er in two synthetic steps from *N*-Boc pyrrolidine **1**.

4.3 Development of Methodology for the Synthesis of Tri-Substituted Pyrrolidines

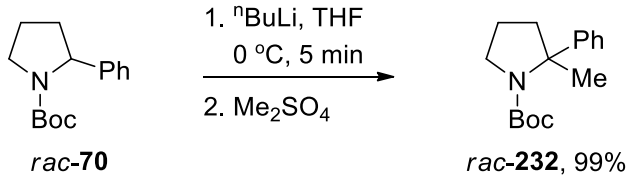
4.3.1 Syntheses of 2,2-Di-Substituted *N*-Boc Pyrrolidines

To start our work on the synthesis of tetra-substituted pyrrolidines, the synthesis of racemic 2-phenyl *N*-Boc pyrrolidine *rac*-**70** was explored. Although this substrate could be prepared following the lithiation-Negishi reaction protocol as reported by our group,[5] on a scale of >1 g low yields of *rac*-**70** were generally obtained. For this reason the synthesis of *rac*-**70** was accomplished using a more scalable literature procedure.[125] Hence, 5 g of 2-pyrrolidinone **236** was treated with Me_3SiCl and PhMgCl to afford **237** (18% yield), which was reduced using $NaBH_4$ to give *rac*-**190**. Then, the formation of *rac*-**70** was achieved by Boc protection (Scheme 4.29).



Scheme 4.29

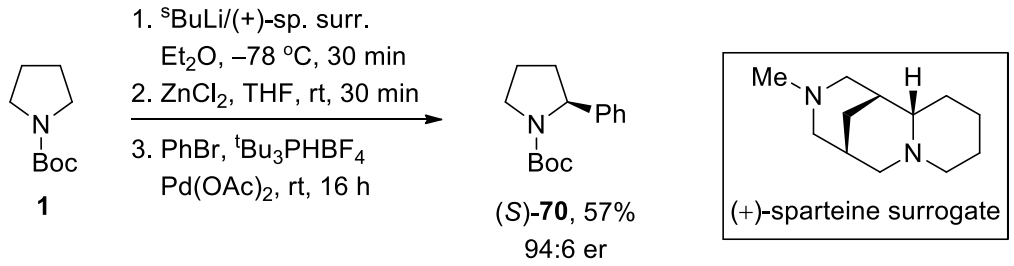
Despite the low yielding arylation of **236**, this synthetic pathway allowed the preparation of 1.6 g of *rac*-**70**. Thus, this substrate was used for the racemic synthesis of *rac*-**232** according to our group's procedure.[123] Benzylic lithiation of *rac*-**70** with *n*-BuLi in THF at 0 °C for 5 minutes and Me_2SO_4 trapping gave *rac*-**232** in an excellent 99% yield (Scheme 4.30).



Scheme 4.30

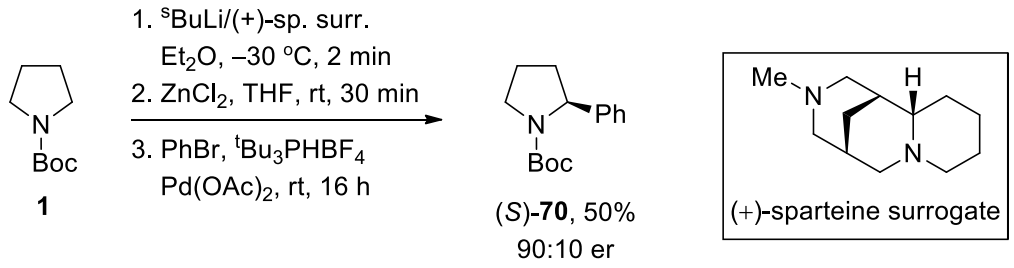
Next, we focussed on the synthesis of enantioenriched **70**. Therefore, as shown in Scheme 4.31, 2-phenyl *N*-Boc pyrrolidine (*S*)-**70** was synthesised using Campos's procedure,[56] but reducing the lithiation time to 30 minutes. Asymmetric lithiation of **1**

with *s*-BuLi and the (+)-sparteine surrogate in Et_2O at –78 °C, transmetallation ($ZnCl_2$) and Negishi reaction afforded (*S*)-**70** in 57% yield and 94:6 er (by CSP-HPLC).



Scheme 4.31

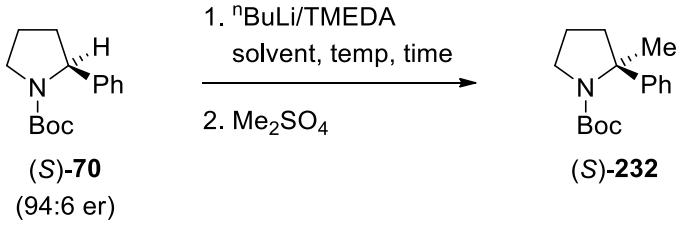
To pursue the idea of synthesising tetra-substituted pyrrolidines using four consecutive steps at temperatures above –78 °C, 2-phenyl *N*-Boc pyrrolidine (*S*)-**70** was also prepared using the high temperature asymmetric lithiation protocol described in Chapter 3. Under those conditions, (*S*)-**70** (50% yield) was isolated in 90:10 er after lithiation using *s*-BuLi/(+)-sparteine surrogate in Et_2O at –30 °C for 2 minutes (Scheme 4.32).



Scheme 4.32

The next aim was the synthesis of enantioenriched di-substituted *N*-Boc pyrrolidine (*S*)-**232**. At this point, understanding the configurational stability of the lithiated intermediate and optimisation of the yield were key aspects for the success of our strategy. According to Gawley, the use of TMEDA in Et_2O at –60 °C should give trapped products with good yields and high er.[124] However, our interest in high temperature lithiations pushed us to investigate temperatures above –60 °C. The results of the lithiation of (*S*)-**70** with *n*-BuLi and TMEDA at different temperatures and reaction times using Me_2SO_4 as electrophile are summarised in Scheme 4.33 and Table 4.2. At –50 °C in Et_2O, the reaction was incomplete after 5 minutes, but a near-quantitative yield of (*S*)-**232** was achieved with a 30 minute lithiation time (Entries 1 and 2). In both cases, the er of the starting material (94:6 er) was maintained in the product. When the temperature was raised to –30 °C, excellent yields were obtained

after 30 and 60 minutes lithiation time and (*S*)-**232** was isolated in 94% and 96% yields respectively (Entries 3 and 4). At this temperature, the er of (*S*)-**232** (~91:9 er) was slightly lower than at –50 °C. Finally, THF was used as solvent and lithiation at –50 °C for 30 minutes gave (*S*)-**232** in 23% yield and 58:42 er (Entry 5). In this case, starting (*S*)-**70** was also recovered in 53% yield.



(*S*)-**70** (94:6 er) (*S*)-**232**

Scheme 4.33

Table 4.2: Exploration of the Configurational Stability of the Lithiated Intermediate in the Benzylic Lithiation-Trapping of *N*-Boc Pyrrolidine (*S*)-**70** at Temperatures ≥ –50 °C

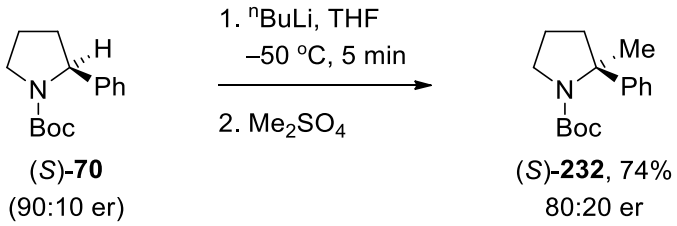
Entry	Solvent	Temp (°C)	Time (min)	Yield of (*S*)-232 (%)[a]	er[b]
1	Et_2O	–50	5	23	93:7
2	Et_2O	–50	30	97	94:6
3	Et_2O	–30	30	94	91:9
4	Et_2O	–30	60	96	92:8
5	THF	–50	30	23	58:42

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

Two main conclusions could be inferred from these data. First, the same level of er of the starting material and product at –50 °C (~94:6 er) indicated that the configuration of the stereogenic centre was preserved in the lithiated intermediate and then transferred to the product. At –30 °C, however, partial configurational instability of the organolithium was found. The use of TMEDA with THF gave a configurationally labile organolithium, possibly due to a competition between the ligand and the solvent for the coordination to the lithium. These results were in agreement with Gawley's study.[124]

For comparison, the benzylic lithiation of 2-phenyl pyrrolidine (*S*)-**70** was also investigated using the O'Brien group conditions.[123] Thus, (*S*)-**70** was treated with *n*-BuLi in THF at –50 °C for 5 minutes and then trapped with Me_2SO_4 to give (*S*)-**232** in 74% yield and 80:20 er (Scheme 4.34). In the absence of TMEDA the reduction in er

was larger, even at –50 °C. Hence, Gawley's conditions (*n*-BuLi, TMEDA, Et_2O, –50 °C, 30 min) were preferred for the preparation of (*S*)-**232**.

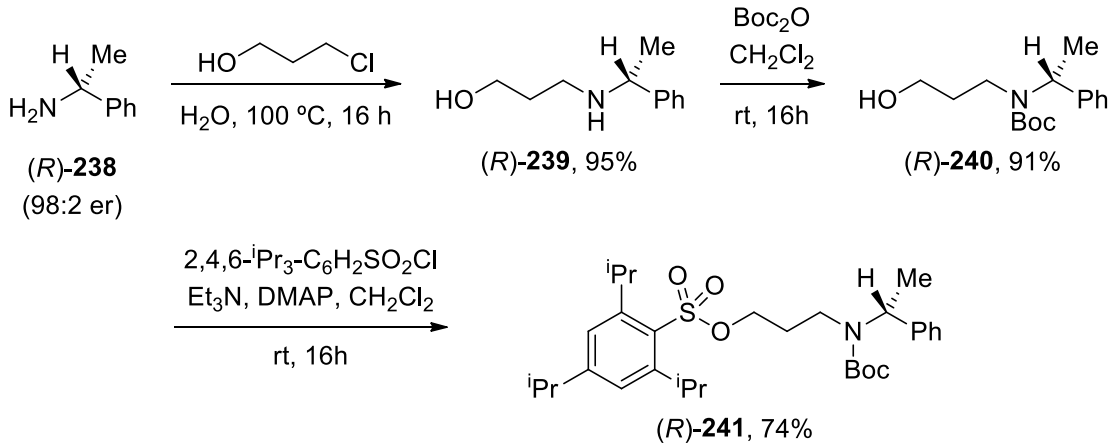


(*S*)-**70** (90:10 er)

(*S*)-**232**, 74% 80:20 er

Scheme 4.34

One of the limitations of the benzylic lithiation route to (*S*)-**232** was the difficulty in preparing >1 g of product, mainly caused by the low yield of the lithiation-Negishi coupling reaction upon scale-up. In order to have sufficient amounts of di-substituted pyrrolidines for exploration of the synthesis of tetra-substituted pyrrolidines, we decided to synthesise both (*R*)-**232** and (*S*)-**232** using a lithiation-cyclisation method previously published by our group.[123] Scheme 4.35 shows the route to (*R*)-**232**, which utilised enantioenriched α-methylbenzylamine (*R*)-**238** (98:2 er) as starting material. (*R*)-**238** was alkylated with 3-chloro propanol and then protected using Boc_2O to afford amino alcohol (*R*)-**240**. Subsequent activation of the hydroxyl group with 2,4,6-tri-*i*-Pr-benzenesulfonyl chloride gave *N*-Boc amino sulfonate (*R*)-**241** (74% yield). Since the last step would use *s*-BuLi, the bulky *i*-propyl groups on the benzenesulfonyl moiety were essential to block ortholithiation, which has been observed previously.[126]



(*R*)-**238** (98:2 er)

(*R*)-**239**, 95%

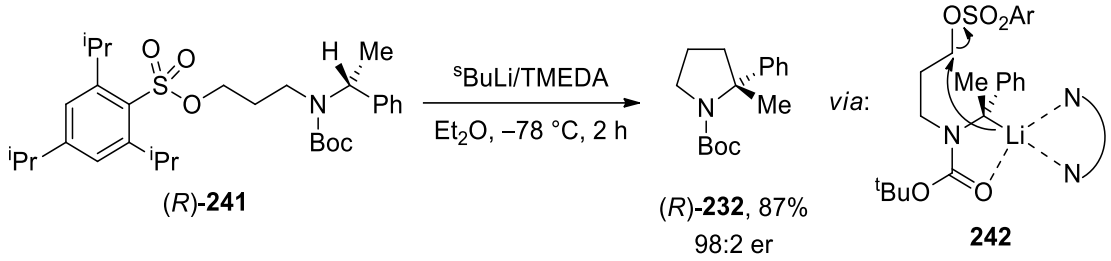
(*R*)-**240**, 91%

(*R*)-**241**, 74%

Scheme 4.35

In the final step, 8.0 mmol of (*R*)-**241** was treated with *s*-BuLi and TMEDA in Et_2O at –78 °C for 2 hours to give 1.81 g of 2,2-di-substituted *N*-Boc pyrrolidine (*R*)-**232** in

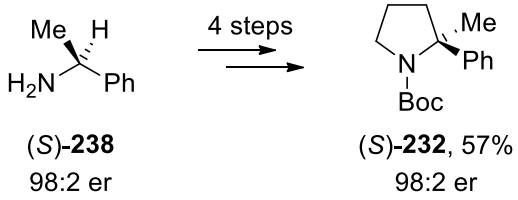
87% yield and 98:2 er (Scheme 4.36). The proposed mechanism proceeds *via* the formation of lithiated intermediate **242** which then cyclises with inversion of configuration[84] at the carbon-lithium centre.



Scheme 4.36

This methodology allowed the synthesis of multi-gram quantities of (*R*)-**232** without reduction of er (98:2 er) and the use of a large-scale lithiation (8.0 mmol) showed the robustness of this approach. In addition, the 5 hour reaction time reported by O'Brien and Coldham was shown to be unnecessary as the 2 hour lithiation gave a very good yield.

N-Boc pyrrolidine (*S*)-**232** was synthesised in 98:2 er and 57% overall yield starting from α-methylbenzylamine (*S*)-**238** of 98:2 er and following the same route described above (Scheme 4.37).

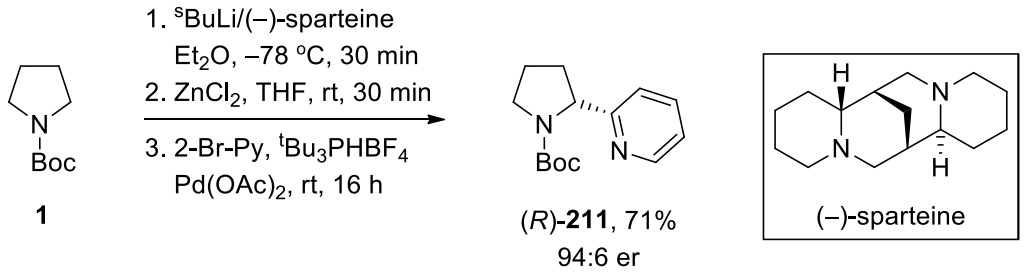


Scheme 4.37

4.3.2 Attempted Synthesis of Heteroaryl *N*-Boc Pyrrolidines

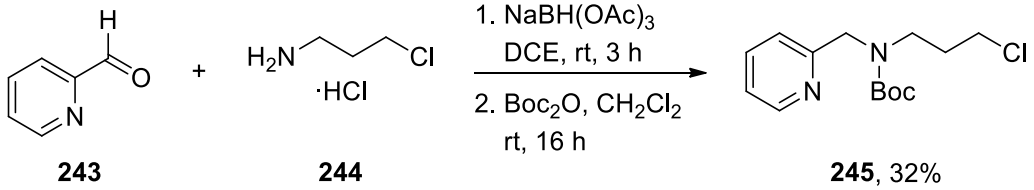
At this point, we also investigated the possibility of replacing the phenyl group with a heteroaromatic ring. This strategy could potentially diversify the range of substituents α to the nitrogen atom and, for example, give access to more interesting products from a pharmaceutical point of view. For this purpose, the pyridine ring would be a suitable substitution and the introduction into *N*-Boc pyrrolidine **1** has already been described by Campos.[30] The lithiation-transmetallation-Negishi protocol with *s*-BuLi and (–)-

sparteine at –78 °C and 2-bromo pyridine was described to give (*R*)-**211** in 71% yield and high enantioselectivity (94:6 er) (Scheme 4.38).



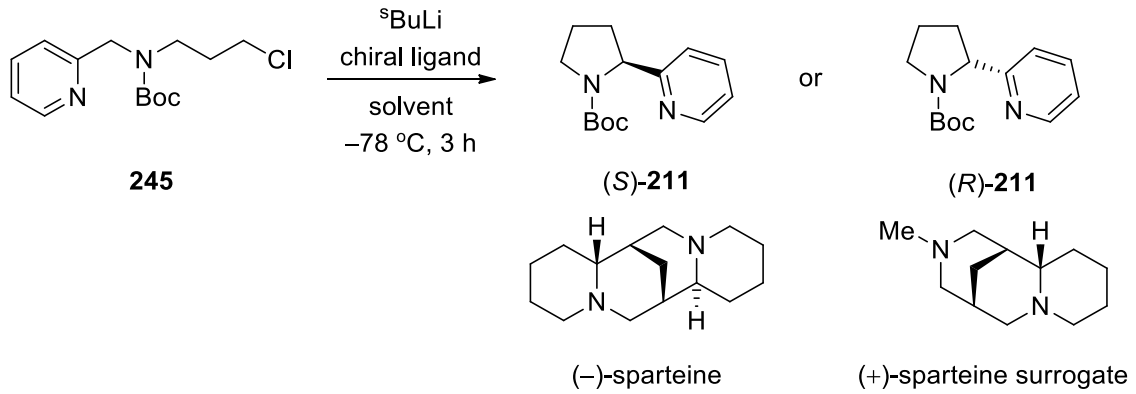
Scheme 4.38

Unfortunately, repeating the reaction several times in our laboratory gave low yields (<25% yield). Therefore, a different synthetic pathway, inspired by the lithiation-cyclisation protocol published by Beak in 1996 (see Scheme 4.14) was explored.[113] For this route, pyridylmethyl-3-chloropropyl *N*-Boc amine **245** was synthesised in two steps from 3-chloropropyl amine hydrochloride **244**. Thus, as shown in Scheme 4.39, reductive amination of amine **244** and aldehyde **243** with $NaBH(OAc)_3$ was followed by Boc protection to give *N*-Boc protected amine **245** in 32% yield.



Scheme 4.39

With **245** in hand, the asymmetric lithiation-cyclisation was carried out according to Beak's procedure: *s*-BuLi and (–)-sparteine in toluene at –78 °C for 3 hours. Cyclised product (*S*)-**211** was obtained in 82% yield (Scheme 4.40, Table 4.3, Entry 1). Although the yield was very good, (*S*)-**211** was formed in 51:49 er, which was much unexpected considering the high er reported in the literature with the phenyl substituent. Next, the same reaction conditions were tried using Et_2O as solvent. However, in this case (*S*)-**211** was obtained in 56% yield and 50:50 er, with 42% of unreacted starting material recovered (Entry 2).



Scheme 4.40

Table 4.3: Exploration of the Asymmetric Lithiation-Cyclisation of **245**

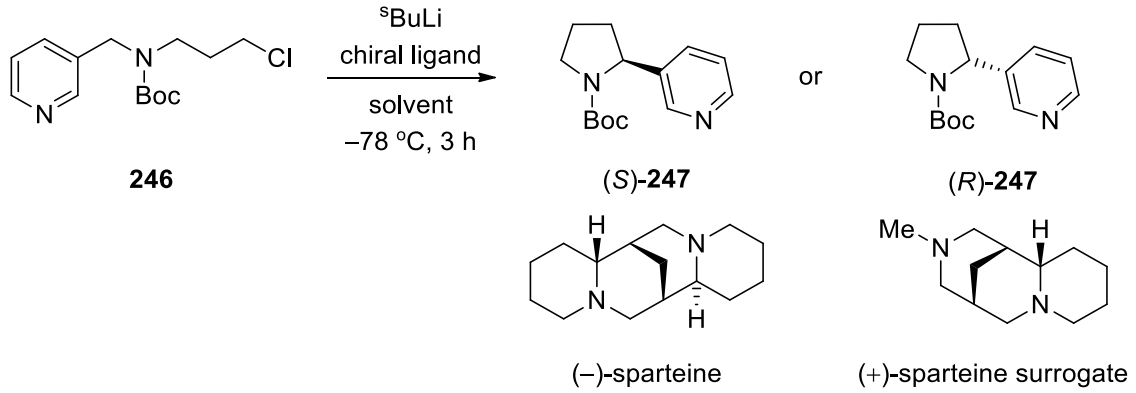
Entry	Chiral ligand	Solvent	Yield of 211 (%)[a]	er[b]	Yield of rec. SM 245 (%)[a]
1	(–)-sparteine	Toluene	82	51:49	-
2	(–)-sparteine	Et_2O	56	50:50	42
3	(+)-sparteine surrogate	Toluene	58	60:40	42
4	(+)-sparteine surrogate	Et_2O	58	62:38	42

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

The lithiation-cyclisation reaction of **245** was also performed with the (+)-sparteine surrogate as chiral ligand (Entries 3 and 4). The use of toluene or Et_2O as solvent gave (*R*)-**211** in 58% yield and 60:40 er or 62:38 er respectively. In both the reactions, unreacted starting material was recovered in 42% yield. A slightly higher level of enantioselectivity was observed with the (+)-sparteine surrogate compared to (–)-sparteine, although very unsatisfying. In addition, the yields were significantly lower.

The low enantioselectivity observed might be due to the formation of an azaenolate intermediate with a similar mechanism to the one shown in Scheme 4.76 (*vide infra*). If the possible delocalisation of the lithiated intermediate was the problem for the low er obtained with **245**, then using a pyridine such as **246** could give the cyclised product with a better enantioselectivity. Thus, pyridylmethyl-3-chloropropyl *N*-Boc amine **246**

was synthesised from 3-chloropropyl amine hydrochloride **244** and 3-pyridinecarboxaldehyde *via* the same route shown in Scheme 4.39. Lithiation of **246** with *s*-BuLi and (–)-sparteine in toluene at –78 °C for 3 hours afforded (*S*)-**247** in 36% yield and 53:47 er and recovered **246** in 40% yield (Scheme 4.41, Table 4.4, Entry 1). The use of Et_2O as solvent gave a 70% yield of (*S*)-**247** in 51:49 er; unreacted starting material was also isolated in 23% yield (Entry 2).



Scheme 4.41

Table 4.4: Exploration of the Asymmetric Lithiation-Cyclisation of **246**

Entry	Chiral ligand	Solvent	Yield of 247 (%)[a]	er[b]	Yield of rec. SM 246 (%)[a]
1	(–)-sparteine	Toluene	36	53:47	40
2	(–)-sparteine	Et_2O	70	51:49	23
3	(+)-sparteine surrogate	Toluene	30	66:34	54
4	(+)-sparteine surrogate	Et_2O	50	64:36	23

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC.

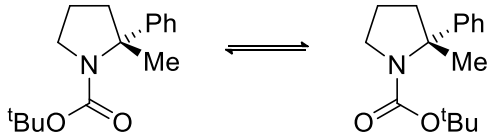
The use of the (+)-sparteine surrogate was then explored. Lithiation-cyclisation of **246** with *s*-BuLi and the (+)-sparteine surrogate at –78 °C for 3 hours in toluene gave (*R*)-**247** (30% yield) in 66:34 er and recovered starting material in 54% yield (Entry 3). With Et_2O, (*R*)-**247** was obtained in 50% yield and 64:36 er (Entry 4).

The low enantioselectivities obtained with the lithiation of **245** and **246** showed that the proposed delocalisation of the electrons on the pyridine nitrogen is not the only mechanism affecting the er of the products. It is possible that the pyridine nitrogen could coordinate to the lithium of the lithiated intermediate, disturbing the formation of the chiral ligand/lithiated intermediate complex, and thus leading to lower enantioselectivity.

Discouraged by the poor quality of these results the exploration of this route to pyridinyl pyrrolidines was abandoned.

4.3.3 Synthesis of α,α'-Tri-Substituted *N*-Boc Pyrrolidines

With di-substituted pyrrolidines *rac*-**232**, (*S*)-**232** and (*R*)-**232** in hand, the next challenge was the synthesis of tri-substituted *N*-Boc pyrrolidines. For the success of this phase, it was important to understand the rate of interconversion of the *N*-Boc rotamers (*S*)-**232a** and (*S*)-**232b** (Scheme 4.42) at the low temperatures used for lithiation reactions. In fact, since the lithiation is directed by the carbonyl of the Boc group, only rotamer **232b** could be α-lithiated; rotamer **232a** will be unreactive as the carbonyl is pointing towards the fully substituted quaternary centre.



(*S*)-**232a** (*S*)-**232b**

Scheme 4.42

Hence, to obtain information on the rate of interconversion of the *N*-Boc rotamers **232a** and **232b**, VT ^{1}H NMR spectroscopy studies were performed with (*R*)-**232** in toluene-d_8. In the ^{1}H NMR spectrum of (*R*)-**232** at 25 °C (298 K) the signals for the methyl group were separated, at δ_H 1.60 (2.1H) and δ_H 1.85 (0.9H), and showed a ~70:30 mixture of rotamers. The separation of those signals was ~124 Hz (Figure 4.5 a). As expected, the methyl signals became broader and closer together on raising the temperature to 45 °C and 60 °C (b, c).

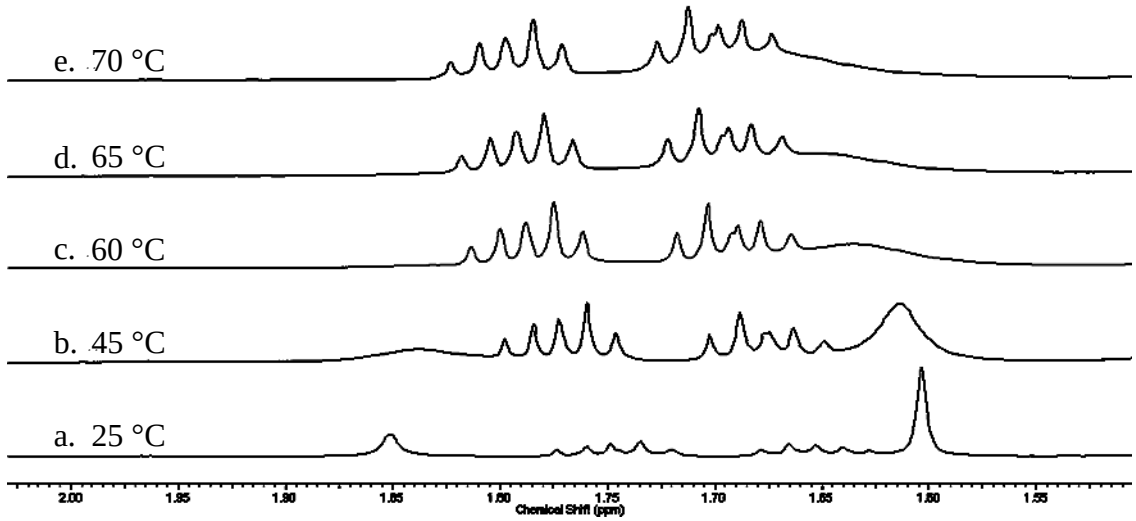


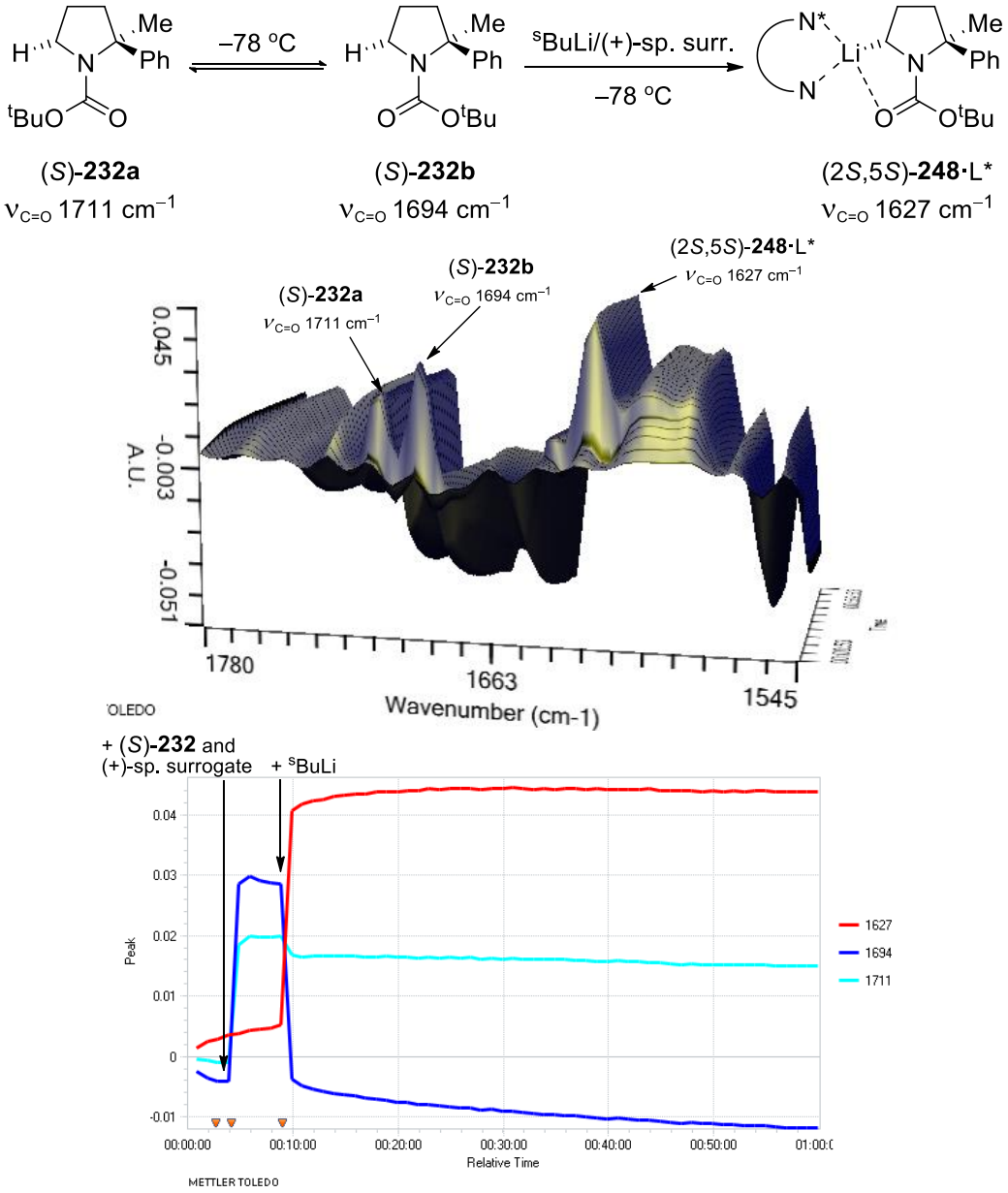
Figure 4.5

Although overlap with other signals made identification difficult, we estimated that the coalescence temperature was ~65 °C (338 K) (d). Therefore, the rate of interconversion at the coalescence temperature would be $k = 275.3\ s^{-1}$ and the half-life for rotation, $t_{1/2} = 2.5 \cdot 10^{-3}$ s. These values corresponded to a free energy of activation, $\Delta G^{\ddagger}$, of 67.3 kJ mol^{-1} at 65 °C. Assuming that the change in entropy is approximately zero, similar values for $\Delta G^{\ddagger}$ could be expected at lower temperatures.[127] Therefore, the half-life for rotation at −78 °C (195 K) was calculated to be >2 days. In contrast, at −40 °C (233 K), $t_{1/2}$ would be ~3 minutes.

These data clearly revealed that only a partial lithiation of **232** could be achieved at −78 °C, since the rotation of the *N*-Boc rotamers would be very slow compared to the usual lithiation timescale. In contrast, a reaction temperature of −40 °C should allow a fast enough interconversion of the unreactive rotamer **232a** to the reactive rotamer **232b**, and this should give full lithiation of the substrate. Assuming that the lithiated intermediate is chemically and configurationally stable at −40 °C, as was observed with lithiated *N*-Boc pyrrolidine **1** (see Scheme 2.23 and Table 2.1), then a 30 minute lithiation time should give high yields and good diastereoselectivities.

In order to further understand the lithiation of 2,2-di-substituted *N*-Boc pyrrolidine **232** at different temperatures, we decided to monitor the progress of the lithiation using *in situ* ReactIR™ spectroscopy studies. In Scheme 4.43, the results of the addition of *s*-

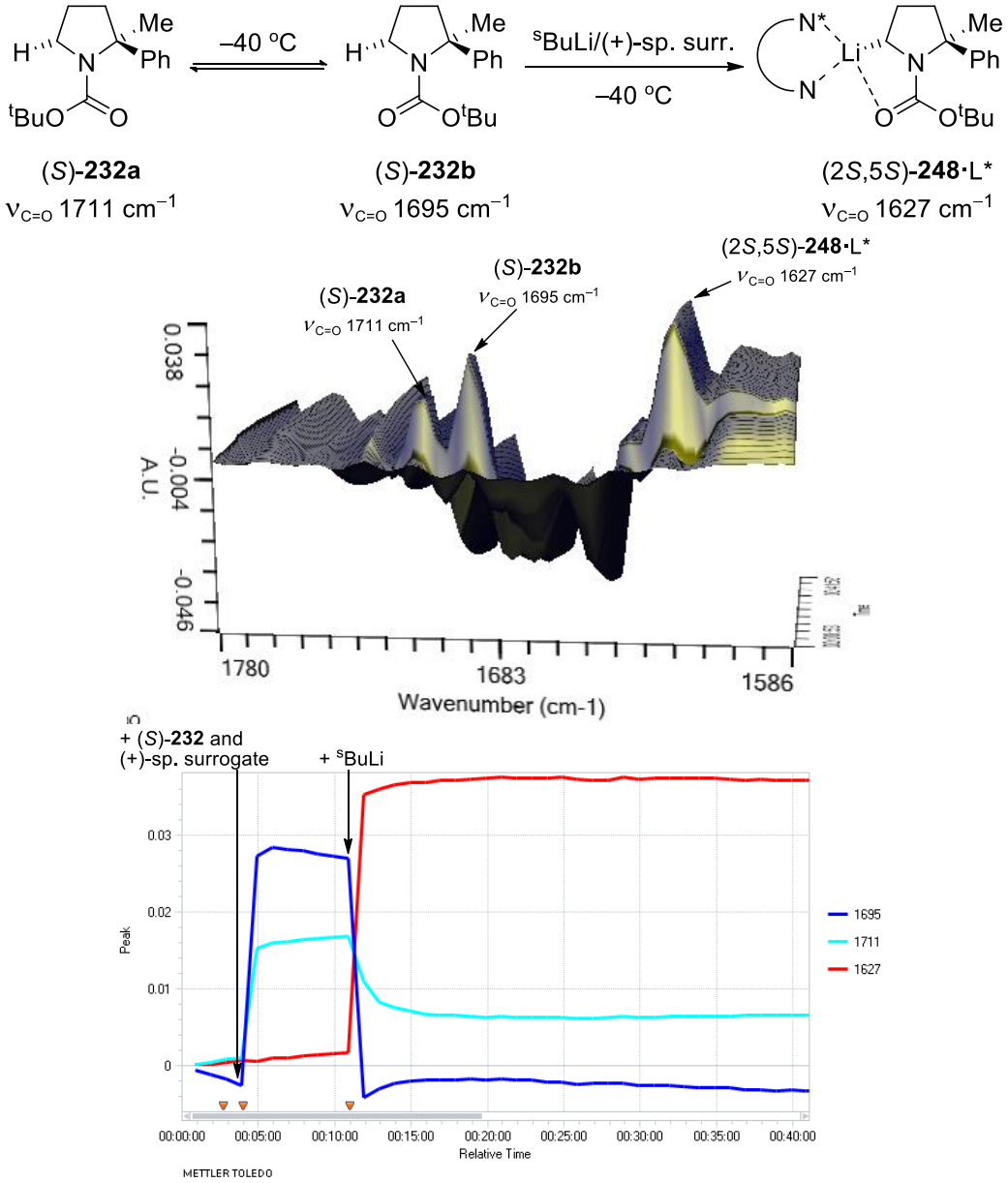
BuLi to a solution of (*S*)-**232** and (+)-sparteine surrogate in Et_2O at –78 °C are presented. Surprisingly, two different peaks for $\nu_{C=O}$, at 1711 cm^{-1} and 1694 cm^{-1}, were observed in the starting material region. Upon addition of *s*-BuLi, a rapid loss (<2 min) of the 1694 cm^{-1} peak and parallel formation of the lithiated intermediate (2*S*,5*S*)-**248**·L* ($\nu_{C=O}$ 1627 cm^{-1}) were observed. In contrast, the absorbance of the peak at 1711 cm^{-1} did not change over the 1 hour period.



Scheme 4.43

We suspected that the 1711 cm^{-1} and 1694 cm^{-1} peaks were associated with rotamers (*S*)-**232a** and (*S*)-**232b** respectively. The different $\nu_{C=O}$ values for the two rotamers could arise from a different planarity of the N–C=O unit. To confirm this hypothesis, an

in situ ReactIR™ spectroscopy experiment was carried out at –40 °C. At this temperature the interconversion of (*S*)-**232a** into (*S*)-**232b** should affect the 1711 cm^{-1} peak. Thus, the progress of the lithiation of di-substituted *N*-Boc pyrrolidine (*S*)-**232** with *s*-BuLi and (+)-sparteine surrogate in Et_2O at –40 °C was followed (Scheme 4.44).



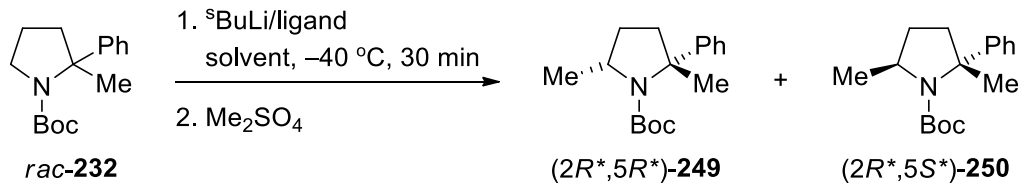
Scheme 4.44

Analysing these traces separately after the addition of *s*-BuLi, we noticed that the 1695 cm^{-1} peak decreased rapidly. Simultaneously, a reduction in intensity of the peak at 1711 cm^{-1} was observed. The 1627 cm^{-1} peak of the lithiated intermediate (2*S*,5*S*)-**248**·L* formed fast and then was constant. The comparison of the traces at 1711 cm^{-1} and 1695 cm^{-1} allowed the assignment of these absorbances to rotamers (*S*)-**232a** and

(*S*)-**232b** respectively. Presumably, the slow decrease of the 1711 cm^{-1} peak represented the interconversion of (*S*)-**232a** into (*S*)-**232b** and its subsequent lithiation.

Some conclusions can be drawn from the ReactIR™ spectroscopy studies. At −78 °C rotamer (*S*)-**232b** was lithiated within 2 minutes after the addition of *s*-BuLi, while rotamer (*S*)-**232a** was left untouched (see Scheme 4.43). This was due to the slow rate of interconversion of the *N*-Boc rotamers at −78 °C. Therefore, complete lithiation of (*S*)-**232** could not be achieved at −78 °C. On the other hand, at −40 °C, rotamer (*S*)-**232a** could interconvert into rotamer (*S*)-**232b**, which was then fully lithiated within 30 minutes. In addition, lithiated intermediate (2*S*,5*S*)-**248**·L* appeared chemically stable at both temperatures for at least 1 hour. Finally, these data were consistent with the results obtained from the VT ^{1}H NMR spectroscopy experiments.

The racemic lithiation-Me_2SO_4 trapping of *rac*-**232** was then explored. With the data obtained from the VT ^{1}H NMR spectroscopy and *in situ* ReactIR™ spectroscopy, –40 °C was chosen as the reaction temperature. Lithiation of *rac*-**232** was performed using *s*-BuLi for 30 minutes and trapping with Me_2SO_4. The lithiation in THF alone gave an inseparable mixture of diastereoisomers (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** in 81% yield (Scheme 4.45, Table 4.5, Entry 1). With the addition of TMEDA in THF, (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** were isolated in 93% yield (Entry 2) and switching solvent to Et_2O with TMEDA resulted in a similar yield of the two diastereoisomers (90% yield, Entry 3). The use of TMEDA clearly improved the yields. Importantly, these data represent the first example of a lithiation-trapping procedure with 2,2-di-substituted *N*-Boc pyrrolidines.



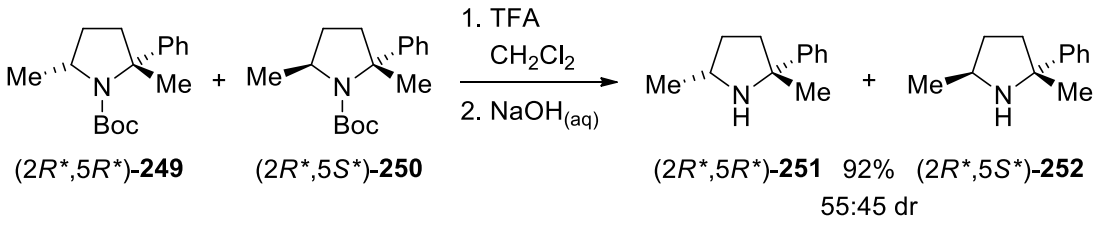
Scheme 4.45

Table 4.5: Racemic Lithiation-Me_2SO_4 Trapping of *rac*-**232**

Entry	Solvent	Ligand	Yield of (2*R**,5*R**)-249 + (2*R**,5*S**)-250 (%)[a,b]
1	THF	-	81
2	THF	TMEDA	93
3	Et_2O	TMEDA	90

[a]Yield after purification by chromatography. [b]dr not determined.

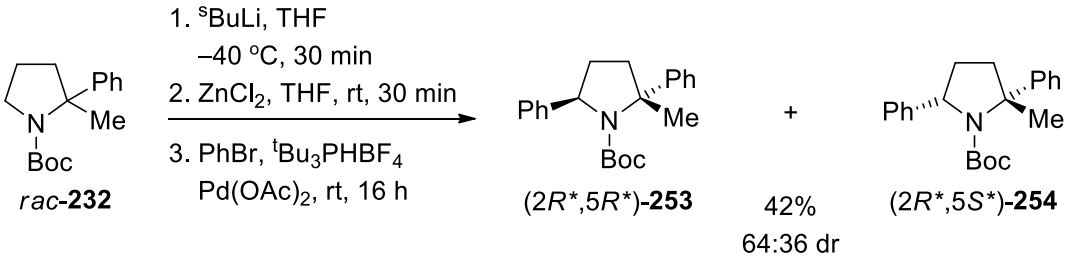
The main issue with (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** was that the two diastereoisomers were not separable using flash chromatography or with CSP-HPLC. Moreover, the presence *N*-Boc rotamers made measurement of the diastereomeric ratio impossible by ^{1}H NMR spectroscopy. The problem was solved by removing the Boc group. Treating diastereoisomers (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (from the reaction in Entry 3) with TFA for 1 hour, followed by basic work-up with aqueous NaOH gave deprotected (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** in 92% yield and 55:45 dr (Scheme 4.46). The dr was measured using the signals for the NCH protons in the ^{1}H NMR spectrum of the crude product. This value indicated little diastereoselectivity in the lithiation-trapping of *rac*-**232** probably due to the similar steric size of the phenyl and the methyl groups.



Scheme 4.46

The high yields obtained for the lithiation of *rac*-**232** were encouraging for the planned synthesis of tetra-substituted pyrrolidines. The next step was the instalment of an aryl group using the lithiation-Negishi protocol. Lithiation of *rac*-**232** was performed with *s*-BuLi in THF at –40 °C for 30 minutes. Subsequent transmetallation with $ZnCl_2$ and

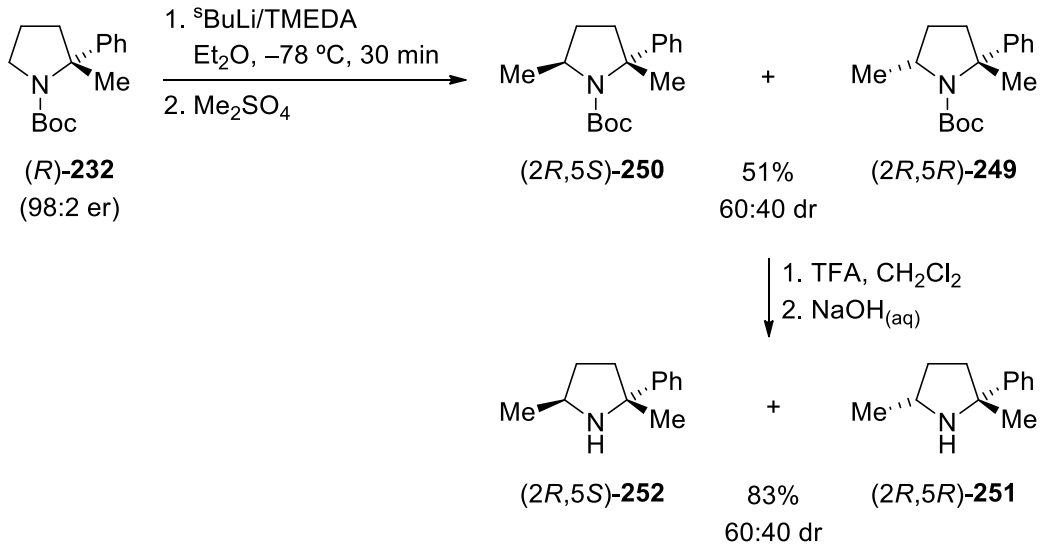
Negishi coupling with bromobenzene gave substituted pyrrolidines (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254** in 42% yield (Scheme 4.47). Luckily, the two diastereoisomers were resolved on CSP-HPLC, which showed a 64:36 mixture of (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254**. The major product was assigned as (2*R**,5*R**)-**253** based on the reactions of (*S*)-**232** and (*R*)-**232** in the presence of chiral ligands, which are described later. The same ratio was also measured by ^{1}H NMR spectroscopy of the deprotected amines, using the signals for the NCH protons.



Scheme 4.47

The yield obtained from the lithiation-Negishi reaction was not as high as the trapping with Me_2SO_4 (~90% yield), but yields of 50-70% are typical in our group for these type of Negishi reactions.

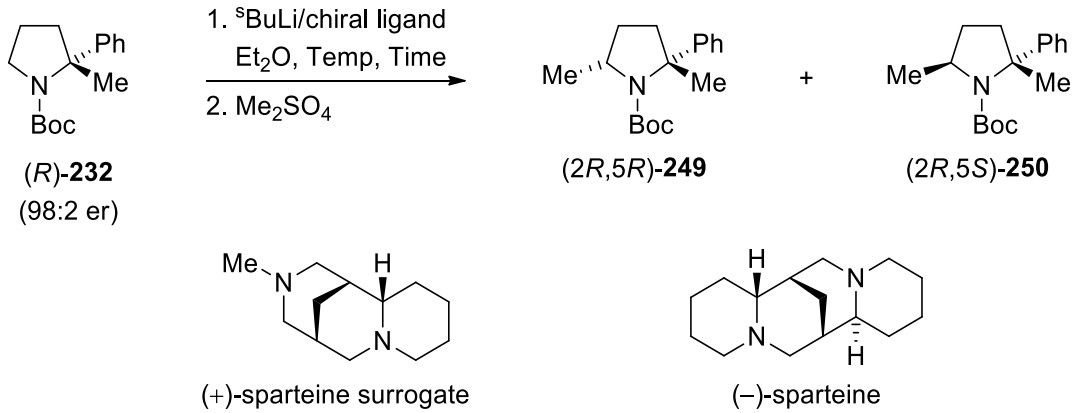
The development of the synthesis of tri-substituted pyrrolidines moved to the investigation of the lithiation-trapping of enantioenriched 2,2-di-substituted *N*-Boc pyrrolidine (*R*)-**232**. Me_2SO_4 was initially chosen as the electrophile for this exploration and −78 °C was used with the hope of a higher diastereoselectivity in the formation of the lithiated intermediate. Thus, (*R*)-**232** (98:2 er) was lithiated with *s*-BuLi and TMEDA in Et_2O at −78 °C for 30 minutes and then trapped with Me_2SO_4 to give an inseparable 60:40 mixture of (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (51% yield) (Scheme 4.48). Starting material (*R*)-**232** was also recovered in 42% yield. The diastereomeric ratio was measured by ^{1}H NMR spectroscopy of the deprotected amine (2*R*,5*S*)-**252** and (2*R*,5*R*)-**251** (83% crude yield, 60:40 dr). The 51% yield was consistent with the calculated half-life for rotation of the *N*-Boc rotamers at −78 °C ($t_{1/2}$ >2 days).



Scheme 4.48

Considering the results obtained with (*R*)-**232** and *rac*-**232**, it is reasonable to assume that there is an intrinsic substrate control on the stereochemistry of the lithiation-trapping reaction. The ~60:40 dr observed suggests that there is a preference for substitution *trans* to the phenyl group of the stereogenic centre.

With the desire of improving the diastereoselectivity, chiral ligands were explored starting with the (+)-sparteine surrogate. In Scheme 4.49 and Table 4.6 are shown the results of the lithiation of (*R*)-**232** (98:2 er) with *s*-BuLi and (+)-sparteine surrogate in Et_2O followed by reaction with Me_2SO_4. Lithiation at −78 °C for 1 hour gave (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** as an 87:13 mixture in 45% yield (Entry 1). Starting (*R*)-**232** was recovered (43% yield). The lithiation at −40 °C for 30 minutes gave an 81:19 mixture of (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** in an improved 82% yield (Entry 2).



Scheme 4.49

Table 4.6: Asymmetric Lithiation-Me_2SO_4 Trapping of (*R*)-**232**

Entry	**Chiral ligand**	**Temp (°C)**	**Time (min)**	**Yield of (2*R*,5*R*)-249 + (2*R*,5*S*)-250 (%)[a]**	**(2*R*,5*R*) : (2*R*,5*S*)[b]**
1	(+)-sparteine surrogate	–78	60	45	87:13
2	(+)-sparteine surrogate	–40	30	82	81:19
3	(–)-sparteine	–78	60	45	2:98
4	(–)-sparteine	–40	30	96	9:91

[a]Yield after purification by chromatography. [b]dr determined by ^{1}H NMR spectroscopy of the deprotected amines.

Next, the lithiation-trapping of (*R*)-**232** was performed using (–)-sparteine as the chiral ligand. In theory, (–)-sparteine should have the opposite sense of induction and give (2*R*,5*S*)-**250** as the major diastereoisomer. This should help in the assignment of the relative stereochemistry of the products. Hence, (*R*)-**232** (98:2 er) was lithiated with *s*-BuLi and (–)-sparteine in Et_2O. Lithiation at −78 °C for 1 hour and trapping with Me_2SO_4 gave a 98:2 mixture of (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (45% yield) and unreacted (*R*)-**232** (53% yield) (Entry 3). A 30 minute lithiation at −40 °C afforded a 91:9 mixture of (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** in 96% yield (Entry 4).

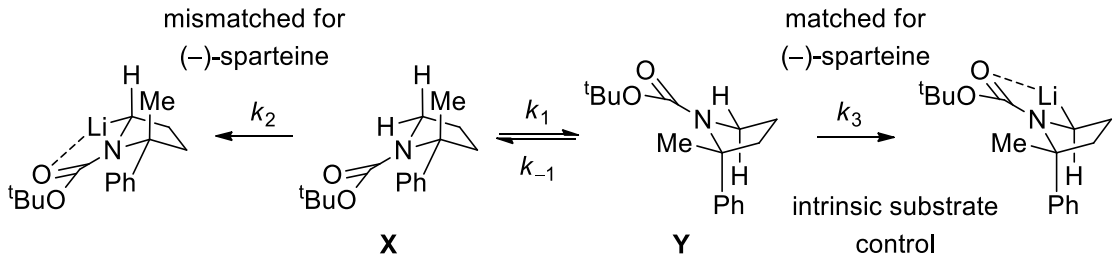
The results obtained were consistent with the calculated half-life for interconversion of the *N*-Boc rotamers at −78 °C ($t_{1/2}$ >2 days) and −40 °C ($t_{1/2}$ ~3 minutes). In fact, at −78 °C, incomplete lithiation was expected and recovered starting material (43% and 53% yields) was obtained. These values indicated that the low yields (45% for both) were not due to chemical instability of the lithiated intermediate. The 82% and 96% yields at −40 °C indicated that the rotamers were interconverting. Despite the improvement of the diastereoselectivity from 60:40 dr (see Scheme 4.48) to 87:13 dr, the stereochemical induction with the (+)-sparteine surrogate at −78 °C was considerably lower with (*R*)-**232** than it was with *N*-Boc pyrrolidine **1**, as described in section 2.2.1. In addition, the 81:19 dr at −40 °C was probably due to a lower kinetic selectivity, as we believe that the lithiated intermediate would be configurationally stable at −40 °C.

The relative stereochemistry of the major diastereoisomer from these reactions was assigned based on the established sense of induction obtained with the (+)-sparteine surrogate and (–)-sparteine in *s*-BuLi-mediated reactions with *N*-Boc pyrrolidine **1**. The relative stereochemistry was supported by X-ray crystallographic analysis of another tri-substituted pyrrolidine (see Figure 4.6), the synthesis of which is described later.

Arguably, the amazing 98:2 dr obtained at −78 °C was the most impressive result from these reactions. At −40 °C, an excellent 96% yield was achieved with a slightly reduced 91:9 dr. The reaction at −78 °C with *s*-BuLi/(–)-sparteine gave the same yield (45%) as that with the (+)-sparteine surrogate (45%). Recalling the ^{1}H NMR spectrum of (*R*)-**232** where a ~70:30 population of the two rotamers was observed (see Figure 4.5) and considering that at −78 °C the $t_{1/2}$ was >2 days, it can be assumed that the major rotamer in (*R*)-**232** has the carbonyl pointing towards the unsubstituted α-carbon. (*i.e.* rotamer **232b** in Scheme 4.42).

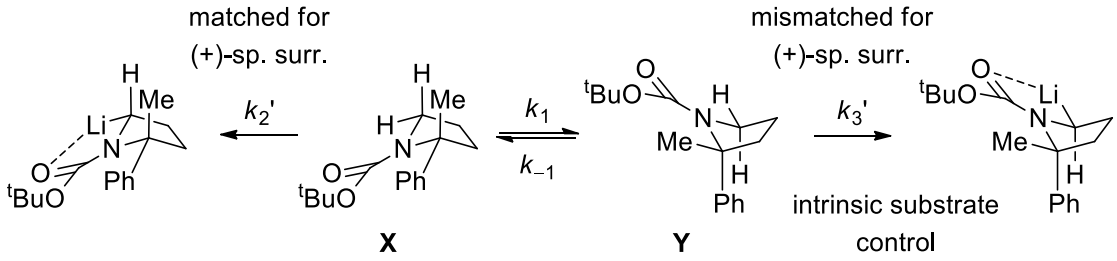
From the results obtained with the two chiral ligands, it was clear that using (*R*)-**232** as starting material, *s*-BuLi/(–)-sparteine had a higher diasteroinduction, in the opposite sense, compared to *s*-BuLi/(+)-sparteine surrogate. Considering that the lithiation will occur on the *pseudo*-equatorial proton, a match/mismatch mechanism is proposed to explain this phenomenon.

First, we have to consider that the substrate, (*R*)-**232**, has an intrinsic, albeit minor, substrate control for a substitution *trans* to the phenyl group of the stereogenic centre. Hence, lithiation of the *pseudo*-equatorial proton in conformation **Y**, which leads to the formation of the lithiated intermediate *trans* to the phenyl, would be favoured (Scheme 4.50). Second, it is known, from studies on other *N*-Boc heterocycles, that *s*-BuLi/(–)-sparteine is selective towards the deprotonation of the *pseudo*-equatorial proton in conformation **Y**. Hence, it is reasonable to assume that conformers **X** and **Y** would form the respective lithiated intermediates at different rates (k_2 and k_3). In particular, the reaction of *s*-BuLi/(–)-sparteine with conformation **Y** will represent the matched case and will have a faster rate (k_3) than the reaction of *s*-BuLi/(–)-sparteine with the mismatched conformer **X**, *i.e.* $k_3 > k_2$. The combination of substrate control and substrate/ligand matching generates the high diastereoselectivity observed.



Scheme 4.50

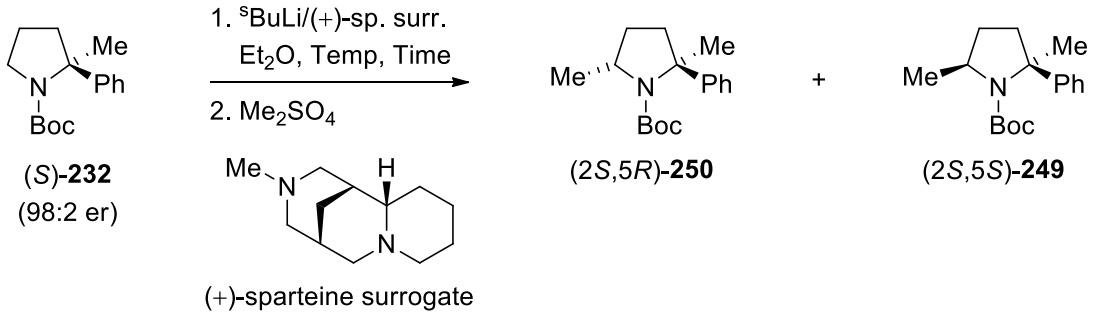
On the other hand, with *s*-BuLi/(+)-sparteine surrogate, the matched situation is lithiation of the *pseudo*-equatorial proton in conformer **X**. This is in opposition to the substrate control and results in lower dr obtained with (*R*)-**232** and *s*-BuLi/(+)-sparteine surrogate.



Scheme 4.51

With these considerations, the (+)-sparteine surrogate should be the matching ligand for the opposite enantiomer of the di-substituted pyrrolidine, (*S*)-**232**. Thus, the lithiation of (*S*)-**232** was explored with *s*-BuLi and the (+)-sparteine surrogate and Me_2SO_4 as

electrophile (Scheme 4.52, Table 4.7). At –78 °C, a 1 hour lithiation afforded a 92:8 mixture of (2*S*,5*R*)-**250** and (2*S*,5*S*)-**249** in 51% yield, and unreacted (*S*)-**232** in 40% yield (Entry 1). At –40 °C for 30 minutes, (2*S*,5*R*)-**250** and (2*S*,5*S*)-**249** were isolated as a 94:6 mixture in a high 85% yield (Entry 2).



Scheme 4.52

Table 4.7: Asymmetric Lithiation-Me_2SO_4 Trapping of (*S*)-**232**

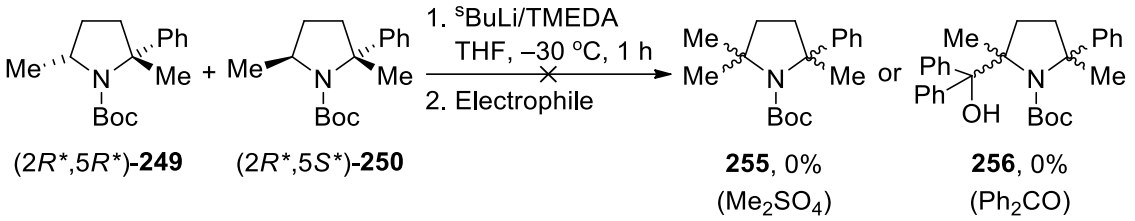
Entry	Temp (°C)	Time (min)	Yield of (2*S*,5*R*)-250 + (2*S*,5*S*)-249 (%)[a]	(2*S*,5*R*) : (2*S*,5*S*)[b]	Yield of rec. (*S*)-232 (%)[a]
1	–78	60	51	92:8	40
2	–40	30	85	94:6	-

[a]Yield after purification by chromatography. [b]dr determined by ^{1}H NMR spectroscopy of the deprotected amines.

The use of *s*-BuLi/(+)-sparteine surrogate in combination with (*S*)-**232** gave excellent diastereoselectivity and this observation was consistent with the proposed matched chiral ligand theory. The high 94:6 dr obtained from the reaction at –40 °C was the highest value achieved using the high temperature asymmetric lithiation-trapping of di-substituted pyrrolidines.

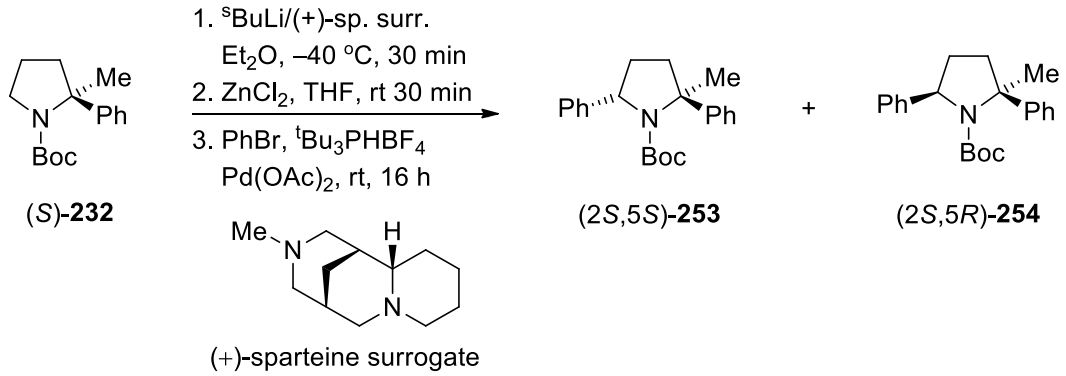
At this point we decided to use methylated tri-substituted pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** to pursue the synthesis of tetra-substituted pyrrolidines, using them as substrates for lithiation-trapping. In order to obtain information on the lithiation-trapping of this tri-substituted pyrrolidine, we started with racemic methodology and thus, (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** were used as substrates. Tri-substituted pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** were lithiated using *s*-BuLi and TMEDA in THF at –30 °C for 1 hour and then trapped with Me_2SO_4 or benzophenone

(Scheme 4.53). In both cases, the reactions were unsuccessful and the ^{1}H NMR spectrum of the crude product showed only unreacted starting mixture. We found the lithiation of (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** harder than expected. Therefore, no further exploration was carried out with this substrate, although lithiation-trapping at 0 °C could be considered in the future.



Scheme 4.53

Therefore, we switched our attention to the introduction of aryl groups, which should favour the fourth lithiation by increasing the acidity of the proton α to nitrogen. The knowledge of the ligand effect on the diastereoselectivity, gained with the methylation of **232**, was fundamental for planning the next synthetic step towards tetra-substituted pyrrolidines. A 30 minute lithiation time and –40 °C were selected as the reaction conditions. Thus, lithiation of (*S*)-**232** was performed with *s*-BuLi and the (+)-sparteine surrogate, followed by transmetallation with $ZnCl_2$ and reaction with $Pd(OAc)_2$, $^tBu_3PHBF_4$ and bromobenzene (Scheme 4.54, Table 4.8). The two diastereoisomers, (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254**, were isolated as an inseparable mixture with (2*S*,5*S*)-**253** as the major product. A 56% yield of a 96:4 mixture of (2*S*,5*S*)-**253** and (2*S*,5*R*)-**253** was obtained with (*S*)-**232** of 98:2 er (Entry 1). CSP-HPLC showed >99:1 er for the major diastereoisomer and 98:2 er for the minor diastereoisomer. Unreacted (*S*)-**232** (42% yield) was also recovered.



Scheme 4.54

Table 4.8: Asymmetric Lithiation-Negishi Coupling Reaction of (*S*)-**232**

Entry	**er of SM**	**Yield of (2*S*,5*S*)-253 + (2*S*,5*R*)-254 (%)[a]**	**(2*S*,5*S*)-253: (2*S*,5*R*)-254 [b]**	**er of (2*S*,5*S*)-253[c]**	**er of (2*S*,5*R*)-254 [c]**
1	98:2	56	96:4	>99:1	98:2
2	94:6	38	94:6	>99:1	76:24
3	80:20	58	86:14	98:2	18:82

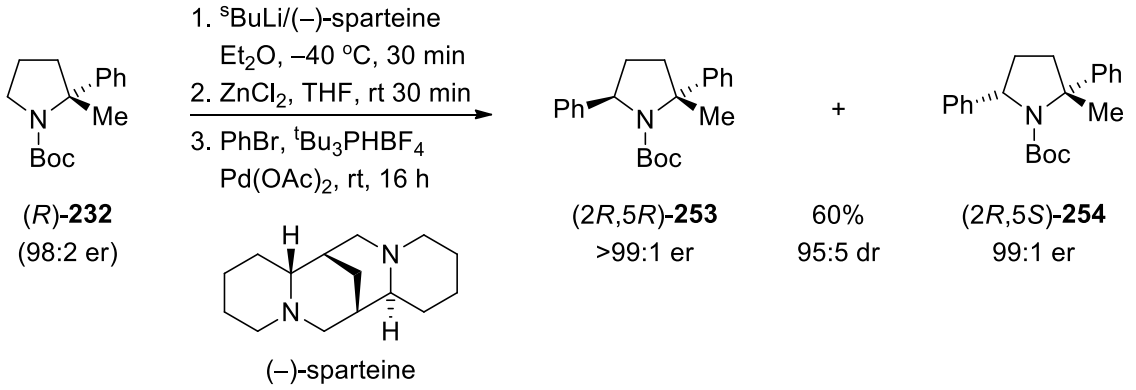
[a]Yield after purification by chromatography. [b]dr determined by CSP-HPLC. [c]er determined by CSP-HPLC.

As outlined at the beginning of this chapter, the plan for this part of the project was to synthesise tetra-substituted pyrrolidines starting from *N*-Boc pyrrolidine **1**. For this purpose, the lithiation-Negishi protocol was performed with (*S*)-**232** of 94:6 er (previously obtained by a Negishi reaction of *N*-Boc pyrrolidine **1**, see Scheme 4.33, Table 4.2). A 94:6 mixture of (2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*R*)-**254** (76:24 er) was obtained in 38% yield (Entry 2). Next, (*S*)-**232** of 80:20 er was used, which was synthesised from *N*-Boc pyrrolidine **1** *via* high temperature asymmetric lithiation-Negishi coupling followed by benzylic lithiation-trapping. In this case, a 84:16 mixture of (2*S*,5*S*)-**253** and (2*R*,5*S*)-**254** in 58% yield, with 98:2 er for the major diastereoisomer and 82:18 er for the minor diastereoisomer was obtained (Entry 3).

Using (*S*)-**232** of 98:2 er and 94:6 er gave the major product, (2*S*,5*S*)-**253**, in >99:1 er. Interestingly, the enantioselectivity (76:24 er) of the minor diastereoisomer in Entry 2 was considerably lower than those observed in the previous examples. On the other hand, the major diastereoisomer was obtained in an excellent >99:1 er. Unfortunately, in

this case, the products were isolated in a mediocre 38% yield. Unexpectedly, with (*S*)-**232** of 80:20 er, an extremely high 98:2 er for the major diastereoisomer was achieved. In addition, it was noticed that the major enantiomer of the minor diastereoisomer was (2*R*,5*S*)-**254**, which is the opposite sense to those obtained from the higher er substrates, (2*S*,5*R*)-**254**. Moreover, a good diastereoselectivity of 86:14 dr was also observed.

With (*R*)-**232** (98:2 er), the lithiation was accomplished with the use of *s*-BuLi and (–)-sparteine at –40 °C for 30 minutes. The lithiated intermediate was then transmetallated with $ZnCl_2$ and subsequent Negishi coupling with bromobenzene gave a 95:5 mixture of (2*R*,5*R*)-**253** and (2*R*,5*S*)-**254** in 60% yield, with >99:1 er for (2*R*,5*R*)-**253** and 99:1 er for (2*R*,5*S*)-**254**. Starting material (*R*)-**232** was also recovered in 32% yield (Scheme 4.55).

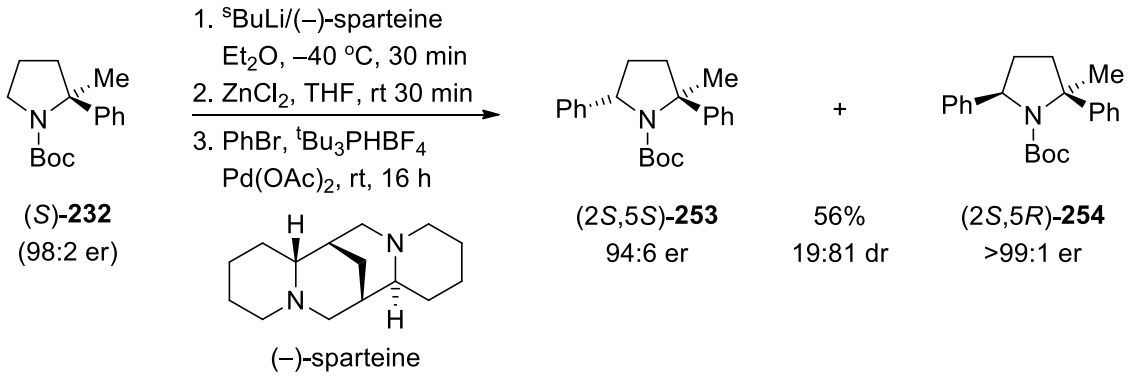


Scheme 4.55

The good diastereoselectivities of ≥95:5 dr achieved with both (*S*)-**232** and (*R*)-**232** were further evidence for the match/mismatch ligand effect. In addition, excellent enantioselectivities of the major diastereoisomers (>99:1 er) and of the minor diastereoisomers (>98:2 er) were observed. Although the yields of these reactions were not as high as the yields using Me_2SO_4 as electrophile (85-96% yield), a range of 50-70% yields is typical for the transmetallation-Negishi coupling.

Next, the lithiation-Negishi coupling method was tested using the mismatching ligand on (*S*)-**232**. The reaction conditions were maintained as in the previous examples, *s*-BuLi at –40 °C for 30 minutes, but (–)-sparteine was used as the chiral ligand. Transmetallation and Negishi reaction with bromobenzene afforded an 81:19 mixture of

(2*S*,5*R*)-**254** and (2*S*,5*S*)-**253** in 56% yield (Scheme 4.56). A >99:1 er for the major diastereoisomer and 94:6 er for the minor diastereoisomer were showed by CSP-HPLC.

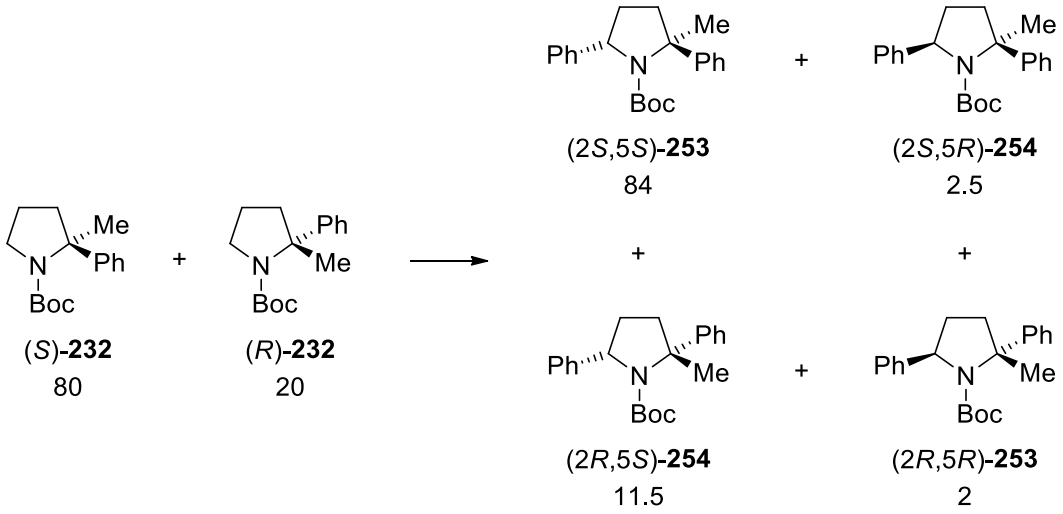


Scheme 4.56

As expected from the use of the mismatching ligand, the diastereoselectivity was lower and of the same level observed in the lithiation of (*R*)-**232** (98:2 er) with *s*-BuLi/(+)-sparteine surrogate at –40 °C and the electrophilic trapping with Me_2SO_4 (81:19 dr) (see Scheme 4.49, Table 4.6, Entry 2). The enantioselectivity of the major diastereoisomer (>99:1 er) was comparable to those measured in the reactions with the matching chiral ligands (see Scheme 4.54 and Scheme 4.8), while the minor diastereoisomer was obtained in a slightly lower 94:6 er.

Analysing the data obtained from all of the lithiation-Negishi coupling reactions, it can be noticed that the er of the major diastereoisomer (>99:1 er) was always higher than those of the starting substrates (98:2 er). In the example with (*S*)-**232** of 80:20 er, this was even more evident as it gave a 98:2 er of the major diastereoisomer. These results can be rationalised with a chiral amplification mechanism and an example is shown in Scheme 4.57, using the results obtained from (*S*)-**232** of 80:20 er. In the substrate, (*S*)-**232** was the major enantiomer (80%) and because the (+)-sparteine surrogate was used, the reaction gave the desired (2*S*,5*S*)-**253** as the major product in a high diastereoselectivity (~97:3 dr). The minor enantiomer (*R*)-**232** also reacted, but with the mismatched ligand, (+)-sparteine surrogate, and therefore the diastereoselectivity was lower (~85:15 dr). The minor diastereoisomer obtained from the minor starting material (*R*)-**232** was (2*R*,5*R*)-**253**. In other words, the opposite enantiomer of the desired product and this can explain the high enantioselectivity observed for (2*S*,5*S*)-**253** (98:2 er). This reaction also showed that (2*R*,5*S*)-**254** was the major enantiomer of the minor

diastereoisomer in contrast to the result obtained using (*S*)-**232** (98:2 er) (see Scheme 4.54). This was due to the larger amount of the minor enantiomer (*R*)-**232** (20%) in the reacting substrate.



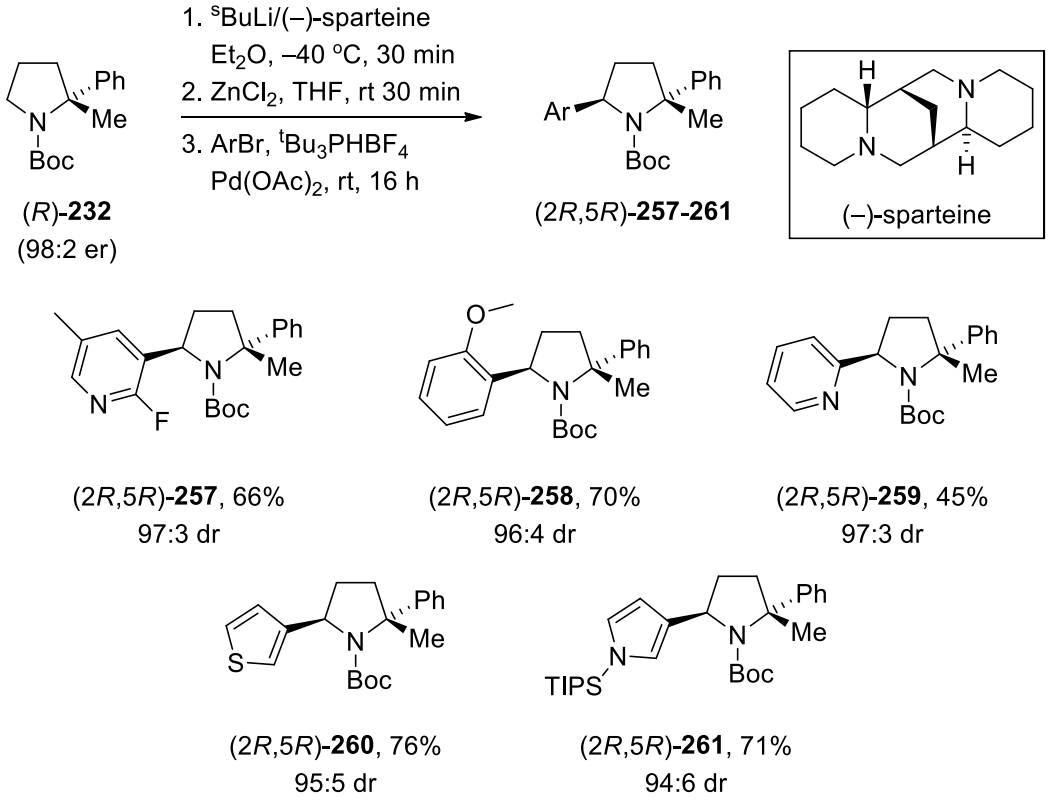
Scheme 4.57

The same principle can be extended to the enantioenriched substrates (*S*)-**232** and (*R*)-**232**, explaining the excellent >99:1 er of the major diastereoisomers. Furthermore, with (*S*)-**232** (96:4 er) the minor diastereoisomer (2*S*,5*R*)-**254** was obtained in 76:24 er (see Scheme 4.54, Table 4.8). This is consistent with an increased amount of (2*R*,5*S*)-**254** from the 4% of the minor enantiomer, (*R*)-**232**, in the starting substrate.

With this exploration, it was shown that the insertion of an aryl group was attainable using the lithiation-Negishi coupling protocol on 2,2-di-substituted pyrrolidines. Amazingly, it was possible to amplify the er of the substrate from 80:20 er to 98:2 er as well as from 98:2 er to >99:1 er. Finally, the chiral amplification mechanism helped to explain the different ers of the minor diastereoisomers. In all this discussion, we could conclude that a lithiation temperature of –40 °C is needed for high yields, as it allows the interconversion of the *N*-Boc rotamers.

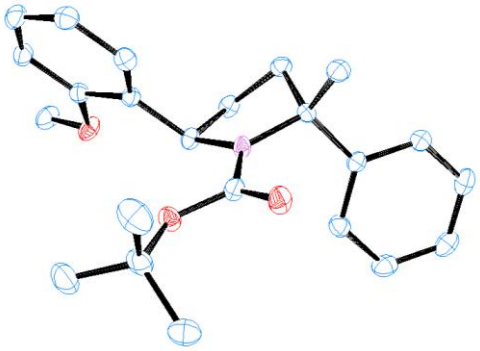
Next, we investigated the lithiation-transmetallation-Negishi coupling reaction using other aryl bromides in order to expand the scope of the methodology. Thus, (*R*)-**232** was lithiated with *s*-BuLi and the matching chiral ligand, (–)-sparteine, at –40 °C for 30 minutes and then transmetallated with $ZnCl_2$. The subsequent Negishi coupling was performed under the standard conditions ($Pd(OAc)_2$, $^tBu_3PHBF_4$ and the aryl bromide)

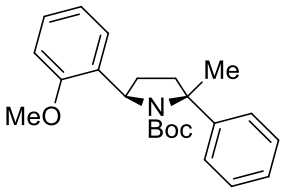
at room temperature. Aryl bromides, which were reported to give above 70% yields in the arylation of *N*-Boc pyrrolidine **1**,[30] were selected for this exploration and the results are shown in Scheme 4.58. Use of 3-bromo-2-fluoro-5-methylpyridine, 2-bromo-pyridine, 3-bromo-thiophene, *N*-tri-*i*-Pr-silyl 3-bromo-pyrrole and 2-bromo-anisole gave arylated products (2*R*,5*R*)-**257**-**261** in 45-76% yields and 94:6-97:3 dr. In all these reactions, the diastereoisomers of each of the products were not separable by flash column chromatography. The diastereoselectivities were measured using ^{1}H NMR spectroscopy of the crude *N*-Boc deprotected amines as described later.



Scheme 4.58

Luckily, tri-substituted pyrrolidine (2*R*,5*R*)-**258** was a crystalline solid and X-ray crystallography analysis was used to determine its relative stereochemistry (Figure 4.6). This analysis showed that the aryl groups were in a *trans* relationship and thus, the lithiation-transmetallation-Negishi coupling reaction proceeded with the stereochemistry expected using of *s*-BuLi/(–)-sparteine. The relative stereochemistry of the other tri-substituted pyrrolidines was assumed to be (2*R*,5*R*) by analogy.

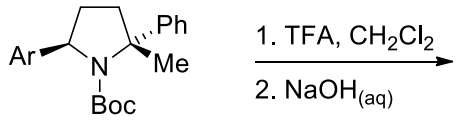




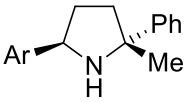
(2*R*,5*R*)-**258**

Figure 4.6

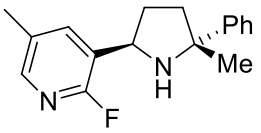
As previously mentioned, the dr of *N*-Boc tri-substituted pyrrolidines (2*R*,5*R*)-**257**-**261** was determined using ^{1}H NMR spectroscopy of the amines. Hence, (2*R*,5*R*)-**257**-**261** were deprotected using TFA in CH_2Cl_2, followed by basic work-up with aqueous NaOH, to give the crude amines (2*R*,5*R*)-**262**-**265**, which were obtained in almost quantitative yields (89-99% yields, Scheme 4.59). They were analysed by ^{1}H NMR spectroscopy without further purification.



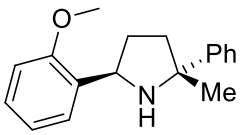
(2*R*,5*R*)-**257**-**261**



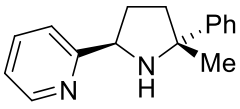
(2*R*,5*R*)-**262**-**266**



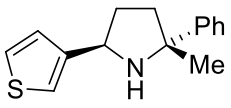
(2*R*,5*R*)-**262**, 89%
97:3 dr



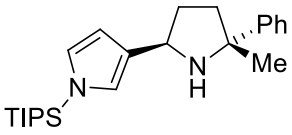
(2*R*,5*R*)-**263**, 97%
96:4 dr



(2*R*,5*R*)-**264**, 92%
97:3 dr



(2*R*,5*R*)-**265**, 99%
95:5 dr

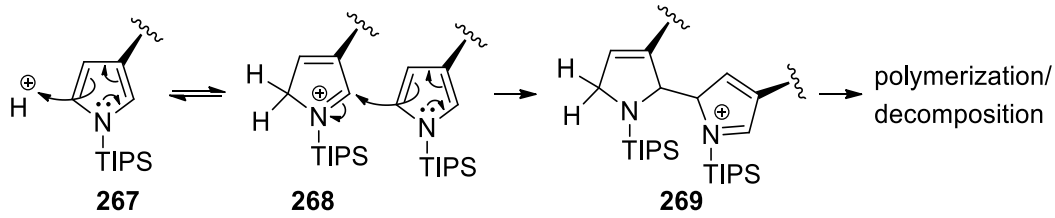


(2*R*,5*R*)-**266**
not isolated

Scheme 4.59

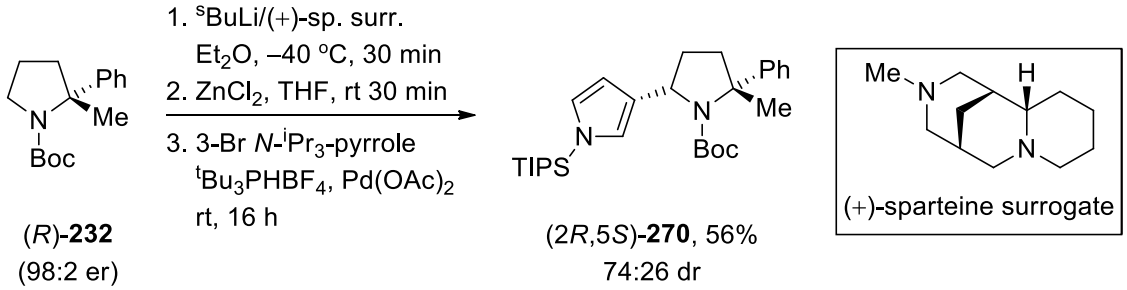
With (2*R*,5*R*)-**261**, addition of TFA caused instantaneous decomposition of the substrate. A mechanism which could explain the instability of this substrate in acid is shown in Scheme 4.60. Thus, the *N*-TIPS protected pyrrole **267** could be protonated to

give iminium ion **268**, which could be attacked by another pyrrole ring to form adduct **269**, which would react again to potentially give polypyrroles.



Scheme 4.60

To determine the diastereoselectivity of (2*R*,5*R*)-**261**, the opposite diastereoisomer was deliberately synthesised. Using (*R*)-**232** as substrate, the lithiation was performed at –40 °C for 30 minutes with *s*-BuLi and the mismatching chiral ligand, the (+)-sparteine surrogate. Transmetallation and Negishi coupling with *N*-tri-*i*-Pr-silyl 3-bromo-pyrrole afforded pyrrolidine (2*R*,5*S*)-**270** in 56% yield and 74:26 dr (Scheme 4.61).



Scheme 4.61

Comparing the ^{1}H NMR spectra of crude products obtained from the lithiation of (*R*)-**232** with (–)-sparteine and the (+)-sparteine surrogate, we were able to confidently determine the dr for both reactions. In the example with the mismatching ligand, a 74:26 dr was observed, a value which was slightly lower than the 81:19 dr obtained when the Negishi coupling was carried out with bromobenzene (see Scheme 4.56).

In summary, a range of tri-substituted *N*-Boc pyrrolidines has been successfully synthesised *via* lithiation-trapping of 2,2-di-substituted pyrrolidines. With the investigation of tri-substituted pyrrolidines it was shown that *in situ* ReactIR™ spectroscopy and VT ^{1}H NMR spectroscopy were extremely important for monitoring the rotamer interconversion process. Hence, the synthesis of tri-substituted pyrrolidines was accomplished in excellent yields (82-96% yield) with the lithiation at –40 °C using

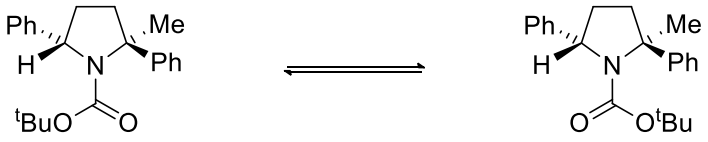
Me_2SO_4 as electrophile. Moreover, the application of the substrate-chiral ligand match/mismatch mechanism allowed the achievement of very high diastereoselectivities (>91:9 dr). Finally, the amazing >99:1 er of the major diastereoisomers was rationalised using the proposed chiral amplification mechanism.

4.4 Development of Methodology for the Synthesis of Tetra-Substituted Pyrrolidines

At this point of our synthetic route towards tetra-substituted *N*-Boc pyrrolidines, we were enthusiastic to be a single synthetic step away from our goal. From the lithiation-trapping of di-substituted and tri-substituted *N*-Boc pyrrolidines, we understood the importance of the rotamer interconversion and the configurational stability of the lithiated intermediate for achieving trapped products in high yields and ers. These parameters needed to be considered for the success of this final step.

4.4.1 Investigation of a Tri-Substituted Pyrrolidine by VT NMR Spectroscopy and *in situ* ReactIR™ Spectroscopy

Considering that tri-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253** exists as a mixture of rotamers (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b** (Scheme 4.62) (from ^{1}H NMR spectroscopy of the pure product), it was clear that we had to investigate in detail (2*S*,5*S*)-**253** in order to successfully perform the final benzylic lithiation.



(2*S*,5*S*)-**253a** (2*S*,5*S*)-**253b**

Scheme 4.62

Therefore, VT ^{1}H NMR spectroscopy studies of tri-substituted (2*S*,5*S*)-**253** were first undertaken to calculate the rate of interconversion of the *N*-Boc rotamers. Thus, (2*S*,5*S*)-**253** was dissolved in deuterated DMSO-d_6 and ^{1}H NMR spectra were recorded at different temperatures starting from 25 °C. Indeed, at 25 °C (298 K), the signals for the benzylic proton of (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b** were well separated, at δ_H 5.22 (dd, 0.5H) and δ_H 5.12 (dd, 0.5H), also showing a ~50:50 mixture of rotamers. The separation of those signals was ~49 Hz (Figure 4.7, a). As predicted, on increasing the temperature, the benzylic proton signals became broader and closer together, 65 °C and 72 °C (Figure 4.7, b and c), and then completely coalesced at 105 °C (e). Although the

^{1}H NMR spectrum at the exact coalescence temperature was not recorded, it was fair to assume that this temperature was between 72 °C and 75 °C.

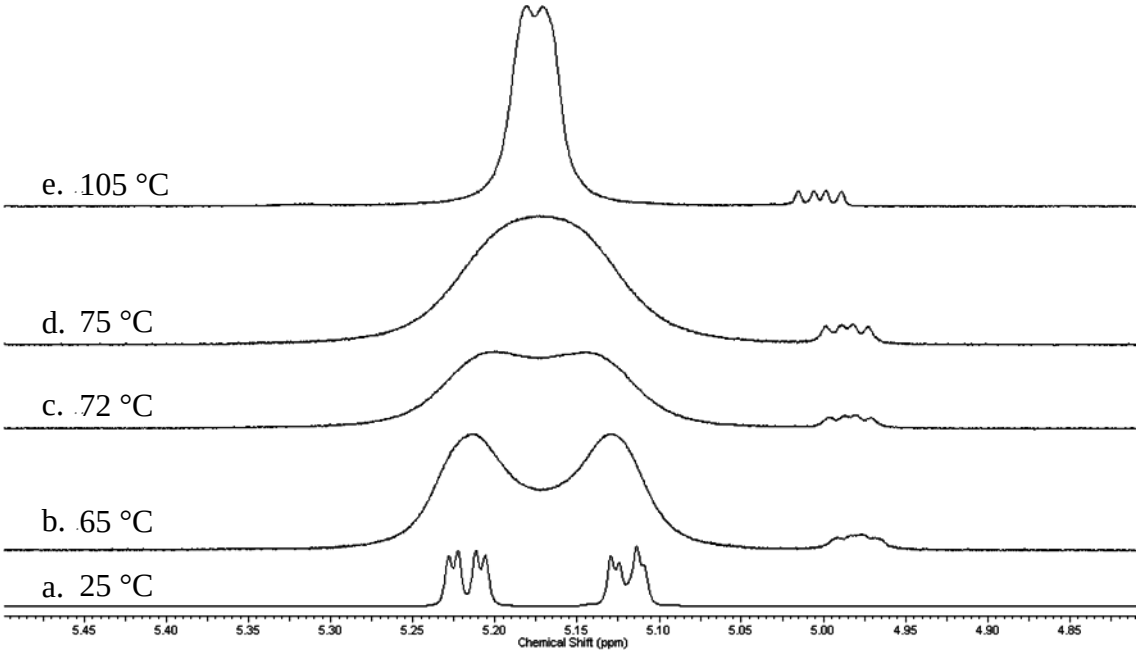
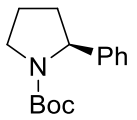


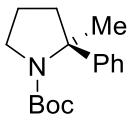
Figure 4.7: VT ^{1}H NMR spectra of (2*S*,5*S*)-**253** in DMSO-d_6.

Using a coalescence temperature of 74 °C (347 K), the free energy of activation ($\Delta G^{\ddagger}$) was calculated to be ~71.9 kJ mol^{-1}. Similar values for $\Delta G^{\ddagger}$ could be assumed at lower temperatures, if the change in entropy is assumed to be zero.[127] Hence, at –78 °C (195 K) a half-life for rotation of ~36 days was calculated, whereas at –30 °C (243 K) the $t_{1/2}$ was ~6.5 minutes.

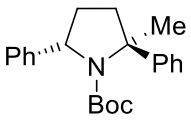
Figure 4.8 shows the half-life for rotation of the *N*-Boc rotamers of substrates (*S*)-**70**, (*S*)-**232** and (2*S*,5*S*)-**253**. These data show that upon increasing the steric hindrance around the Boc group, the $t_{1/2}$ at –78 °C progressively increases. As a result, higher temperatures are needed to allow *N*-Boc rotation to occur on a timescale that would be compatible with the lithiation methodology.



(*S*)-**70**
–78 ºC: $t_{1/2}$ ~10 h
–50 ºC: $t_{1/2}$ ~3.5 min



(*S*)-**232**
–78 ºC: $t_{1/2}$ >2 days
–40 ºC: $t_{1/2}$ ~3 min

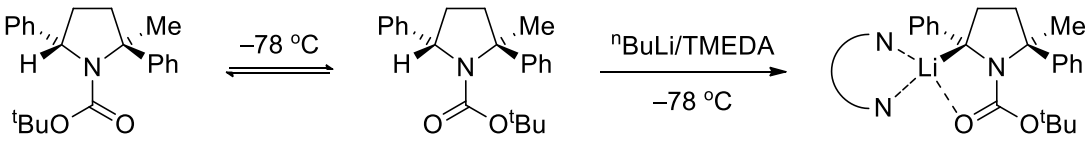


(2*S*,5*S*)-**253**
–78 ºC: $t_{1/2}$ ~36 days
–30 ºC: $t_{1/2}$ ~6.5 min

Figure 4.8

The VT ^{1}H NMR data showed that high temperatures should be used to achieve high yields from the lithiation-trapping of (2*S*,5*S*)-**253**. As was observed for other unsymmetrical substrates, the use of high temperatures should allow the unreactive rotamer (2*S*,5*S*)-**253a** to interconvert into the reactive rotamer (2*S*,5*S*)-**253b**. It could be predicted that for (2*S*,5*S*)-**253**, a 1 hour lithiation time at –30 °C should give >99% lithiation of the substrate.

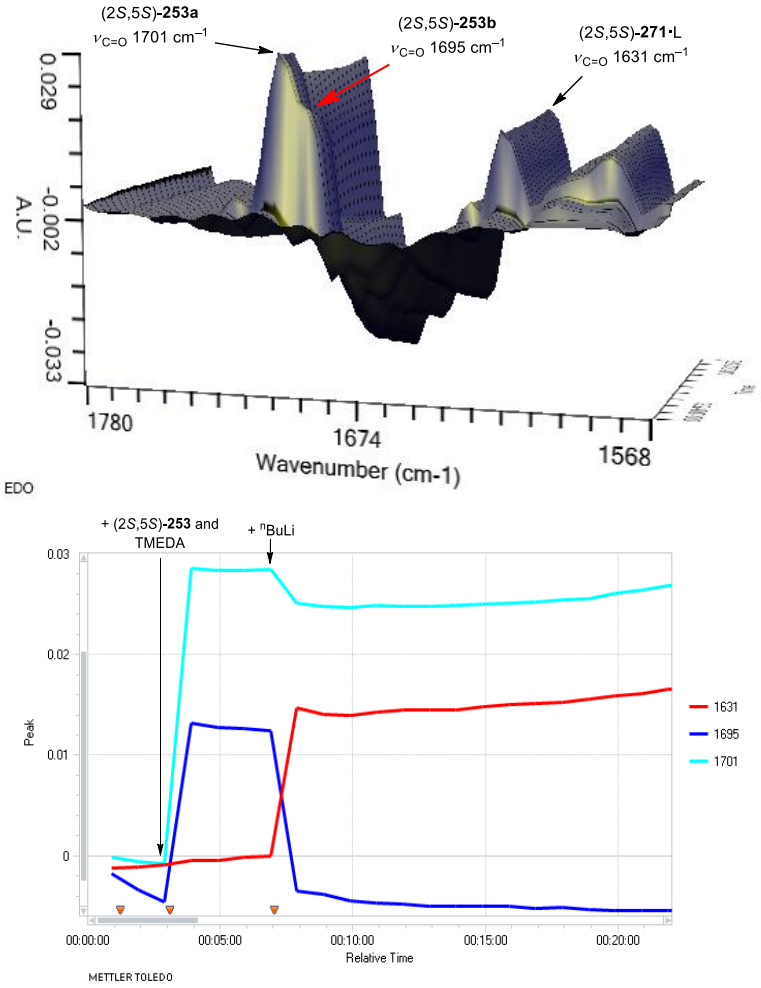
Next, lithiation of tri-substituted pyrrolidine (2*S*,5*S*)-**253** was examined using *in situ* ReactIR™ spectroscopy. First, (2*S*,5*S*)-**253** was treated at –78 °C with *n*-BuLi in the presence of TMEDA in Et_2O (Scheme 4.63). A major peak for the $\nu_{C=O}$ of *N*-Boc group of the substrate was observed at 1701 cm^{-1} with a shoulder at 1695 cm^{-1}. These were interpreted as being due to the two rotamers. Addition of *n*-BuLi caused fast disappearance of the 1695 cm^{-1} peak with formation of a new peak at 1631 cm^{-1} signal, corresponding to the $\nu_{C=O}$ of the lithiated intermediate (2*S*,5*S*)-**271**·L. These signals remained stable for the entire process. The peak at 1701 cm^{-1} was unaffected by the addition of *n*-BuLi and could thus be associated with the $\nu_{C=O}$ of the unreactive rotamer (2*S*,5*S*)-**253a**.



(2*S*,5*S*)-**253a**
$\nu_{C=O}$ 1701 cm^{-1}

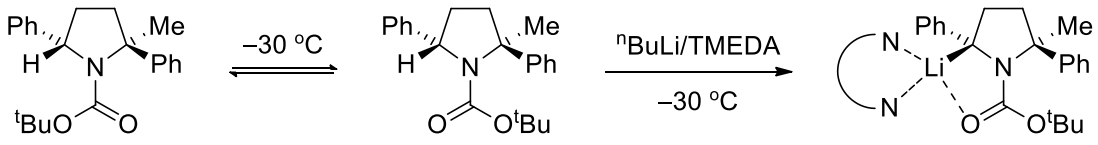
(2*S*,5*S*)-**253b**
$\nu_{C=O}$ 1695 cm^{-1}

(2*S*,5*S*)-**271**·L
$\nu_{C=O}$ 1631 cm^{-1}



Scheme 4.63

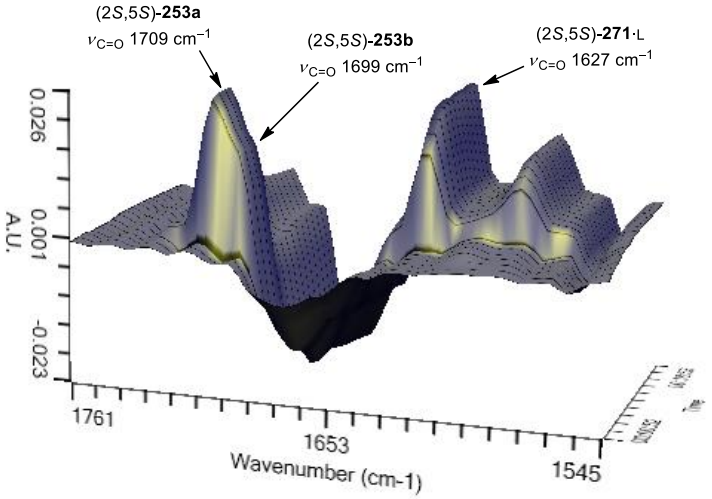
Then, the lithiation of (2*S*,5*S*)-**253** using *n*-BuLi/TMEDA in Et_2O was monitored at –30 °C, a temperature which should allow the rotamers to interconvert. Two different peaks for the $\nu_{C=O}$ of (2*S*,5*S*)-**253** were identified, at 1709 cm^{-1} and 1699 cm^{-1} (Scheme 4.64). When *n*-BuLi was added, a rapid (~1 minute) decrease of the 1699 cm^{-1} peak was observed. At the same time, the lithiated intermediate peak (1627 cm^{-1}) appeared and the intensity gradually increased during the whole period of observation. The 1709 cm^{-1} peak slowly decreased and this could be easily seen from the two-dimensional plot (b).



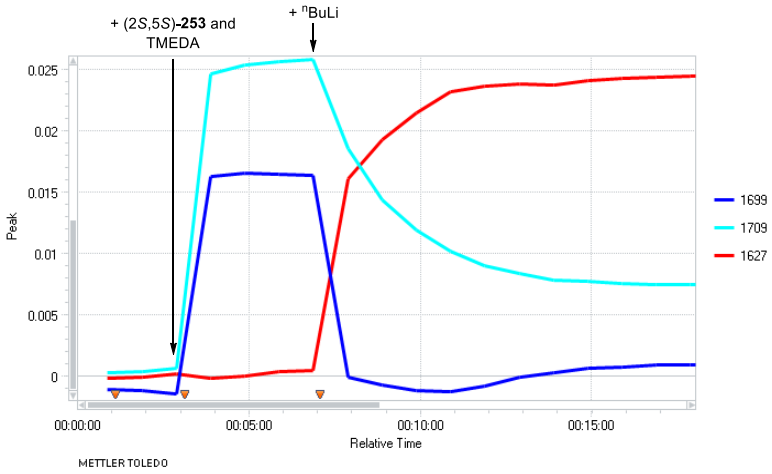
(2*S*,5*S*)-**253a**
$\nu_{C=O}$ 1709 cm^{-1}

(2*S*,5*S*)-**253b**
$\nu_{C=O}$ 1699 cm^{-1}

(2*S*,5*S*)-**271**·L
$\nu_{C=O}$ 1627 cm^{-1}



(a)



(b)

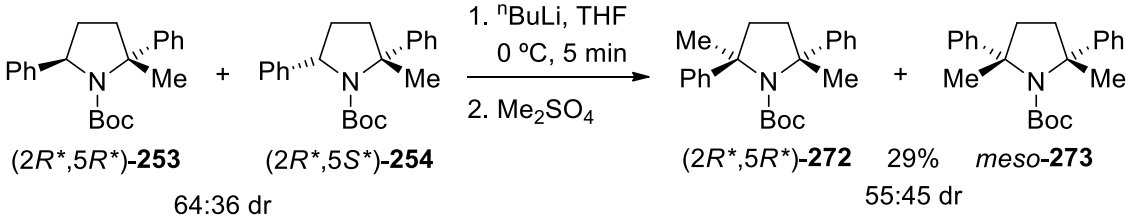
Scheme 4.64

From the data observed with the *in situ* ReactIR™ spectroscopy at –78 °C and –30 °C, it was possible to assign the 1709 cm^{-1} and 1699 cm^{-1} peaks to rotamers (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b** respectively. At –78 °C only rotamer (2*S*,5*S*)-**253b** reacted. The slow decrease of the 1709 cm^{-1} peak at –30 °C could be explained by the slow interconversion of rotamer (2*S*,5*S*)-**253a** into rotamer (2*S*,5*S*)-**253b**, which was then lithiated. These results were consistent with the rotamer interconversion half-life

calculated from the VT ^{1}H NMR spectroscopy studies. In addition, the almost instantaneous disappearance of the reactive rotamer (2*S*,5*S*)-**253b** peak (1695 cm^{-1} or 1699 cm^{-1}) showed that the lithiation of (2*S*,5*S*)-**253b** was extremely fast even at –78 °C. Finally, it was clear that a reaction temperature of –30 °C for at least 10 minutes was needed to achieve high yields with the lithiation-trapping of (2*S*,5*S*)-**253**.

4.4.2 Investigation of the Configurational Stability of Lithiated Tri-Substituted *N*-Boc Pyrrolidine 271: Synthesis of Tetra-Substituted Pyrrolidines

The requirement of high temperatures and long reaction times for the final benzylic lithiation reaction raised an important question about the configurational stability of the lithiated intermediate. This was explored in a series of experiments. To start with, lithiation of a 64:36 mixture of (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254** using *n*-BuLi in THF at 0 °C for 5 minutes and then trapping with Me_2SO_4 was carried out. This gave a 55:45 mixture (by ^{1}H NMR spectroscopy of the crude product) of (2*R**,5*R**)-**272** and *meso*-**273** in 29% yield (Scheme 4.65). The diastereoselectivity obtained from the reaction at 0 °C (55:45 dr) showed that at such a high temperature the configuration of the lithiated intermediate was not maintained, but a *trans* substitution to the phenyl group was favoured. In addition, the low yield obtained was possibly due to decomposition of the lithiated intermediate, as there was no starting material recovered after purification.



Scheme 4.65

Next, we explored the benzylic lithiation of (2*S*,5*S*)-**253** at –78 °C and –50 °C in order to study the configurational stability of the lithiated intermediate. This specific exploration was carried out using an 86:14 mixture of (2*S*,5*S*)-**253** and (2*R*,5*S*)-**254**. Our interest was to observe whether *n*-BuLi in THF with no ligand (*e.g.* TMEDA) could maintain the dr of the substrate. Hence, the mixture was lithiated with *n*-BuLi in THF and then trapped with Me_2SO_4 (Scheme 4.66 and Table 4.9). At –78 °C, lithiation for 1 hour followed by reaction with Me_2SO_4 gave a 78:22 mixture of (2*S*,5*S*)-**272** and *meso*-

273. The diastereoisomers were separated by flash chromatography to give (2*S*,5*S*)-**272** (35% yield) in 97:3 er (by CSP-HPLC) and an 8% yield of *meso*-**273** (Entry 1). When the reaction was carried out at –50 °C for 3 minutes, Me_2SO_4 trapping afforded a 70:30 mixture of (2*S*,5*S*)-**272** in 34% yield and 97:3 er and *meso*-**273** (10% yield) (Entry 2). Unreacted starting material was recovered in 56% yield from both of the reactions.

Scheme 4.66

Table 4.9: Exploration of the Benzylic Lithiation-Trapping of (2*S*,5*S*)-**253** and (2*R*,5*S*)-**254** at –78 °C and –50 °C

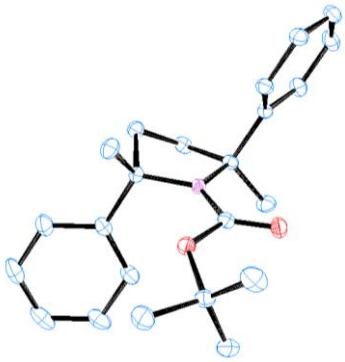
Entry	**Temp (°C)**	**Time (min)**	**Yield of (2*S*,5*S*)-272 (%)[a]**	**er[b]**	**Yield of *meso*-273 (%)[a]**	**(2*S*,5*S*)-272 : *meso*-273[c]**
1	–78	60	35	97:3	8	78:22
2	–50	3	34	97:3	10	70:30

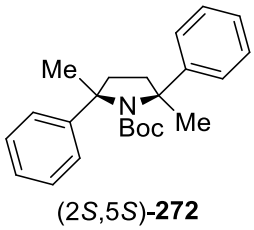
[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC. [c]ratio determined by ^{1}H NMR spectroscopy of the crude product.

The overall yield of ~45% for (2*S*,5*S*)-**272** and *meso*-**273** isolated in these reactions was not surprising, as the half-life for the rotamer interconversion was ~3 hours at –50 °C and >35 days at –78 °C. The high recovered yield for unreacted (2*S*,5*S*)-**253** and (2*S*,5*S*)-**254** (56% yield) proved the slow rate of rotamer interconversion and indicated that the lithiated intermediate was chemically stable under these conditions. The decrease of the 86:14 dr of the starting material to 78:22 dr (–78 °C) and to 70:30 dr (–50 °C) was significant. It clearly revealed that the lithiated intermediate was partially configurationally unstable even at –78 °C. Therefore, *n*-BuLi in THF was not suitable for good yields and high diastereoselectivities.

Since (2*S*,5*S*)-**272** was a solid and suitable crystals could be grown, X-ray crystallography was used to establish the relative stereochemistry of this tetra-

substituted pyrrolidine (Figure 4.9). The *trans* geometry of the phenyl groups showed that the benzylic lithiation process occurred predominantly with retention of configuration of the stereogenic centre.

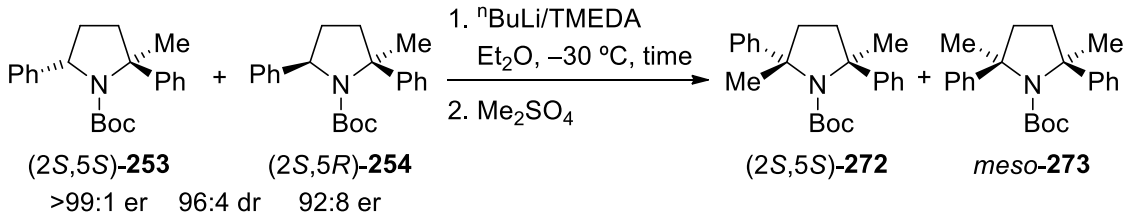




(2*S*,5*S*)-**272**

Figure 4.9

The VT ^{1}H NMR spectroscopy and *in situ* IR studies with (2*S*,5*S*)-**253** showed that at –30 °C the rotamers should interconvert and high yields could be expected. In addition, from the studies carried out with (*S*)-**70** (see Scheme 4.33 and Table 4.2), it was known that the use of *n*-BuLi in the presence of TMEDA increased the configurational stability of the lithiated intermediate. Thus, the benzylic lithiation of a 96:4 mixture of (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** was performed using *n*-BuLi and TMEDA in Et_2O at –30 °C, followed by trapping with Me_2SO_4 (Scheme 4.67, Table 4.10). A 30 minute lithiation gave a 91:9 mixture of (2*S*,5*S*)-**272** and *meso*-**273**, which after separation were isolated in 85% yield (99:1 er) and 2% yield respectively (Entry 1). In the 60 minute lithiation experiment, flash column chromatography of the crude mixture of (2*S*,5*S*)-**272** and *meso*-**273** (90:10 dr) afforded (2*S*,5*S*)-**272** in 87% yield (99:1 er) and *meso*-**273** in 3% yield (Entry 2).



Scheme 4.67

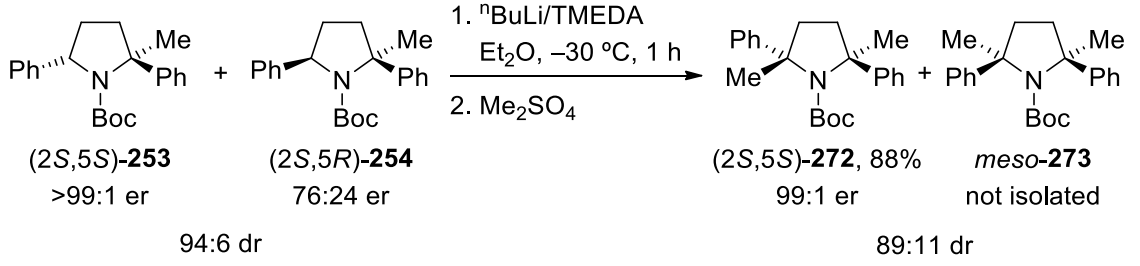
Table 4.10: Benzylic Lithiation-Trapping of (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** at –30 °C

Entry	**Time (min)**	**Yield of (2*S*,5*S*)-272 (%)[a]**	**er[b]**	**Yield of *meso*-273 (%)[a]**	**(2*S*,5*S*)-272 : *meso*-273[c]**
1	30	85	99:1	2	91:9
2	60	87	99:1	3	90:10

[a]Yield after purification by chromatography. [b]er determined by CSP-HPLC. [c]ratio determined by ^{1}H NMR spectroscopy of the crude product.

First, excellent isolated yields were achieved under both conditions (≥85%), proving that the rotamers were able to interconvert at –30 °C. Furthermore, the 91:9 dr showed a lower value of diastereoselectivity compared to the 96:4 dr of the starting material. The reduction of dr was probably due to a partial configurational instability of the lithiated intermediate. However, the similar dr observed in the 30 minute and 60 minute experiments suggested that there was no further loss of dr over 1 hour.

In order to complete the synthesis of a tetra-substituted pyrrolidine *via* four lithiation-trapping steps starting from *N*-Boc pyrrolidine **1**, the benzylic lithiation (*n*-BuLi, TMEDA, –30 °C in Et_2O for 1 hour) was performed using the 94:6 mixture of (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (see Scheme 4.54, Table 4.8, Entry 2). From this, an 89:11 mixture of (2*S*,5*S*)-**272** (88% yield and 99:1 er) and *meso*-**273** was obtained (Scheme 4.68).



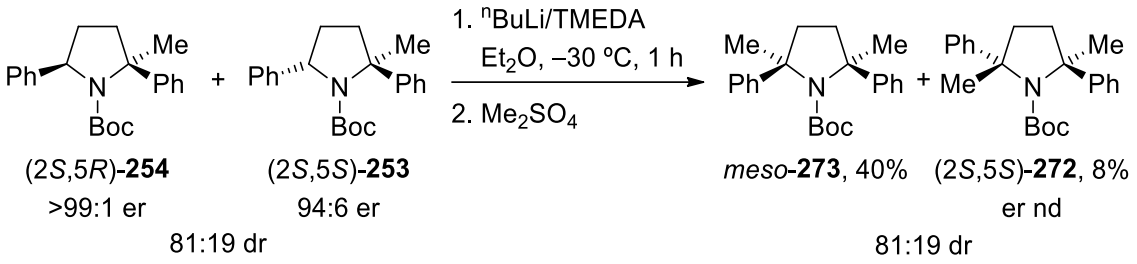
Scheme 4.68

The 88% yield of this reaction represented the highest yield achieved in the exploration of the benzylic lithiation-trapping of tri-substituted pyrrolidines. Moreover, the diastereoselectivity level (89:11 dr) was comparable with those observed in Scheme 4.67 and Table 4.10 (~90:10 dr).

At this point, we wanted to explore the configurational stability at even higher temperatures. For that reason, a 95:5 mixture of (2*R*,5*R*)-**253** and (2*R*,5*S*)-**254** was treated at 0 °C for 1 minute with *n*-BuLi and TMEDA in Et_2O. Subsequent trapping with Me_2SO_4 produced an 89:11 mixture of (2*R*,5*R*)-**272** and *meso*-**273**. After flash column chromatography, (2*R*,5*R*)-**272** was isolated in 85% yield and 99:1 er, while *meso*-**273** was not recovered (Scheme 4.69). Amazingly, a very high 89:11 dr was observed even at 0 °C with a 1 minute reaction. This value was of the same level with those achieved at −30 °C, showing a diastereoselectivity and configurational stability of the lithiated intermediate at such a high temperature for a lithiation reaction.

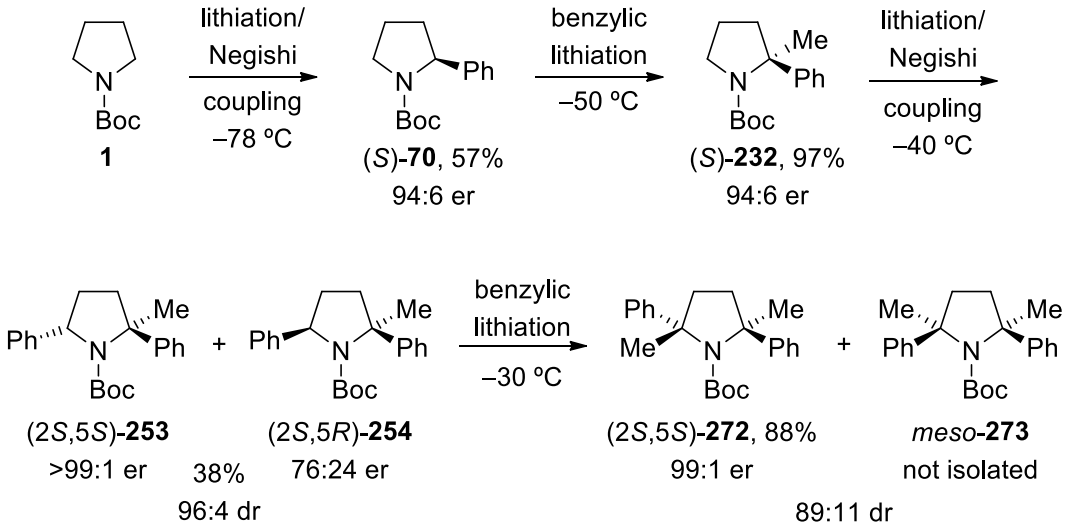
Scheme 4.69

Finally, the optimised protocol was applied to the 81:19 mixture of (2*S*,5*R*)-**254** and (2*S*,5*S*)-**253**. Lithiation with *n*-BuLi, TMEDA in Et_2O at −30 °C for 1 hour and Me_2SO_4 trapping gave an 81:19 mixture of *meso*-**273** and (2*S*,5*S*)-**272**, which were isolated in 40% yield and 8% yield respectively after flash column chromatography (Scheme 4.70). This result demonstrated that compounds with a *cis* relative stereochemistry between the aryl groups were attainable *via* this route. Interestingly, no reduction in dr was observed with this substrate, showing a high configurational stability of the lithiated intermediate.



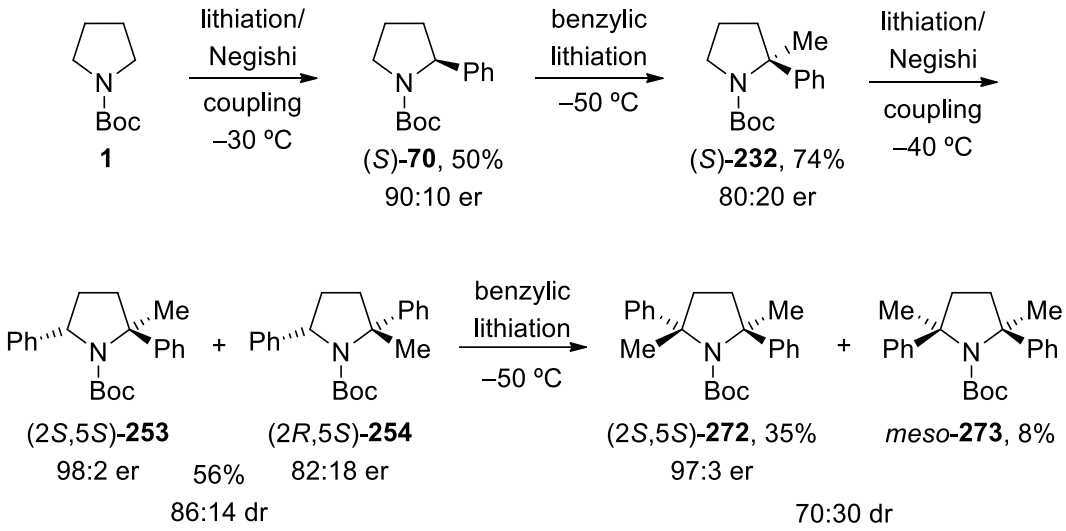
Scheme 4.70

In this last section, the accomplishment of our original aim for this project, the synthesis of tetra-substituted pyrrolidines *via* four sequential lithiation reactions starting from *N*-Boc pyrrolidine **1** has been realised. The synthetic pathway which led to the isolation of (2*S*,5*S*)-**272** in an excellent 99:1 er is shown in Scheme 4.71. It can be seen that reaction temperatures of –50 °C, –40 °C and –30 °C were needed in order to have high yields of the products. In fact, the appropriate temperature had to be selected to obtain high yields in each step.



Scheme 4.71

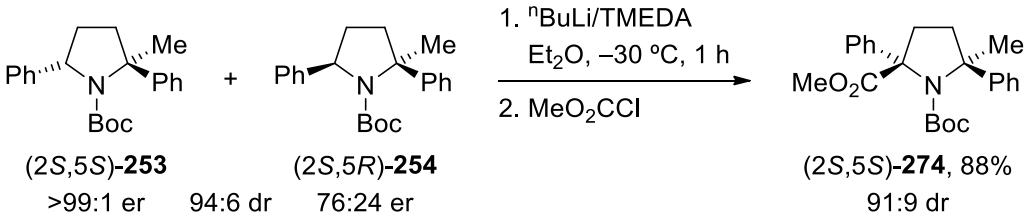
We have also developed a synthetic route which used reaction temperatures which were all above –50 °C. In this case, it was also possible to obtain tetra-substituted pyrrolidine (2*S*,5*S*)-**272**, but the yields and the stereoselectivities of each reaction were considerably lower (Scheme 4.72). In addition, the benzylic lithiations were performed without TMEDA as ligand, causing a larger reduction in dr in the second and in the last steps.



Scheme 4.72

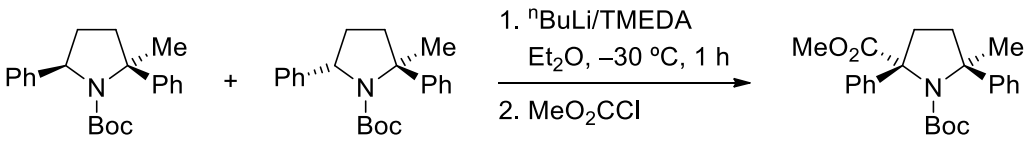
4.4.3 Synthesis of α,α'-Tetra-Substituted *N*-Boc Pyrrolidines

As a final demonstration of our methodology, we wanted to introduce a different electrophile in the final benzylic lithiation. Hence, the electrophilic trapping was performed with methyl chloroformate. Using the 94:6 mixture of (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** under the optimised benzylic lithiation conditions, ester (2*S*,5*S*)-**274** was obtained in a high 88% yield and 91:9 dr (Scheme 4.73). This result showed that a good yield could be obtained with methyl chloroformate as electrophile. The diastereoselectivity was comparable to those observed earlier.



Scheme 4.73

Similarly, an 81:19 mixture of (2*S*,5*R*)-**254** and (2*S*,5*S*)-**253** was treated with *n*-BuLi/TMEDA in Et_2O at –30 °C for 1 hour and then trapped with methyl chloroformate (Scheme 4.74). The product with the phenyl groups in a *cis* relative stereochemistry, (2*R*,5*S*)-**275**, was isolated in 57% yield and 86:14 dr. In this case, only moderate yields could be achieved and the diastereoselectivity observed (86:14 dr) was slightly higher than the starting material (81:19 dr).

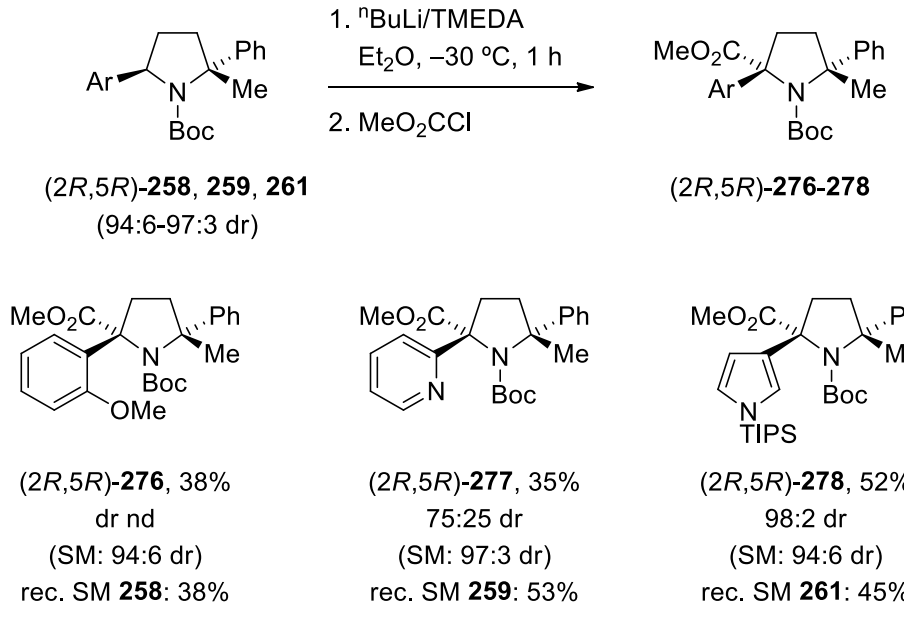


(2*S*,5*R*)-**254** (2*S*,5*S*)-**253** (2*R*,5*S*)-**275**, 57%

>99:1 er 81:19 dr 94:6 er 86:14 dr

Scheme 4.74

Next, the final benzylic lithiation was carried out on some of the tri-substituted pyrrolidines with a non-phenyl aromatic ring, the syntheses of which were described earlier (see Scheme 4.58). To increase the variation of the substituents α to the nitrogen and to prepare tetra-substituted pyrrolidines with four different substituents, methyl chloroformate was chosen as the electrophile. Pyrrolidines (2*R*,5*R*)-**258**, **259**, **261** were lithiated with *n*-BuLi and TMEDA in Et_2O at –30 °C for 1 hour and then trapped using methyl chloroformate (Scheme 4.75). (2*R*,5*R*)-**276**-**278** were obtained in 35-52% yield and 75:25-98:2 dr. Unreacted starting materials were also isolated after flash column chromatography in 45%, 53% and 38% yields respectively. The diastereoselectivities for (2*R*,5*R*)-**277** and (2*R*,5*R*)-**278** were measured using ^{1}H NMR spectroscopy of the crude products.



(2*R*,5*R*)-**258**, **259**, **261** (94:6-97:3 dr)

(2*R*,5*R*)-**276-278**

(2*R*,5*R*)-**276**, 38%
dr nd
(SM: 94:6 dr)
rec. SM **258**: 38%

(2*R*,5*R*)-**277**, 35%
75:25 dr
(SM: 97:3 dr)
rec. SM **259**: 53%

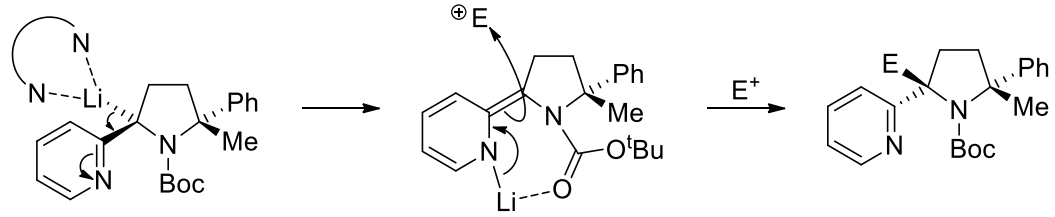
(2*R*,5*R*)-**278**, 52%
98:2 dr
(SM: 94:6 dr)
rec. SM **261**: 45%

Scheme 4.75

The yields obtained with these substrates (35-52%) were considerably lower than expected and could be due to a reduced rate of interconversion of the *N*-Boc rotamers.

This might be due to an increased steric hindrance of the aryl groups, which could interfere with the rotation of the Boc group. The recovery of unreacted starting materials could be evidence of the slow rotamer interconversion. Thus, to achieve high yields with these substrates, longer reaction times or higher temperatures might be needed. Unfortunately, we could not investigate this in detail as only small amounts of material were available.

Furthermore, the results showed that the dr of the products differed from the dr of the starting material. This was particularly evident with (2*R*,5*R*)-**277**, the 75:25 dr obtained represented a large reduction from the 97:3 dr of the starting material. This observation could be explained with the mechanism proposed in Scheme 4.76. In the lithiated intermediate (2*R*,5*R*)-**279**·L, the C-Li bond could be labile *via* delocalisation onto the nitrogen atom of the pyridine, forming azaenolate **280**. The negative charge on the nitrogen of azaenolate **280** could be stabilised by coordination to the lithium atom, which could coordinate with the carbonyl oxygen, increasing the stability of this intermediate.[128] The just-formed double bond represents loss of stereochemistry at that carbon. Next, it could be possible that azaenolate **280** would attack the electrophile from the least hindered face, which should be opposite to the phenyl substituent. This would explain the large drop in diastereomeric ratio observed in the benzylic lithiation-trapping of (2*R*,5*R*)-**259**.



(2*R*,5*R*)-**279**·L **280** (2*S*,5*R*)-**281**

Scheme 4.76

Importantly, these results showed that we accomplished the aim of this part of the project and a range of tetra-substituted *N*-Boc pyrrolidines could be achieved in good yields (57-88%) and high dr (75:25-98:2 dr) with the benzylic lithiation-trapping of tri-substituted pyrrolidines. These results would not have been possible without a preliminary investigation of the rotamer interconversion and lithiated intermediate configurational stability.

4.5 Conclusions and Future Work

The synthesis of tri- and tetra-substituted pyrrolidines, which were previously unknown in the literature, has been reported in this chapter. VT ^{1}H NMR spectroscopy allowed the calculation of the half-life for rotation of the *N*-Boc group of the di-substituted pyrrolidine **232** and tri-substituted pyrrolidine **253**. With **232** at −40 °C, $t_{1/2} \approx 3$ minutes and the lithiation-trapping gave high yields both in the racemic protocol (81-90% yields) and in the asymmetric procedure (82-96% yields). Furthermore, with this substrate an interesting match/mismatch mechanism was discovered to be at the basis of the high diastereoselectivities observed in the asymmetric protocol. In fact, di-substituted pyrrolidine (*R*)-**232** (98:2 er) and *s*-BuLi/(−)-sparteine at −78 °C gave a 98:2 dr when trapped with Me_2SO_4. Using (*S*)-**232** and the matching (+)-sparteine surrogate, the highest diastereoselectivity was 96:4 dr, in the opposite sense, when the reaction was performed at −40 °C.

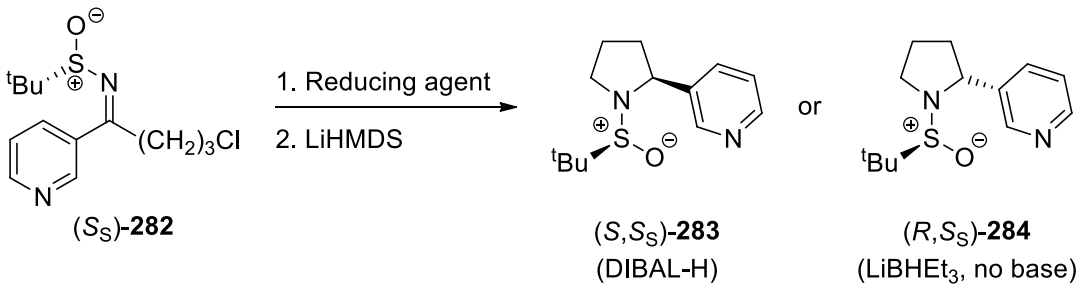
A lithiation-transmetallation-Negishi reaction protocol was also reported with **232** as substrate. Good dr and excellent ers of the major diastereoisomers (>98:2 er) were observed. This was explained using a chiral amplification mechanism. This effect meant that (2*S*,5*S*)-**253** was obtained in an excellent 98:2 er, starting from an 80:20 er of substrate (*S*)-**232**. The lithiation-Negishi protocol was then used with (*R*)-**232** to synthesise five different tri-substituted pyrrolidines in good yields (45-76% yield) and high drs (>94:6 dr).

Furthermore, the synthesis of α,α'-tetra-substituted pyrrolidines was reported. It was shown that the use of TMEDA as a ligand in the benzylic lithiation of **253** increased the configurational stability of the lithiated intermediate and tetra-substituted pyrrolidines were obtained in ~90:10 dr. Moreover, the first synthesis of (2*S*,5*S*)-**272** starting from *N*-Boc pyrrolidine **1** *via* four sequential lithiation-trapping steps was presented. When the lithiation-transmetallation-Negishi reaction of **1** was performed at −78 °C and TMEDA was used in the benzylic lithiation step, (2*S*,5*S*)-**272** was obtained in 99:1 er and 89:11 dr. In contrast, the use of high temperature (−30 °C) in the first lithiation reaction and no ligand in the benzylic step afforded (2*S*,5*S*)-**272** in 97:3 er and 70:30 dr. Finally, the first synthesis of tetra-substituted pyrrolidines with four different

substituents α to the nitrogen was reported. Products were obtained in moderate to good yields (35-88% yield).

Unfortunately, the introduction of aryl substituents other than a phenyl group into *N*-Boc pyrrolidine **1** was unsatisfactory with low yields and modest ers. This represented the major limitation of the developed protocol.

As future work, we identified that the installation of heterocycles α to the nitrogen in *N*-Boc pyrrolidine **1** should be the main aim for the subsequent development in the tetra-substituted pyrrolidines part of the project. This approach would lead to the synthesis of novel tri- and tetra-substituted pyrrolidines. We also propose the use of electrophiles other than Me_2SO_4 and methyl chloroformate, although compatibility with the lithiation conditions must be taken into account. One of our objectives remains the introduction of a pyridine ring as the first heterocycle and thus, new synthetic strategies aimed to solve this issue should be explored. We propose to start this exploration with the reductive cyclisation of *N*-sulfinyl ketimine (S_S)-**282** following Reddy's procedure.[109] With this synthetic pathway, both enantiomeric series of 2-pyridyl pyrrolidine would be accessed by selecting the appropriate reducing agent (Scheme 4.77).



Scheme 4.77

In addition, we propose to differentiate the aryl groups by using nitrogen heteroaromatic rings such as pyrroles, pyridines, pyrimidines and thiazoles. Examples of designed tetra-substituted pyrrolidines are shown in Figure 4.10.

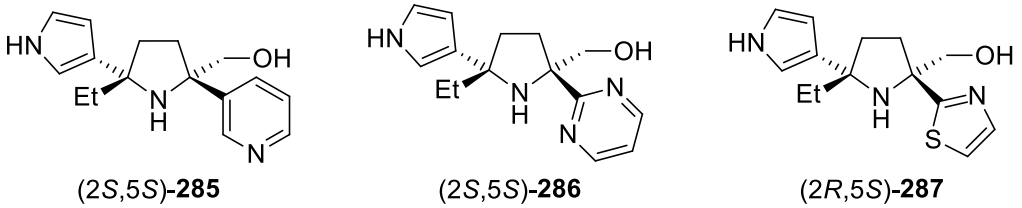
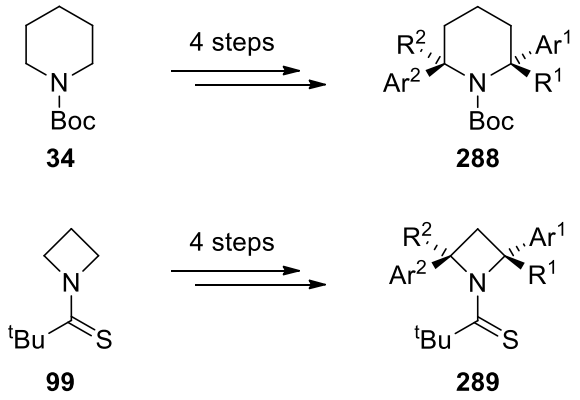


Figure 4.10

Moreover, the methodology for the synthesis of α,α'-tetra substituted *N*-Boc pyrrolidines could be extended to other heterocycles. Hence, we propose to apply the two sequential asymmetric lithiation-Negishi coupling reactions and benzylic lithiation steps to *N*-Boc piperidine **34** and *N*-thiopivaloyl azetidine **99**[78] (Scheme 4.78).



Scheme 4.78

Chapter Five: Experimental

5.1 General Methods

All-non aqueous reactions were carried out under oxygen free Ar using flame-dried glassware. Et_2O and THF were freshly distilled from sodium and benzophenone respectively. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[129] All diamines used in lithiations 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 $CHCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) 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 give 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. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. In situ ReactIR™ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR™ iC10 spectrometer equipped with a silicon-tipped (SiComp) probe.

5.2 General Procedures

General Procedure A: Asymmetric Lithiation-trapping of *N*-Boc Pyrrolidine 1 and *N*-Boc piperidine 34 using *s*-BuLi/Chiral Ligand at temperatures above −78 °C

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc heterocycles (*N*-Boc Pyrrolidine **1** or *N*-Boc piperidine **34**) (1.0 eq.) and diamine (1.3 eq.) in solvent (Et_2O, THF, TBME) (3.5-7 mL) at the specified temperature (−50 - 0 °C) under Ar. The resulting solution was stirred at the specified temperature for the specified time (1 s - 1 h). Then, the electrophile (PhCHO, Me_2SO_4, phenyl isocyanate, methyl chloroformate or benzophenone in Et_2O (1 mL)) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (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 (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure B: High Temperature Lithiation-trapping of *N*-Boc Imidazolidine 36

s-BuLi (1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (1.0 eq.) and (+)-sparteine surrogate (1.3 eq.) in solvent (Et_2O, THF) (3.5 - 7 mL) at −40 °C or −30 °C under Ar. The resulting solution was stirred at the specified temperature for the specified time (5 min - 1 h). Then, the electrophile (phenyl isocyanate, methyl iodide, or benzophenone in solvent (Et_2O, THF) (1 mL)) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and Et2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure C: Lithiation-trapping of 4-phenyl *N*-Boc piperidine 147

s-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (1.3 eq.) in Et_2O (3.8 mL) at −78 °C or −40 °C under Ar. The resulting solution

was stirred at the specified temperature for 1 h or 3 h. Then, electrophile (Me_2SO_4, Me_3SiCl, $PhMe_2SiCl$, phenyl isocyanate, $PhCONMe_2$ or benzophenone in Et_2O (1 mL)) (2.3 mmol, 2.0 eq.) was added. The resulting solution was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure D: Methylation of 2-phenyl *N*-Boc Pyrrolidine (*S*)-70

n-BuLi (1.1 eq.) was added dropwise to a stirred solution of phenyl pyrrolidine (*S*)-**70** (1.0 eq., 94:6 er) and TMEDA (1.1 eq.) in specified solvent (Et_2O, THF) at the specified temperature (–50, –30 °C) under Ar. The resulting solution was stirred at the specified temperature for the specified time (5 min - 1 h). Then, Me_2SO_4 (1.5 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 - 10 mL) and Et_2O (2 - 10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 - 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure E: Alkylation of α-methylbenzylamine 238

3-Chloro-1-propanol (2.3 g, 2.0 mL, 23.9 mmol, 1.0 eq.) was added dropwise to a stirred mixture of α-methylbenzylamine ((*R*)-**238** or (*S*)-**238**) (5.8 g, 6.1 mL, 47.9 mmol, 2.0 eq.) and water (0.7 mL) at rt. The resulting solution was stirred and heated at reflux for 16 h. After being allowed to cool to rt, 20% $NaOH_{(aq)}$ (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure F: Boc protection of Amino Alcohol 239

A solution of di-*tert*-butyl dicarbonate (1.0 eq.) in CH_2Cl_2 (11, 14 mL) was added dropwise to a stirred solution of amino alcohol ((*R*)-**239** or (*S*)-**239**) (1.0 eq.) in CH_2Cl_2 (45, 57 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, water (50 mL) was added and the two layers were separated. The aqueous layer was extracted

with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure G: Sulfonylation of *N*-Boc Amino Alcohol 240

2,4,6-Tri-*i*-propyl-benzenesulfonyl chloride (1.05 eq.) was added to a stirred solution of the *N*-Boc amino alcohol ((*R*)-**240** or (*S*)-**240**) (1.0 eq.), Et_3N (1.2 eq.) and DMAP (0.1 eq.) in CH_2Cl_2 (50 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Water (50 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 ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure H: Lithiation-Cyclisation of *N*-Boc Amino Sulfonate 241

s-BuLi (8.0 mL of a 1.3 M solution in hexanes, 10.4 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc amino sulfonate ((*R*)-**241** or (*S*)-**241**) (4.36 g, 8.0 mmol, 1.0 eq.) and TMEDA (1.2 g, 1.56 mL, 10.4 mmol, 1.3 eq.) in Et_2O (56 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, MeOH (1 mL) was added and the resulting solution was allowed to warm to rt over 1 h. Et_2O (30 mL) and 1 M $HCl_{(aq)}$ (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 ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure I: Synthesis of *N*-Boc Chloro-Propylamine 245 and 246

$NaBH(OAc)_3$ (5.9 g, 28 mmol, 1.4 eq.) was added to a stirred solution of 3-chloropropylamine hydrochloride (2.6 g, 20 mmol, 1.0 eq.) and aldehyde (2-pyridinecarboxaldehyde or 3-pyridinecarboxaldehyde) (2.14 g, 1.9 mL, 20 mmol, 1.eq.) in 1,2-dichloroethane (80 mL) at rt for 3 h. Saturated $NaHCO_{3(aq)}$ (50 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amine. The amine was dissolved in CH_2Cl_2 *(*10 mL) and added to a stirred solution of di-*tert*-butylcarbonate (4.36 g, 20 mmol, 1.0 eq.) in CH_2Cl_2 *(*30 mL) at 0 °C. The resulting mixture was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was 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 ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure J: Lithiation-cyclisation of *N*-Boc Chloro-Propylamine 245 and 246

s-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc chloro-propylamine (**245** or **246**) (57 mg, 0.2 mmol, 1.0 eq.) and diamine (1.3 eq.) in the specified solvent (toluene, Et_2O) (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, MeOH (1 mL) was added and the resulting solution was allowed to warm to rt over 1 h. Et_2O (5 mL) and saturated $NH_4Cl_{(aq)}$ (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 ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure K: Lithiation-Methylation of Di-substituted Pyrrolidine 232

s-BuLi (1.3 eq.) was added dropwise to a stirred solution of pyrrolidine ((*R*)-**232** of 98:2, (*S*)-**232** of 98:2 er or *rac*-**232**) (1.0 eq.) and diamine ((+)-sparteine surrogate, (–)-sparteine, TMEDA) (1.3 eq.) in the specified solvent (Et_2O, THF) (1.4, 2.6, 2.8, 3.5 mL) at the specified temperature (–78, –40 °C) under Ar. The resulting solution was stirred at the specified temperature for the specified time (30, 60 min). Then, Me_2SO_4 (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2, 4, 5 mL) and Et_2O (2, 4, 5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 2, 4, 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure L: TFA Deprotection

TFA (10.0 eq.) was added to a stirred solution of a mixture of pyrrolidines ((2*R*,5*R*) and (2*R*,5*S*) or (2*S*,5*R*) and (2*S*,5*S*)) (1.0 eq.) in CH_2Cl_2 (0.3 - 1 mL). The resulting mixture was stirred at rt for 1 h. Then, 1 M $NaOH_{(aq)}$ (1 mL) was added and the two layers were separated. The organic layer was washed with 1 M $NaOH_{(aq)}$ (2 × 1 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure M: Lithiation-Negishi Coupling of Di-substituted Pyrrolidine 232

s-BuLi (1.1, 1.2, 1.3 eq.) was added dropwise to a stirred solution of pyrrolidine ((*S*)-**232** or (*R*)-**232**) (1.0 eq.) and diamine ((+)-sparteine surrogate, (−)-sparteine) (1.1, 1.2, 1.3 eq.) in Et_2O (1 - 7 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, $ZnCl_2$ (0.6 eq.) was added and the resulting mixture was stirred at −40 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, aryl-bromide (bromobenzene, 3-bromo-2-fluoro-5-methylpyridine, 3-bromo-*N*-triisopropylsilyl-pyrrole, 2-bromo-anisole, 2-bromo-pyridine, 2-bromo-thiophene) (0.83, 1.2, 1.3 eq.) and a mixture of *t*-Bu_3PHBF_4 (0.05 eq.) and $Pd(OAc)_2$ (0.04 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.1 mL) and Et_2O (5 mL) were added and mixture stirred for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (5 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (5 mL) and water (2 × 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure N: Benzylic Lithiation-Methylation of Tri-substituted Pyrrolidines in THF without TMEDA

n-BuLi (1.3 eq.) was added dropwise to a stirred solution of a known mixture phenyl pyrrolidines ((2*S*,5*S*)-**253** (98:2 er) and (2*S*,5*R*)-**254** (82:18 er) or (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254**) (1.0 eq.) in THF (3, 4, 4.5 mL) at the specified temperature (−78, −50, 0 °C) under Ar. The resulting solution was stirred at the specified temperature for the specified time (3, 5, 60 min). Then, Me_2SO_4 (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure O: Benzylic Lithiation-Trapping of Tri-substituted Pyrrolidines in Et_2O with TMEDA

n-BuLi (1.1 eq.) was added dropwise to a stirred solution of a known mixture of phenyl pyrrolidines ((2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*R*)-**254** (92:8 er) or (2*S*,5*S*)-**253** (>99:1 er)

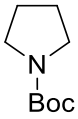
and (2*S*,5*R*)-**254** (76:24 er) or (2*R*,5*R*)-**253** (>99:1 er) and (2*R*,5*S*)-**254** (99:1 er) or (2*S*,5*R*)-**254** (>99:1 er) and (2*S*,5*S*)-**253** (94:6 er)) (1.0 eq.) and TMEDA (1.1 eq.) in Et_2O (1, 1.6, 2 mL) at the specified temperature (0, –30 °C under Ar. The resulting solution was stirred at the specified temperature for the specified time (1, 30, 60 min). Then, electrophile (Me_2SO_4, methyl chloroformate) (1.5 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (2 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 2 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure P: Benzylic Lithiation-Trapping of Tri-substituted Heteroaryl Pyrrolidines

n-BuLi (1.1 eq.) was added dropwise to a stirred solution of a known mixture of heteroaryl pyrrolidines (2*R*,5*R*)-**258** and (2*R*,5*S*)-**296** or (2*R*,5*R*)-**259** and (2*R*,5*S*)-**297** or (2*R*,5*R*)-**261** and (2*R*,5*S*)-**270** (1.0 eq.) and TMEDA (1.1 eq.) in Et_2O (1, 1.5 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 1 h. Then, methyl chloroformate (1.5 eq.) was added. The resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (2 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 2 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

5.3 Experimental for Chapter Two

Pyrrolidine-1-carboxylic acid *tert*-butyl ester 1

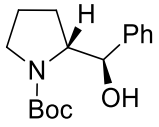


1

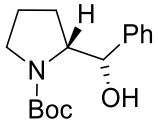
A solution of di-*tert*-butyl dicarbonate (27.5 g, 125.8 mmol, 1.05 eq.) in CH_2Cl_2 (77 mL) was added dropwise to a solution of pyrrolidine (8.5 g, 119.8 mmol, 1.0 eq.) in CH_2Cl_2 (130 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for 3 h. Then, 10% $NaHCO_{3(aq)}$ (120 mL) and CH_2Cl_2 (200 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc pyrrolidine **1** (20 g, 98%) as a colourless oil, bp 86-92 °C/2.0 mmHg (lit.,[130] 70-75 °C/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42-3.19 (m, 4H, NCH_2), 1.89-1.76 (m, 4H, NCH_2CH_2), 1.45 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[130]

Lab Book Reference: GG2/39/1

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-29 and (1*S*,2*R*)-30



(1*R*,2*R*)-**29**



(1*S*,2*R*)-**30**

(Table 2.1, Entry 1)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar for 1 sec. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (18 mg, 6%, 92:8 er by CSP-HPLC) as a colourless oil, R_F (98:2

CH_2Cl_2-acetone) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H, Ph), 5.87 (br s, 1H, OH), 4.52 (br d, J = 8.0 Hz, 1H, CHO), 4.09 (td, J = 8.0, 3.5 Hz, 1H, NCH), 3.51-3.42 (m, 1H, NCH), 3.41-3.31 (m, 1H, NCH), 1.85-1.65 (m, 2H, 2 × CH), 1.64-1.40 (m, 2H, 2 × CH), 1.52 (s, 9H, CMe_3); CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.2 min, (1*S*,2*S*)-**29** 28.5 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (10 mg, 4%, 91:9 er by CSP-HPLC) as an off-white solid, R_F (98:2 CH_2Cl_2-acetone) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.41-7.21 (m, 5H, Ph), 5.48 (br s, 0.65H, OH), 5.17 (br s, 0.35H, OH), 4.87 (br s, 0.65H, CHO), 4.32 (br s, 0.65H, NCH), 4.01 (br s, 0.35H, CHO), 3.57 (br s, 0.35H, NCH), 3.29 (br s, 1H, NCH), 2.82 (br s, 0.65H, NCH), 2.30 (br s, 0.35H, NCH), 2.02-1.85 (m, 1H, CH), 1.84-1.70 (m, 1H, CH), 1.57 (s, 3.15H, CMe_3), 1.55-1.41 (m, 1H, CH), 1.52 (s, 5.85H, CMe_3), 1.23-1.07 (m, 1H, CH); CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.5 min, (1*R*,2*S*)-**30** 18.0 min. Spectroscopic data consistent with those reported in the literature.[28]

Lab Book Reference: GG2/29

(Table 2.1, Entry 2)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (160 mg, 58%, 93:7 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.5 min, (1*S*,2*S*)-**29** 28.5 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (72 mg, 26%, 91:9 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.6 min, (1*R*,2*S*)-**30** 17.9 min.

Lab Book Reference: GG2/44

(Table 2.1, Entry 3)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar for 20 min. Then,

PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (160 mg, 58%, 92:8 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.5 min, (1*S*,2*S*)-**29** 28.8 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (80 mg, 29%, 92:8 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.9 min, (1*R*,2*S*)-**30** 18.0 min.
Lab Book Reference: GG2/51

(Table 2.1, Entry 4)
Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine (152 mg, 150 μL, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at −40 °C under Ar for 1 h. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (72 mg, 52%, 92:8 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.5 min, (1*S*,2*S*)-**29** 28.8 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (38 mg, 27%, 90:10 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 15.5 min, (1*R*,2*S*)-**30** 19.6 min.
Lab Book Reference: GG5/21

(Table 2.2, Entry 1)
Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (−)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −30 °C under Ar for 1 sec. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (34 mg, 12%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.0 min, (1*S*,2*S*)-**29** 28.5 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (20 mg, 7%, 89:11 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.4 min, (1*R*,2*S*)-**30** 17.9 min.

Lab Book Reference: GG2/30

(Table 2.2, Entry 2)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (161 mg, 58%, 90:10 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 25.7 min, (1*S*,2*S*)-**29** 29.9 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (94 mg, 34%, 89:11 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.7 min, (1*R*,2*S*)-**30** 18.2 min.

Lab Book Reference: GG2/4

(Table 2.2, Entry 3)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar for 20 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (135 mg, 49%, 88:12 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.4 min, (1*S*,2*S*)-**29** 28.5 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (77 mg, 28%, 87:13 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.7 min, (1*R*,2*S*)-**30** 18.0 min.

Lab Book Reference: GG2/50

(Table 2.2, Entry 4)

Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (–)-sparteine (152 mg, 150 μL, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –30 °C under Ar for 1 h. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy

pyrrolidine (1*R*,2*R*)-**29** (59 mg, 42%, 87:13 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.7 min, (1*S*,2*S*)-**29** 29.1 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (42 mg, 30%, 84:16 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 14.7 min, (1*R*,2*S*)-**30** 18.9 min.
Lab Book Reference: GG5/22

(Table 2.3, Entry 1)
Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –20 °C under Ar for 1 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (147 mg, 53%, 86:14 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.8 min, (1*S*,2*S*)-**29** 29.1 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (91 mg, 33%, 85:15 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.5 min, (1*R*,2*S*)-**30** 17.9 min.
Lab Book Reference: GG2/7

(Table 2.3, Entry 2)
Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –20 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (141 mg, 51%, 87:13 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 25.5 min, (1*S*,2*S*)-**29** 29.7 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (86 mg, 31%, 85:15 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.8 min, (1*R*,2*S*)-**30** 18.2 min.
Lab Book Reference: GG2/5

(Table 2.3, Entry 3)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −10 °C under Ar for 30 sec. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (120 mg, 43%, 80:20 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.6 min, (1*S*,2*S*)-**29** 29.1 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (80 mg, 29%, 80:20 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.9 min, (1*R*,2*S*)-**30** 18.4 min.

Lab Book Reference: GG2/13

(Table 2.3, Entry 4)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at 0 °C under Ar for 10 sec. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*R*,2*R*)-**29** (110 mg, 40%, 75:25 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.4 min, (1*S*,2*S*)-**29** 29.0 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (75 mg, 27%, 75:25 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.5 min, (1*R*,2*S*)-**30** 17.8 min.

Lab Book Reference: GG2/8

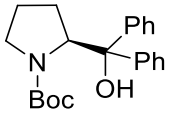
(Table 2.3, Entry 5)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (–)-sparteine (304 mg, 299 μL, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at 0 °C under Ar for 1 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy

pyrrolidine (1*R*,2*R*)-**29** (97 mg, 35%, 65:35 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.8 min, (1*S*,2*S*)-**29** 28.6 min and hydroxy pyrrolidine (1*S*,2*R*)-**30** (69 mg, 25%, 62:38 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.8 min, (1*R*,2*S*)-**30** 18.2 min.

Lab Book Reference: GG2/6

2-(Hydroxydiphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-62



(*S*)-**62**

(Table 2.4, Entry 1)

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 pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (403 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (290 mg, 82%, 95:5 er by CSP-HPLC) as a white solid, mp 146-148 °C (lit.,[11] 147-149 °C); $[\alpha]_D$ −127.4 (*c* 1.0 in $CHCl_3$) (lit.,[11] $[\alpha]_D$ +132.1 (*c* 1.97 in $CHCl_3$) for (*R*)-**3** of 90:10 er); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.36 (m, 4H, Ph), 7.35-7.24 (m, 6H, Ph), 6.48 (br s, 1H, OH), 4.90 (dd, *J* = 9.0, 4.0 Hz, 1H, NCH), 3.35 (br m, 1H, NCH), 2.86 (br s, 1H, NCH), 2.09 (dddd, *J* = 13.0, 9.0, 9.0, 9.0 Hz, 1H, CH), 1.96-1.87 (m, 1H, CH), 1.53-1.35 (m, 1H, CH), 1.43 (s, 9H, CMe_3), 0.76 (br s, 1H, CH); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 13.3 min, (*S*)-**62** 15.2 min. Spectroscopic data consistent with those reported in the literature.[11]

Lab Book Reference: GG2/19/1

(Table 2.4, Entry 2)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (403 mg, 1.3 mmol, 1.3 eq.) at −40 °C for 1 sec. Then, benzophenone (364 mg, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (53 mg, 15%, 86:14 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 13.1 min, (*S*)-**62** 15.2 min and starting material **1** (87 mg, 50%).
Lab Book Reference: GG2/22/1

(Table 2.4, Entry 3)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (403 mg, 1.3 mmol, 1.3 eq.) at −40 °C for 2 min. Then, benzophenone (364 mg, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (173 mg, 49%, 86:14 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 13.2 min, (*S*)-**62** 15.5 min.
Lab Book Reference: GG2/20/1

(Table 2.4, Entry 4)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (403 mg, 1.3 mmol, 1.3 eq.) at −30 °C for 1 sec. Then, benzophenone (364 mg, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (50 mg, 14%, 80:20 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 12.8 min, (*S*)-**62** 14.6 min and starting material **1** (94 mg, 55%).
Lab Book Reference: GG2/23/1

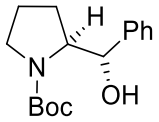
(Table 2.4, Entry 5)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (403 mg,

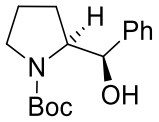
1.3 mmol, 1.3 eq.) at −30 °C for 2 min. Then, benzophenone (364 mg, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (159 mg, 45%, 81:19 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 12.9 min, (*S*)-**62** 14.7 min and starting material **1** (26 mg, 15%).

Lab Book Reference: GG2/21/1

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*S*)-29 and (1*R*,2*S*)-30



(1*S*,2*S*)-**29**



(1*R*,2*S*)-**30**

(Table 2.5, Entry 1)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*S*,2*S*)-**29** (181 mg, 65%, 90:10 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.4 min, (1*S*,2*S*)-**29** 28.5 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (83 mg, 30%, 92:8 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.8 min, (1*R*,2*S*)-**30** 17.7 min.

Lab Book Reference: GG2/40

(Table 2.5, Entry 2)

Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O at –40 °C under Ar for 1 h. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave and hydroxy

pyrrolidine (1*S*,2*S*)-**29** (63 mg, 46%, 90:10 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.0 min, (1*S*,2*S*)-**29** 29.0 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (27 mg, 20%, 91:9 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 14.8 min, (1*R*,2*S*)-**30** 18.5 min.
Lab Book Reference: GG3/37

(Table 2.6, Entry 1)
Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −30 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*S*,2*S*)-**29** (187 mg, 67%, 90:10 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.0 min, (1*S*,2*S*)-**29** 28.6 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (75 mg, 27%, 90:10 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.8 min, (1*R*,2*S*)-**30** 17.7 min.
Lab Book Reference: GG2/41

(Table 2.6, Entry 2)
Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O at −30 °C under Ar for 1 h. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave and hydroxy pyrrolidine (1*S*,2*S*)-**29** (56 mg, 41%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.7 min, (1*S*,2*S*)-**29** 28.7 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (31 mg, 23%, 90:10 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 14.9 min, (1*R*,2*S*)-**30** 18.6 min.
Lab Book Reference: GG3/38

(Table 2.6, Entry 3)

Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O at −20 °C under Ar for 2 min. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave and hydroxy pyrrolidine (1*S*,2*S*)-**29** (69 mg, 50%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.6 min, (1*S*,2*S*)-**29** 28.9 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (32 mg, 23%, 91:9 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 15.3 min, (1*R*,2*S*)-**30** 19.6 min.

Lab Book Reference: GG5/26

(Table 2.6, Entry 4)

Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O at −20 °C under Ar for 1 h. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave and hydroxy pyrrolidine (1*S*,2*S*)-**29** (55 mg, 40%, 83:17 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.6 min, (1*S*,2*S*)-**29** 28.6 min and hydroxy pyrrolidine (1*R*,2*S*)-**30** (28 mg, 20%, 85:15 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**x30** 15.2 min, (1*R*,2*S*)-**30** 19.4 min.

Lab Book Reference: GG5/27

(Table 2.7, Entry 2)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in THF (7 mL) at −30 °C under Ar for 2 min. Then, PhCHO (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave starting material **1** (34 mg, 38%) and hydroxy pyrrolidine (1*S*,2*S*)-**29** (105 mg, 38%,

86:14 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 23.8 min, (1*S*,2*S*)-**29** 28.4 and hydroxy pyrrolidine (1*R*,2*S*)-**30** (58 mg, 21%, 86:14 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 13.8 min, (1*R*,2*S*)-**30** 17.0 min.
Lab Book Reference: GG2/80

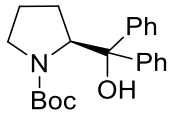
(Table 2.7, Entry 3)
Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in TBME (3.5 mL) at −30 °C under Ar for 2 min. Then, PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (1*S*,2*S*)-**29** (43 mg, 31%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.0 min, (1*S*,2*S*)-**29** 29.0 and hydroxy pyrrolidine (1*R*,2*S*)-**30** (16 mg, 12%, 89:11 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 14.6 min, (1*R*,2*S*)-**30** 18.6 min.
Lab Book Reference: GG3/39

(Scheme 2.30)
n-BuLi (0.26 mL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at −30 °C under Ar. The resulting solution was stirred at −30 °C for 1 h. Then, a solution of PhCHO (106 mg, 100 μL, 1.0 mmol, 1.0 eq.) was added. The resulting solution was stirred at −30 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) 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 recovered starting material **1** (30 mg, 35%) and hydroxy pyrrolidine (1*S*,2*S*)-**29** (18 mg, 13%, 86:14 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (98:2

hexane-*i*-PrOH, 0.5 mL min^{-1}) (1*R*,2*R*)-**29** 24.0 min, (1*S*,2*S*)-**29** 29.0 and hydroxy pyrrolidine (1*R*,2*S*)-**30** (10 mg, 7%, 88:12 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel AD-H (98:2 hexane-*i*-PrOH, 1.0 mL min^{-1}) (1*S*,2*R*)-**30** 14.6 min, (1*R*,2*S*)-**30** 18.6 min.

Lab Book Reference: GG6/87

2-(Hydroxydiphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-62



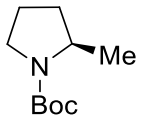
(S)-**62**

(Scheme 2.32)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (256 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar for 2 min. Then, a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 99.5:0.5 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine (*S*)-**62** (198 mg, 56%, 86:14 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –114.7 (*c* 1.0 in $CHCl_3$) (lit.,[11] $[\alpha]_D$ +132.1 (*c* 1.97 in $CHCl_3$) for (*R*)-**62** of 90:10 er); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**62** 12.2 min, (*S*)-**62** 13.7 min.

Lab Book Reference: GG2/67/1

2-Methylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-68



(R)-**68**

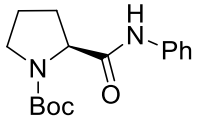
(Scheme 2.32)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar for 2 min. Then, Me_2SO_4 (252 mg, 190 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave methyl

pyrrolidine (*R*)-**68** (102 mg, 55%, 92:8 er by CSP-GC) as a colourless oil, $[\alpha]_D$ −22.6 (*c* 1.0 in $CHCl_3$) (lit.,[11] $[\alpha]_D$ +31.2 (*c* 2.76 in $CHCl_3$) for (*S*)-**68** of 97.5:2.5 er); R_F (96:4 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (br s, 1H, NCH), 3.35 (br s, 2H, 2 × CH), 2.05-1.91 (m, 1H, CH), 1.91-1.82 (m, 1H, CH), 1.91-1.71 (m, 1H, CH), 1.58-1.49 (m, 1H, CH), 1.46 (s, 9H, CMe_3), 1.15 (br d, *J* = 6.0 Hz, 3H, Me); CSP-GC: (*S*)-**68** 4.2 min, (*R*)-**68** 4.7 min. Spectroscopic data consistent with those reported in the literature.[11]

Lab Book Reference: GG2/45/1

2-(Phenylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-69



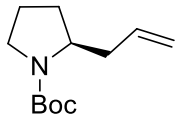
(*S*)-**69**

(Scheme 2.32)

Using general procedure A: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-Boc pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −30 °C under Ar for 2 min. Then, phenyl isocyanate (238 mg, 220 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 80:20 petrol- EtOAc as eluent gave pyrrolidine (*S*)-**69** (168 mg, 58%, 89:11 er by CSP-HPLC) as a white solid, mp 160-162 °C (lit.,[131] 185-188 °C); $[\alpha]_D$ −106.1 (*c* 1.0 in $CHCl_3$) (lit.,[131] $[\alpha]_D$ −138.3 (*c* 0.24 in $CHCl_3$) for (*S*)-**69** of 90:10 er); R_F (80:20 petrol-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H, NH), 7.52 (dd, *J* = 8.5, 1.0 Hz, 2H, Ph), 7.38-7.23 (m, 2H, Ph), 7.07 (br s, 1H, Ph), 4.60-4.20 (m, 1H, NCH), 3.70-3.21 (m, 2H, NCH), 2.62-1.75 (m, 4H, CH), 1.49 (s, 9H, CMe_3); CSP-HPLC: Chiralcel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**69** 5.8 min, (*S*)-**69** 6.7 min. Spectroscopic data consistent with those reported in the literature.[131]

Lab Book Reference: GG2/68/1

2-Allylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-23



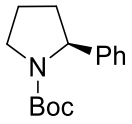
(S)-**23**

(Scheme 2.33)

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 pyrrolidine **1** (85 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at −30 °C under Ar. The resulting solution was stirred at −30 °C for 2 min. Then, CuCN·2LiCl (420 μL of a 0.6 M solution in THF, 0.25 mmol, 0.5 eq. of CuCN) was added dropwise. The resulting solution was allowed to warm to 0 °C over 15 min and then re-cooled to −30 °C. Then, allyl bromide (121 mg, 86 μL, 1.0 mmol, 2.0 eq.) was added and the reaction mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (10 mL) and Et_2O (5 mL) were added and mixture was stirred for 20 min. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (5 mL). The two layers of the filtrate were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) 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 allyl pyrrolidine (*S*)-**23** (77 mg, 73%, 86:14 er by CSP-GC) as a colourless oil, $[\alpha]_D$ −31.4 (*c* 1.0 in $CHCl_3$) (lit.,[132] $[\alpha]_D$ −45.4 (*c* 1.26 in $CHCl_3$) for (*S*)-**23** of 96:4 er); R_F (9:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dddd, J = 17.5, 10.0, 7.0, 7.0 Hz, 1H, =CH), 5.09-5.04 (m, 1H, =CH_AH$_B$), 5.03-5.01 (m, 1H, =CH$_A$$H_B$), 3.93-3.69 (br m, 1H, NCH), 3.42-3.23 (br m, 2H, 2 × NCH), 2.64-2.32 (br m, 1H, CH_AH$_B$CH=CH$_2$), 2.17-2.06 (m, 1H, CH$_A$$H_B$CH=CH$_2$), 1.95-1.65 (m, 4H, 2 × CH$_2$), 1.47 (s, 9H, CMe$_3$); CSP-GC: (*R*)-**23** 8.7 min, (*S*)-**23** 9.0 min. Spectroscopic data consistent with those reported in the literature.[13]

Lab Book Reference: GG5/23/1

2-Phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-70



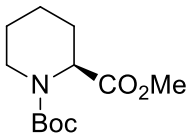
(S)-**70**

(Scheme 2.34)

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 pyrrolidine **1** (171 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 2 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 eq.) was added and the resulting mixture was stirred at –30 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, bromobenzene (204 mg, 140 μL, 1.3 mmol, 1.3 eq.) and a mixture of $^tBu_3PHBF_4$ (11 mg, 0.0625 mmol, 0.0625 eq.) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.3 mL) and Et_2O (5 mL) were added and mixture stirred for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (5 mL). The organic layer was extracted with 1 M $HCl_{(aq)}$ (5 mL) and water (2 × 5 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-Et_2O as eluent gave phenyl pyrrolidine (*S*)-**70** (142 mg, 58%, 92:8 er by CSP-HPLC) as a white solid, mp 57-58 °C (lit.,[56] 61.9-62.7 °C); $[\alpha]_D$ –81.5 (*c* 1.0 in acetone) (lit.,[13] $[\alpha]_D$ +83.2 (*c* 0.7 in acetone) for (*R*)-**70** of 95:5 er); R_F (99:1 CH_2Cl_2-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (67:33 mixture of rotamers) δ 7.33-7.26 (m, 2H, Ph), 7.25-7.13 (m, 3H, Ph), 4.96 (br s, 0.33H, NCH), 4.77 (br s, 0.67H, NCH), 3.74-3.41 (m, 2H, 2 × NCH), 2.40-2.19 (br m, 1H, CH), 1.98-1.75 (m, 3H, 3 × CH), 1.46 (s, 3H, CMe_3), 1.18 (s, 6H, CMe_3); CSP-HPLC: Chiralcel AD-H (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**70** 11.5 min, (*S*)-**70** 12.5 min. Spectroscopic data consistent with those reported in the literature.[56]

Lab Book Reference: GG2/47/1

1-*tert*-Butyl 2-methyl piperidine-1,2-dicarboxylate (*S*)-71



(*S*)-**71**

(Table 2.9, Entry 1)

Using general procedure A: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperidine **34** (93 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –50 °C under Ar for 30 min. Then, methyl chloroformate (94 mg, 77 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave starting material **34** (19 mg, 21%) as a colourless oil and ester (*S*)-**71** (56 mg, 46%, 80:20 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –26.0 (*c* 1.5 in $CHCl_3$) (lit.,[61] $[\alpha]_D$ –31.7 (*c* 1.0 in $CHCl_3$) for (*S*)-**71** of 88:12 er); R_F (95:5 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.90 (br s, 0.5H, NCH), 4.73 (br s, 0.5H, NCH), 4.09-3.86 (br m, 1H, NCH), 3.73 (s, 3H, OMe), 3.05-2.76 (br m, 1H, NCH), 2.27-2.13 (br m, 1H, CH), 1.71-1.33 (m, 5H, CH), 1.49-1.40 (br m, 9H, CMe_3); CSP-HPLC: Chiralcel OD (99.7:0.3 hexane-*i*-PrOH, 0.4 mL min^{-1}) (*R*)-**71** 34.5 min, (*S*)-**71** 40.1 min. Spectroscopic data consistent with those reported in the literature.[61]

Lab Book Reference: GG4/22/1

(Table 2.9, Entry 2)

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 piperidine **34** (185 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar for 20 min. Then, methyl chloroformate (189 mg, 150 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave starting material **34** (28 mg, 15%) as a colourless oil and ester (*S*)-**71** (155 mg, 64%, 79:21 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –30.4 (*c* 1.0 in $CHCl_3$) (lit.,[61] $[\alpha]_D$ –31.7 (*c* 1.0 in $CHCl_3$) for (*S*)-**71** of 88:12 er); CSP-HPLC: Chiralcel OD (99.7:0.3 hexane-*i*-PrOH, 0.4 mL min^{-1}) (*R*)-**71** 33.2 min, (*S*)-**71** 38.4 min.

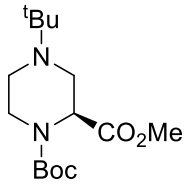
Lab Book Reference: GG2/55/1

(Table 2.9, Entry 3)

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 piperidine **34** (185 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at −30 °C under Ar for 5 min. Then, methyl chloroformate (189 mg, 150 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave starting material **34** (48 mg, 26%) as a colourless oil and ester (*S*)-**71** (115 mg, 47%, 77:23 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (99.7:0.3 hexane-*i*-PrOH, 0.4 mL min^{-1}) (*R*)-**71** 33.6 min, (*S*)-**71** 38.5 min.

Lab Book Reference: GG2/54/1

1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate (*S*)-72



(*S*)-**72**

(Table 2.10, Entry 1)

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'-tert*-butyl piperazine **35** (121 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –50 °C under Ar. The resulting solution was stirred at –50 °C for 3 min. Then, methyl chloroformate (94 mg, 76 μL, 1.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –50 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (1 mL) and $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**72** (106 mg, 71%, 82:18 er by CSP-HPLC) as a colourless oil, R_F (80:20 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.71 (br s, 0.5H, NCH), 4.54 (br s, 0.5H, NCH), 3.84 (br d, J = 12.5 Hz, 0.5H, NCH), 3.79-3.70 (m, 3.5H, NCH + OMe), 3.49 (br dd, J = 14.0, 14.0 Hz, 1H, NCH), 3.14 (br dd, J = 12.5, 12.5 Hz, 0.5H, NCH), 3.04 (br dd, J = 12.5, 12.5 Hz, 0.5H, NCH), 2.92 (br d, J = 11.0 Hz, 0.5H, NCH), 2.85 (br d, J = 11.0 Hz, 0.5H, NCH),

2.32-2.21 (m, 1H, NCH), 2.11 (ddd, *J* = 11.0, 11.0, 3.5 Hz, 1H, NCH), 1.47 (s, 4.5H, $OCMe_3$), 1.42 (s, 4.5H, $OCMe_3$), 1.00 (s, 9H, $NCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.5 (CO_2Me), 171.2 (CO_2Me), 155.8 (NC=O), 155.4 (NC=O), 80.1 (CMe_3), 56.2 (NCH), 55.0 (NCH), 53.6 ($NCMe_3$), 52.0 (OMe), 47.5 (NCH_2), 45.2 (NCH_2), 42.8 (NCH_2), 41.9 (NCH_2), 28.3 (Me_3), 25.8 (Me_3); MS (ESI) *m/z* 301 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}N_2O_4$ $(M + H)^+$ 301.2122, found 301.2111 (+3.4 ppm error); CSP-HPLC: Chiralcel AD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**72** 12.1 min, (*S*)-**72** 25.6 min.

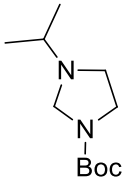
Lab Book Reference: GG3/64/1

(Table 2.10, Entry 2)

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'*-*tert*-butyl piperazine **35** (242 mg, 1.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 2 min. Then, methyl chloroformate (189 mg, 150 μL, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (1 mL) and $NaHCO_{3(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**72** (265 mg, 88%, 78:22 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**72** 14.7 min, (*S*)-**72** 18.1 min.

Lab Book Reference: GG2/81/1

3-Isopropylimidazolidine-1-carboxylic acid *tert*-butyl ester 36



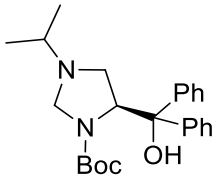
36

N-*i*-Pr-ethylene diamine (4.1 g, 40.1 mmol, 1.0 eq.) was added dropwise to a stirred solution of paraformaldehyde (1.2 g, 40.1 mmol, 1.0 eq.), K_2CO_3 (18.7 g, 135.2 mmol,

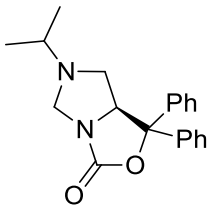
3.9 eq.) and $MgSO_4$ (18.65 g, 155.0 mmol, 3.9 eq.) in $CHCl_3$ (135 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, di-*tert*-butyl dicarbonate (8.8 g, 40.1 mmol, 1.0 eq.) was added and the resulting solution was stirred at rt for 24 h. The solids were removed by filtration through Celite® and washed with $CHCl_3$ (150 mL). The filtrate was evaporated under reduced pressure and the residue was partitioned between saturated brine (50 mL) and CH_2Cl_2 (50 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (8.2 g, 95%) as a colourless oil, bp 97-102 °C/3.0 mmHg (lit.,[5] 165-167 °C/12.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.04 (s, 1H, NCH_2N), 3.96 (s, 1H, NCH_2N), 3.48 (t, J = 6.5 Hz, 1H, $BocNCH_2$), 3.43 (t, J = 6.5 Hz, 1H, $BocNCH_2$), 2.83 (t, J = 6.5 Hz, 1H, NCH_2), 2.82 (t, J = 6.5 Hz, 1H, NCH_2), 2.44 (septet, J = 6.5 Hz, 0.5 H, NCH), 2.43 (septet, J = 6.5 Hz, 0.5 H, NCH), 1.46 (s, 9H, CMe_3), 1.12 (br d, J = 6.5 Hz, 6H, $NCHMe_2$). Spectroscopic data consistent with those reported in the literature.[5]

Lab Book Reference: GG2/16/1

3-*i*-Propyl-5-hydroxydiphenylmethylimidazolidine-1-carboxylic acid *tert*-butyl ester (*S*)-74 and 6-*i*-propyl-1,1-diphenyltetrahydroimidazo[1,5-c]oxazol-3-one (*S*)-76



(*S*)-**74**



(*S*)-**76**

(Table 2.11, Entry 2)

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*′-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 30 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in THF (1 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 55:23:22 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (103 mg, 52%, 90:10 er

by CSP-HPLC) as a yellow solid, $[\alpha]_D$ +103.0 (*c* 1.5 in $CHCl_3$) (lit.,[44] $[\alpha]_D$ −129.7 (*c* 4.58 in $CHCl_3$) for (*R*)-**74** of 92:8 er); R_F (85:15 petrol-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 7.49-7.12 (m, 8H, Ph), 5.02-4.69 (br m, 1H, NCH), 4.65-4.24 (br m, 1H, NCHN), 3.99-3.62 (br m, 1H, NCHN), 3.11 (d, *J* = 8.5 Hz, 1H, NCH), 2.67 (dd, *J* = 8.5, 6.0 Hz, 1H, NCH), 2.56 (br s, 1H, NC*H*Me), 1.38-0.96 (br m, 9H, CMe_3), 1.11 (d, *J* = 6.5 Hz, 3H, NCH*Me*), 1.03 (d, *J* = 6.5 Hz, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.2 (C=O), 146.3 (*ipso*-Ph), 145.4 (*ipso*-Ph), 129.3 (Ph), 127.7 (Ph), 127.2 (Ph), 127.1 (Ph), 126.7 (Ph), 80.6 (CMe_3), 80.1 (Ph_2CO), 67.0 (NCH_2N), 62.8 (NCH), 53.2 (NCH_2), 52.2 (NCH), 27.5 (CMe_3), 20.8 (Me), 20.6 (Me); CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**74** 6.7 min, (*S*)-**74** 16.7 min, cyclic carbamate (*S*)-**76** (39 mg, 24%, 70:30 er by CSP-HPLC) as a white solid, mp 119-121 °C (lit.,[44] 117-120 °C); R_F (80:20 petrol-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 2H, Ph), 7.41-7.26 (m, 8H, Ph), 4.81 (dd, *J* = 9.0, 6.0 Hz, 1H, NCH), 4.29 (d, *J* = 7.0 Hz, 1H, NCHN), 4.09 (d, *J* = 7.0 Hz, 1H, NCHN), 2.79 (dd, *J* = 9.0, 6.0 Hz, 1H, NCH), 2.59 (septet, *J* = 6.5 Hz, 1H, NC*H*Me), 2.06 (dd, *J* = 9.0, 9.0 Hz, NCH), 1.01 (d, *J* = 6.5 Hz, 3H, NCH*Me*), 1.00 (d, *J* = 6.5 Hz, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.8 (C=O), 142.6 (*ipso*-Ph), 139.6 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 125.8 (Ph), 125.1 (Ph), 86.0 (Ph_2CO), 67.6 (NCH_2N), 67.3 (NCH), 52.8 (NCH), 51.9 (NCH_2), 21.5 (Me), 21.1 (Me); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**76** 12.3 min, (*R*)-**76** 18.0 min, and recovered *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (22 mg, 20%). Spectroscopic data consistent with those reported in the literature.[44]

Lab Book Reference: GG5/4

(Table 2.11, Entry 1)

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*′-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at −40 °C under Ar for 1 h. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 56:18:26 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (81 mg, 40%, 93:7 er by CSP-HPLC) as a yellow solid, CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL

min^{-1}) (*R*)-**74** 6.6 min, (*S*)-**74** 15.3 min and recovered *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (18 mg, 17%).
Lab Book Reference: GG3/45/1

(Table 2.11, Entry 3)
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*′-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 30 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 56:17:27 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (72 mg, 36%, 92:8 er by CSP-HPLC) as a yellow solid, CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**74** 6.7 min, (*S*)-**74** 16.7 min, cyclic carbamate (*S*)-**76** (16 mg, 10%, 77:23 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**76** 12.2 min, (*R*)-**76** 17.9 min, and recovered *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (28 mg, 26%).
Lab Book Reference: GG5/11

(Table 2.11, Entry 4)
Using general procedure X B: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 20 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in THF (1 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 45:24:31 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (98 mg, 50%, 93:7 er by CSP-HPLC) as a yellow solid, CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**74** 6.7 min, (*S*)-**74** 16.7 min, cyclic carbamate (*S*)-**76** (33 mg, 20%, 71:29 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**76** 12.1 min, (*R*)-**76** 17.7 min, and recovered *N*-Boc-*N*′-*i*-Pr imidazolidine **36** (28 mg, 26%).
Lab Book Reference: GG5/8

(Table 2.11, Entry 5)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) in Et_2O (1 mL) at –40 °C under Ar for 20 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 54:10:36 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (86 mg, 43%, 91:9 er by CSP-HPLC) as a yellow solid, CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**74** 6.6 min, (*S*)-**74** 16.4 min, cyclic carbamate (*S*)-**76** (10 mg, 6%, 75:25 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**76** 12.2 min, (*R*)-**76** 17.9 min, and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (36 mg, 34%).

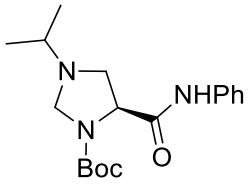
Lab Book Reference: GG5/17

(Table 2.11, Entry 6)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 10. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in THF (1 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) a 48:26:26 mixture of (*S*)-**74**, (*S*)-**76** and **36**. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave substituted imidazolidine (*S*)-**74** (90 mg, 45%, 91:9 er by CSP-HPLC) as a yellow solid, CSP-HPLC: Chiralcel AD (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**74** 6.8 min, (*S*)-**74** 16.5 min, and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (23 mg, 21%).

Lab Book Reference: GG3/70/1

3-Isopropyl-5-phenylcarbamoylimidazolidine-1-carboxylic acid *tert*-butyl ester (*S*)-75



(*S*)-**75**

(Table 2.12, Entry 1)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 30 min. Then, phenyl isocyanate (119 mg, 110 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (19 mg, 18%) and substituted imidazolidine (*S*)-**75** (97 mg, 58%, 85:15 er by CSP-HPLC) as a colourless oil, R_F (80:20 petrol-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 9.27 (br s, 0.5H, NH), 8.29 (br s, 0.5H, NH), 7.57-7.49 (m, 2H, Ph), 7.38-7.29 (m, 2H, Ph), 7.17-7.05 (m, 1H, Ph), 4.65-4.47 (m, 0.5H, NCH), 4.47-4.26 (m, 1H, NCH_2N), 4.25-3.93 (m, 1.5H, NCH + NCH_2N), 3.64-3.43 (m, 0.5H, NCH), 3.34-3.16 (m, 0.5H, NCH), 3.15-2.88 (m, 1H, NCH), 2.70-2.47 (m, 1H, NC*H*Me), 1.62-1.38 (m, 9H, CMe_3), 1.25-1.06 (m, 6H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 169.6 (C=O), 168.7 (C=O), 155.1 (C=O), 153.4 (C=O), 137.8 (*ipso*-Ph), 137.5 (*ipso*-Ph), 128.8 (Ph), 124.0 (Ph), 119.6 (Ph), 81.4 (*C*Me_3), 67.3 (NCH_2N), 66.9 (NCH_2N), 61.1 (NCH), 59.7 (NCH), 55.0 (NCH_2), 52.5 (NCH), 28.2 (C*Me*$_3$), 21.3 (Me); CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**75** 11.3 min, (*S*)-**75** 17.5 min. Spectroscopic data consistent with those reported in the literature.[44]

Lab Book Reference: GG5/10

(Table 2.12, Entry 2)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 30 min. Then, phenyl isocyanate (119 mg, 110 μL, 1.0 mmol, 2.0 eq.) gave the crude product.

Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (28 mg, 26%) and substituted imidazolidine (*S*)-**75** (81 mg, 48%, 88:12 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**75** 11.0 min, (*S*)-**75** 17.1 min.

Lab Book Reference: GG5/13

(Table 2.12, Entry 3)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 20 min. Then, phenyl isocyanate (119 mg, 110 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (27 mg, 25%) and substituted imidazolidine (*S*)-**75** (118 mg, 71%, 85:15 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**75** 10.9 min, (*S*)-**75** 17.0 min.

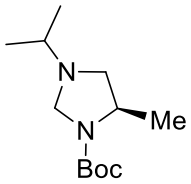
Lab Book Reference: GG5/16

(Table 2.12, Entry 4)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 20 min. Then, phenyl isocyanate (119 mg, 110 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (12 mg, 11%) and substituted imidazolidine (*S*)-**75** (51 mg, 30%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**75** 10.9 min, (*S*)-**75** 16.9 min.

Lab Book Reference: GG5/19

3-Isopropyl-5-methylimidazolidine-1-carboxylic acid *tert*-butyl ester (*R*)-80



(*R*)-**80**

(Table 2.13, Entry 1)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 30 min. Then, methyl iodide (142 mg, 60 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc as eluent gave substituted imidazolidine (*R*)-**80** (64 mg, 56%) as a colourless oil, R_F (70:30 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.37-4.26 (m, 0.6H, NCH_2N), 4.18-4.08 (m, 0.4H, NCH_2N), 4.02-3.88 (m, 2H, NCH + NCH_2N), 3.19-3.02 (m, 1H, NCH), 2.47-2.34 (m, 2H, NCH + NC*H*Me), 1.46 (s, 9H, CMe_3), 1.14-1.09 (m, 6H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 153.9 (C=O), 79.7 (*C*Me_3), 67.0 (NCH_2N), 59.5 (NCH_2) 58.6 (NCH_2), 53.6 (NCH), 52.3 (NCH), 28.3 (C*Me*$_3$), 21.1 (Me), 19.4 (Me), 18.7 (Me) and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (20 mg, 19%). Spectroscopic data consistent with those reported in the literature.[44]

Lab Book Reference: GG5/9

(Table 2.13, Entry 2)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 30 min. Then, methyl iodide (142 mg, 60 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc as eluent gave substituted imidazolidine (*R*)-**80** (44 mg, 39%) as a colourless oil and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (24 mg, 22%).

Lab Book Reference: GG5/12

(Table 2.13, Entry 3)

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′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at –40 °C under Ar for 20 min. Then, methyl iodide (142 mg, 60 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc as eluent gave substituted imidazolidine (*R*)-**80** (60 mg, 52%) as a colourless oil and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (41 mg, 38%).

Lab Book Reference: GG5/15

(Table 2.13, Entry 4)

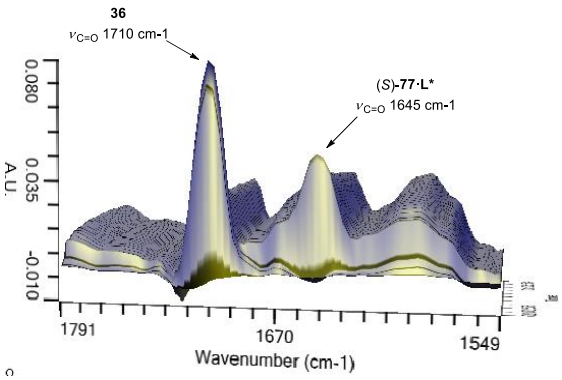
Using general procedure B: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (107 mg, 0.5 mmol, 1.0 eq.) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 20 min. Then, methyl iodide (142 mg, 60 μL, 1.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc as eluent gave substituted imidazolidine (*R*)-**80** (42 mg, 37%) as a colourless oil and recovered *N*-Boc-*N′*-*i*-Pr imidazolidine **36** (34 mg, 32%).

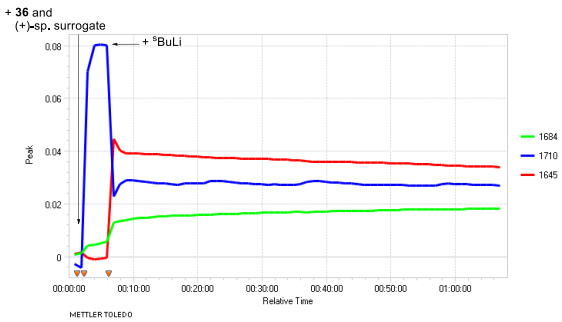
Lab Book Reference: GG5/18

ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-*i*-Pr imidazolidine 36 in Et_2O

Et_2O (10 mL) was added to a flask equipped with a stirred bar and ReactIR™ probe at rt under Ar. After cooling to –40 °C, a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc imidazolidine **36** (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 the 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 –40 °C for 64 min. For *N*-Boc imidazolidine **36**, a peak at 1710 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1684 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 1 min, approximately half of *N*-Boc imidazolidine **36** had been lithiated to give the lithiated intermediate.

Lab Book Reference: JDF6_559

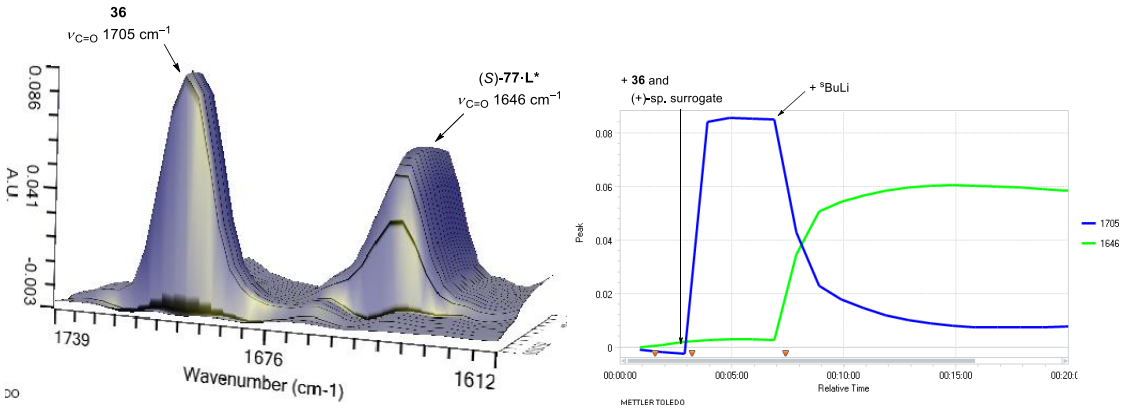




ReactIR™ monitoring of the lithiation of *N*-Boc-*N′*-*i*-Pr imidazolidine 36 in THF

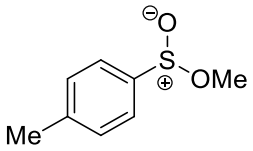
THF (10 mL) was added to a flask equipped with a stirred bar and ReactIR™ probe at rt under Ar. After cooling to –40 °C, a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in THF (2 mL) was added followed by a solution of *N*-Boc imidazolidine **36** (214 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL). The solution was stirred for 5 min (to verify the stability of the 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 –40 °C for 13 min. For *N*-Boc imidazolidine **36**, a peak at 1705 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, 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 9 min, complete lithiation of *N*-Boc imidazolidine **36** to give the lithiated intermediate was observed.

Lab Book Reference: PJR 6/448



5.4 Experimental for Chapter Three

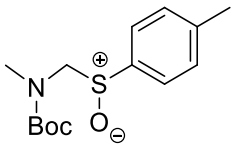
Methyl *p*-toluenesulfinate 92



92

Bromine (4.86 g, 1.56 mL, 30.4 mmol, 3.0 eq.) was added to stirred suspension of Na_2CO_3 (5.37 g, 50.7 mmol, 5.0 eq.) and *p*-tolyl disulfide (2.5 g, 10.1 mmol, 1.0 eq.) in MeOH (215 mL) at rt. The resulting yellow suspension was stirred at rt for 3 h during which time the suspension became colourless. Then, the solvent was evaporated under reduced pressure. CH_2Cl_2 (100 mL) and water (100 mL) were added to the residue and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by Kügelrohr short path distillation gave sulfinate **92** (3.2 g, 92% yield) as a colourless oil, bp 91-94 °C/2.0 mmHg (lit.,[133] 129-130 °C/16.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.35 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.47 (s, 3H, OMe), 2.43 (s, 3H, Me). Spectroscopic data consistent with those reported in the literature.[134]

***N*-Methyl *N*-*p*-tolylsulfinylmethyl carbamic acid *tert*-butyl ester 106**



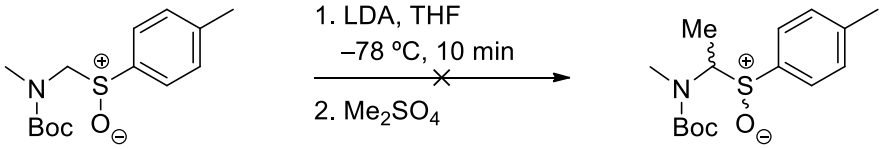
106

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 dimethylamine **105** (145 mg, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 194 μL, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, *p*-tolylsulfinate **92** (340 mg, 2.0 mmol, 2.0 eq.) was added. The resulting solution was allowed to warm to rt over 16 h. Then, MeOH (1 mL), saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (10 mL) were added and the

two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone with 1% Et_3N as eluent gave sulfoxide **106** (203 mg, 71%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone with 1% Et_3N) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.56 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.52 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.38-7.31 (m, 2H, *o*-C_6H_4Me), 4.59 (d, J = 13.0 Hz, 0.5H, NCH), 4.38 (d, J = 13.0 Hz, 0.5H, NCH), 4.30 (d, J = 13.0 Hz, 0.5H, NCH), 4.10 (d, J = 13.0 Hz, 0.5H, NCH), 3.07 (s, 1.5H, NMe), 2.94 (s, 1.5H, NMe), 2.42 (s, 1.5H, C_6H_4*Me*), 2.41 (s, 1.5H, C_6H_4*Me*), 1.45 (s, 4.5H, CMe_3), 1.38 (s, 4.5H, CMe_3). Spectroscopic data consistent with those reported previously in the group.[71]

Lab Book Reference: GG2/96/1

Attempted synthesis of *tert*-butyl methyl(1-(p-tolylsulfinyl)ethyl)carbamate 114

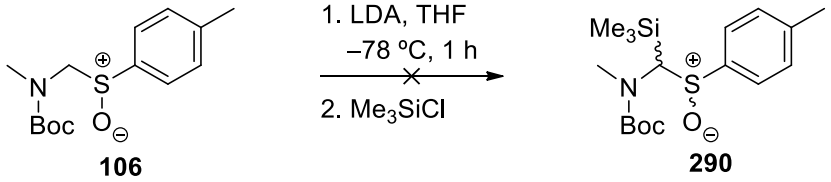


106 **114**

n-BuLi (170 μL of a 2.5 M solution in hexanes, 0.49 mmol, 1.3 eq.) was added dropwise to a stirred solution of isopropylamine (42 mg, 58 μL, 0.42 mmol, 1.3 eq.) in THF (1.7 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C and stirred for 15 min and then re-cooled to −78 °C. Then, a solution of sulfoxide **106** (100 mg, 0.35 mmol, 1.0 eq.) in THF (3.4 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 10 min. Then, Me_2SO_4 (62 mg, 46 μL, 0.52 mmol, 1.5 eq.) was added and the mixture was allowed to warm to rt over 2 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed only starting sulfoxide **106** and therefore purification was not attempted.

Lab Book Reference: GG3/6

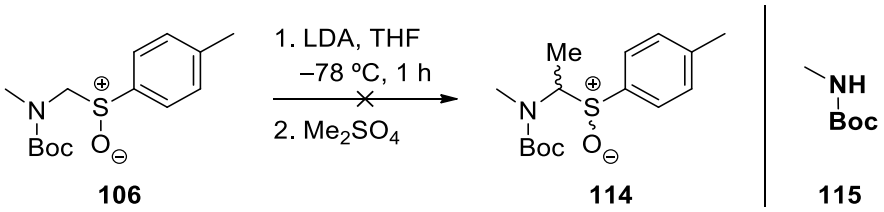
Attempted synthesis of *tert*-butyl methyl(*p*-tolylsulfinyl(trimethylsilyl)methyl) carbamate 290



n-BuLi (170 μL of a 2.5 M solution in hexanes, 0.49 mmol, 1.3 eq.) was added dropwise to a stirred solution of isopropylamine (42 mg, 58 μL, 0.42 mmol, 1.3 eq.) in THF (1.7 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C and stirred for 15 min and then re-cooled to −78 °C. Then, a solution of sulfoxide **106** (100 mg, 0.35 mmol, 1.0 eq.) in THF (3.4 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 10 min. Then, Me_3SiCl (56 mg, 66 μL, 0.52 mmol, 1.5 eq.) was added and the mixture was allowed to warm to rt over 2 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/16

***N*-Boc methylamine 115**

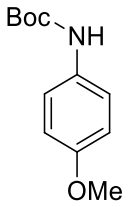


n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of isopropylamine (26 mg, 36 μL, 0.26 mmol, 1.3 eq.) in THF (1 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C and stirred for 15 min and then re-cooled to −78 °C. Then, a solution of sulfoxide **106** (67 mg, 0.22 mmol, 1.0 eq.) in THF (2 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 1 h. Then, Me_2SO_4 (42 mg, 31 μL, 0.49 mmol, 1.5 eq.) was added and the mixture was allowed to warm to rt over 2 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer

was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-acetone with 1% Et_3N as eluent gave *N*-Boc methylamine **115** (17 mg, 59%) as a colourless oil, R_F (96:4 CH_2Cl_2-acetone with 1% Et_3N) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (br s, 1H, NH), 2.83 (br s, 3H, NMe), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 156.2 (C=O), 155.9 (C=O), 80.1 (*C*Me_3), 79.8 (*C*Me_3), 32.7 (Me), 32.5 (Me), 28.3 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[135]

Lab Book Reference: GG3/7

tert-Butyl 4-methoxyphenylcarbamate 120

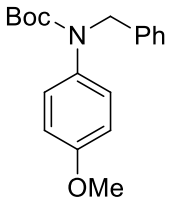


120

A solution of di-*tert*-butyl dicarbonate (13.63 g, 62.4 mmol, 1.0 eq.) in THF (40 mL) was added dropwise to a stirred solution of *p*-anisidine (10.0 g, 81.2 mmol, 1.3 eq.) in THF (40 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. Then, water (100 mL) and CH_2Cl_2 (100 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc as eluent gave *N*-Boc *p*-anisidine **120** (13.8 g, 99%) as a white solid, mp 84-87 °C (lit.,[87] 92-94 °C), R_F (70:30 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (br d, J = 9.0 Hz, 2H, Ar), 6.84 (d, J = 9.0 Hz, 2H, Ar), 6.36 (br s, 1H, NH), 3.78 (s, 3H, OMe), 1.51 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[87]

Lab Book Reference: GG2/97/1

tert-Butyl benzyl(4-methoxyphenyl)carbamate 117

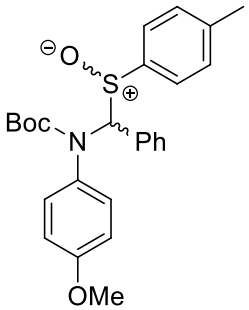


117

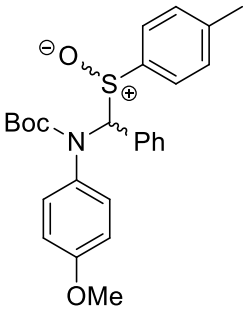
A solution of *N*-Boc *p*-anisidine **120** (4.0 g, 18.0 mmol, 1.0 eq.) in THF (47 mL) was added to a stirred suspension of NaH (792 mg of a 60% wt dispersion in mineral oil, 19.8 mmol, 1.1 eq.) and benzyl bromide (3.4 g, 2.35 mL, 19.8 mmol, 1.1 eq.) in THF (31 mL) at 0 °C under Ar. The resulting mixture was stirred at rt for 16 h. Then, water (50 mL) and Et_2O (50 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 to 80:20 petrol-Et_2O as eluent gave *N*-Boc *N*-benzyl *p*-anisidine **117** (5.1 g, 90%) as a white solid, mp 44-46 °C (lit.,[86] 42-43 °C), R_F (80:20 petrol- Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H, Ar), 7.27-7.21 (m, 3H, Ar), 7.11-6.92 (m, 2H, Ar), 6.79 (br d, J = 8.5 Hz, 2H, Ar), 4.78 (s, 2H, NCH_2), 3.78 (s, 3H, OMe), 1.43 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[86]

Lab Book Reference: GG3/17/1

tert-Butyl 4-methoxyphenyl(phenyl(p-tolylsulfinyl)methyl)carbamate 40a and 40b



40a



40b

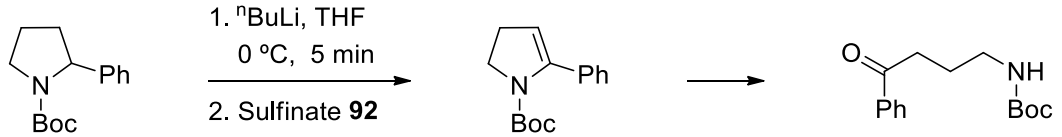
s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc *N*-benzyl *p*-anisidine **117** (313 mg, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 194 μL, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, *p*-tolylsulfinate **92** (255 mg, 1.5 mmol, 1.5 eq.) was added. The resulting solution was stirred at −30 °C for 10 min

and then allowed to warm to rt over 1 h. Then, MeOH (1 mL), saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone with 0.5% Et_3N as eluent gave sulfoxide **40a** (135 mg, 30%) as a yellow solid, mp 65-68 °C, R_F (98:2 CH_2Cl_2-acetone with 0.5% Et_3N) 0.2; IR ($CHCl_3$) 2963, 1691 (C=O), 1494, 1347, 1224, 1142, 1018, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H, Ar), 7.33-7.22 (m, 7H, Ar), 6.68 (d, J =9.0 Hz, 2H, Ar), 6.56 (br d, J = 8.0 Hz, 2H, Ar), 5.57 (s, 1H, NCH), 3.77 (s, 3H, OMe), 2.43 (s, 3H, C_6H_4*Me*), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 158.3 (C=O), 155.6 (*ipso*-Ar), 153.1 (*ipso*-Ar), 142.1 (*ipso*-Ar), 140.9 (*ipso*-Ar), 140.7 (*ipso*-Ar), 137.9 (*ipso*-Ar), 136.4 (*ipso*-Ar), 135.4 (Ar), 134.4 (Ar), 131.1 (Ar), 130.1 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.0 (Ar), 127.8 (Ar), 126.7 (Ar), 124.3 (Ar), 114.3 (Ar), 113.3 (Ar), 80.1 (*C*Me_3), 55.4 (OMe or NCH), 55.2 (OMe or NCH), 28.3 (C*Me*$_3$), 28.1 (C*Me*$_3$), 21.3 (Me), 21.2 (Me); MS (ESI) *m/z* 474 [$(M + Na)^+$, 2], 452 [$(M + H)^+$, 1], 393 (20), 352 (50), 312 (100), 256 (20); HRMS (ESI) *m/z* calcd for $C_{26}H_{29}NO_4S$ $(M + H)^+$ 452.1890, found 452.1919 (+5.5 ppm error) and sulfoxide **40b** (92 mg, 20%) as a yellow solid, mp 68-70 °C, R_F (98:2 CH_2Cl_2-acetone with 0.5% Et_3N) 0.1; IR ($CHCl_3$) 2964, 1691 (C=O), 1494, 1224, 1143, 1042, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.17 (m, 3H, Ar), 7.17-7.03 (m, 6H, Ar), 6.88-6.76 (m, 4H, Ar), 6.33-5.93 (m, 1H, NCH), 3.84 (s, 3H, OMe), 2.31 (s, 3H, C_6H_4*Me*), 1.74-1.27 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 158.3 (C=O), 155.6 (*ipso*-Ar), 153.1 (*ipso*-Ar), 142.0 (*ipso*-Ar), 141.0 (*ipso*-Ar), 140.7 (*ipso*-Ar), 137.9 (*ipso*-Ar), 136.7 (*ipso*-Ar), 135.4 (Ar), 134.4 (Ar), 131.4 (Ar), 131.0 (Ar), 130.0 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.0 (Ar), 127.8 (Ar), 126.8 (Ar), 124.3 (Ar), 114.1 (Ar), 113.3 (Ar), 80.1 (*C*Me_3), 55.5 (OMe or NCH), 55.2 (OMe or NCH), 28.3 (C*Me*$_3$), 28.1 (C*Me*$_3$), 21.5 (Me), 21.2 (Me); MS (ESI) *m/z* 474 [$(M + Na)^+$, 10], 452 [$(M + H)^+$, 5], 393 (40), 352 (60), 312 (100), 256 (20); HRMS (ESI) *m/z* calcd for $C_{26}H_{29}NO_4S$ $(M + H)^+$ 452.1890, found 452.1902 (+4.1 ppm error).

Subsequent attempts to repeat this lithiation-trapping reaction were unsuccessful and sulfoxide **40a** and **40b** were not isolated probably due to their instability.

Lab Book Reference: GG3/26

tert-Butyl 5-phenyl-2,3-dihydro-1H-pyrrole-1-carboxylate 122 and _tert_-butyl 4-oxo-4-phenylbutylcarbamate 123

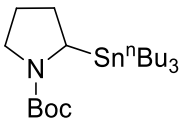


70 **122** **123**

n-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added to a stirred solution of *N*-Boc 2-Ph-pyrrolidine **70** (247 mg, 1.0 mmol, 1.0 eq.) in THF (10 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 5 min. Then, *p*-tolylsulfinate **92** (340 mg, 2.0 mmol, 2.0 eq.) was added. The reaction was stirred at 0 °C for 10 min and then allowed to warm to rt over 30 min. Then, MeOH (0.6 mL), saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O with 0.5% Et_3N as eluent gave dihydropyrrole **122** (178 mg, 72%) as a yellow oil, R_F (90:10 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H, Ph), 5.23 (t, J = 3.0 Hz, 1H, C=CH), 4.05 (t, J = 9.0 Hz, 2H, NCH_2), 2.62 (td, J = 9.0, 3.0 Hz, 2H, CH_2), 1.19 (s, 9H, CMe_3). On standing, this compound was unstable and converted into *N*-Boc aminophenone **123** (158 mg, 60%) as an off-white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H, *o*-Ph), 7.55 (t, J = 7.5 Hz, 1H, *p*-Ph), 7.45 (t, J = 7.5 Hz, 2H, *m*-Ph), 4.75 (br s, 1H, NH), 3.22 (q, J = 7.0 Hz, 2H, NCH_2), 3.02 (t, J = 7.0 Hz, 2H, CH_2CO), 1.93 (quin, J = 7.0 Hz, 2H, CH_2), 1.41 (s, 9H, CMe_3). Spectroscopic data of **123** consistent with those reported in the literature.[88]

Lab Book Reference: GG3/56

2-(Tributylstannyl)pyrrolidine-1-carboxylic acid _tert_-butyl ester 47



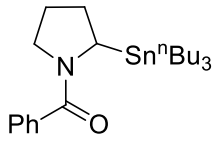
47

s-BuLi (10.0 mL of a 1.3 M solution in hexanes, 13.0 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (1.71 g, 10.0 mmol, 1.0 eq.) and TMEDA (1.51 g, 1.94 mL, 13.0 mmol, 1.3 eq.) in Et_2O (56 mL) at –78 °C under Ar.

The resulting solution was stirred at −78 °C for 15 min. Then, Bu_3SnCl (4.0 mL, 15.0 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (40 mL) and Et_2O (100 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were dried ($MgSO_4$) 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 stannyl pyrrolidine **47** (3.64 g, 79%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 3.69 (dd, J = 8.5, 2.0 Hz, 0.25H, NCH), 3.45-3.23 (m, 2H, NCH), 3.22-3.12 (m, 0.75H, NCH), 2.27-2.03 (m, 1H, CH), 1.97-1.75 (m, 2H, CH), 1.56-1.40 (m, 6H, CH), 1.48 (s, 2.25H, CMe_3), 1.43 (s, 6.75H, CMe_3), 1.35-1.23 (m, 6H, CH), 0.95-0.81 (m, 15H, CH). Spectroscopic data consistent with those reported in the literature.[11]

Lab Book Reference: GG3/63/1

Phenyl(2-(tributylstannyl)pyrrolidin-1-yl)methanone 129



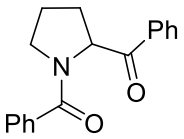
129

Me_3SiI (0.71 mL, 5.0 mmol, 1.3 eq.) was added to a stirred solution of stannyl pyrrolidine **47** (1.78 g, 3.9 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (6 mL) and CH_2Cl_2 (100 mL) were added and the two layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and then DMAP (47 mg, 0.39 mmol, 0.1 eq.), benzoyl chloride (0.49 mL, 4.3 mmol, 1.1 eq.) and Et_3N (0.81 mL, 5.8 mmol, 1.5 eq.) were added. The resulting mixture was stirred at rt for 20 h. Then, $NaHCO_{3(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The organic layer was washed with $NH_4Cl_{(aq)}$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine **129** (1.27 g, 70%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2911, 2881, 1653 (C=O), 1526, 1427, 1380, 1342, 707, 623 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H, Ph), 7.41-7.36 (m, 3H, Ph), 3.57 (dd, *J* = 8.5, 8.5 Hz, 1H, NCH), 3.50 (ddd, *J* = 11.0, 7.0, 4.5 Hz, 1H, NCH), 3.39 (ddd, *J* = 11.0, 7.0, 7.0 Hz, 1H, NCH), 2.26 (ddddd, *J* = 12.5, 7.0, 7.0, 7.0, 7.0 Hz, 1H, CH), 2.05-1.93 (m, 1H, CH), 1.93-1.77 (m, 2H, CH), 1.68-1.42 (m, 6H, CH_2), 1.32 (sextet, *J* = 7.5 Hz, 6H, C*H*$_2$Me), 0.97-0.91 (m, 6H, CH_2), 0.89 (t, *J* = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8 (C=O), 137.3 (*ipso*-Ph), 129.5 (Ph), 128.2 (Ph), 127.1 (Ph), 50.1 (NCH_2), 47.7 (NCH), 29.6 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 13.8 (Me), 10.2 (CH_2); MS (ESI) *m/z* 466 [$(M + H)^+$, 100], 408 (70); HRMS (ESI) *m/z* calcd for $C_{23}H_{39}NOSn$ $(M + H)^+$ 466.2130, found 466.2122 (+1.1 ppm error).
Lab Book Reference: GG3/20/1

TFA (0.75 mL, 9.8 mmol, 20.0 eq.) was added to a stirred solution of stannyl pyrrolidine **47** (230 mg, 0.5 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) at 0 °C under Ar. After stirring for 1 h at rt, the solvent was evaporated under reduced pressure to give a yellow oil. The residue was dissolved in CH_2Cl_2 (0.4 mL) and benzoyl chloride (84 mg, 70 μL, 1.2 eq.) and $NaOH_{(aq)}$ (1.0 M, 3.2 mL) were added. The biphasic system was vigorously stirred at rt for 16 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 petrol-Et_2O as eluent gave pyrrolidine **129** (17 mg, 7%) as a colourless oil.
Lab Book Reference: GG2/82/2

Pyrrolidine-1,2-diylbis(phenylmethanone) 132



132

(Table 3.1, Entry 2)
n-BuLi (210 μL of a 2.5 M solution in hexanes, 0.5 mmol, 1.0 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **129** (232 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, *p*-tolylsulfinate **92** (340 mg, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (1

mL), saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 petrol-EtOAc with 1% Et_3N as eluent gave pyrrolidine **132** (44 mg, 62%) as a white solid, mp 93-95 °C; R_F (50:50 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2962, 2835, 1667 (C=O, ketone), 1598 (C=O, amide), 1553, 1400, 1208, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H, Ph), 7.65-7.57 (m, 3H, Ph), 7.54-7.48 (m, 2H, Ph), 7.45-7.39 (m, 3H, Ph), 5.72 (dd, *J* = 8.5, 5.0 Hz, 1H, NCH), 3.75 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 1H, NCH), 3.63 (ddd, *J* = 10.5, 6.5, 6.5 Hz, 1H, NCH), 2.45-2.36 (m, 1H, CH), 2.09-1.90 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3 (C=O), 169.7 (C=O), 136.6 (*ipso*-Ph), 135.6 (*ipso*-Ph), 133.5 (Ph), 130.3 (Ph), 128.9 (Ph), 128.8 (Ph), 128.4 (Ph), 127.5 (Ph), 61.2 (NCH), 49.9 (NCH_2), 29.2 (CH_2), 25.1 (CH_2); MS (ESI) *m/z* 302 [$(M + Na)^+$, 40], 280 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_2$ $(M + H)^+$ 280.1332, found 280.1329 (+1.2 ppm error).

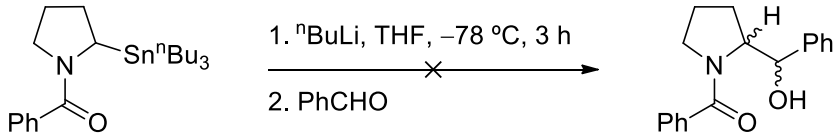
Lab Book Reference: GG3/23/1

(Table 3.1, Entry 1)

n-BuLi (260 μL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **129** (232 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (32 mg, 40 μL, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 petrol-EtOAc as eluent gave pyrrolidine **132** (35 mg, 48%) as a colourless oil.

Lab Book Reference: GG3/25/1

Attempted synthesis of 2-(hydroxyphenylmethyl)pyrrolidin-1-yl)(phenyl) methanone 291

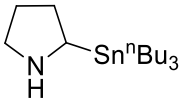


129 **291**

n-BuLi (210 μL of a 2.5 M solution in hexanes, 0.5 mmol, 1.0 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **129** (232 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, PhCHO (80 mg, 75 μL, 1.5 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/24

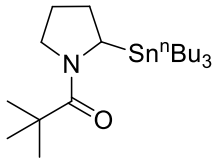
2-(Tributylstannyl)pyrrolidine 292



292

Me_3SiI (790 μL, 5.5 mmol, 1.3 eq.) was added to a stirred solution of stannyl pyrrolidine **47** (1.97 g, 4.3 mmol, 1.0 eq.) in CH_2Cl_2 (32 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (6 mL) and CH_2Cl_2 (75 mL) were added and the two layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude stannyl pyrrolidine **292**, which was sufficiently pure (by ^{1}H NMR spectroscopy) for use in the next step.

2,2-Dimethyl-1-(2-(tributylstannyl)pyrrolidin-1-yl)propan-1-one 130

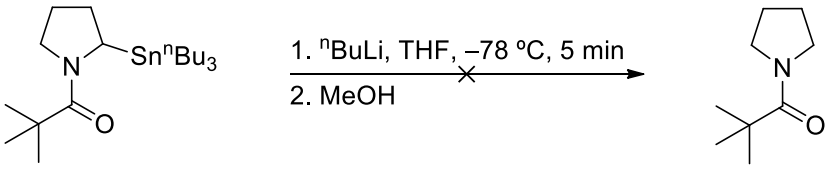


130

Pivaloyl chloride (133 mg, 136 μL, 1.5 mmol, 1.5 eq.) was added to a stirred solution of stannyl pyrrolidine **292** (360 mg, 1.0 mmol, 1.0 eq.) and DMAP (12 mg, 0.1 mmol, 0.1 eq.) in CH_2Cl_2 (11 mL) at rt under Ar. Then, Et_3N (152 mg, 210 μL, 1.5 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 60 h. Then, saturated $NaHCO_{3(aq)}$ (15 mL) and CH_2Cl_2 (15 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave stannyl pyrrolidine **130** (330 mg, 74%) as a yellow oil, R_F (80:20 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (ddd, J = 10.5, 6.0, 6.0 Hz, 1H, NCH), 3.53-3.44 (m, 2H, NCH), 2.14-2.04 (m, 1H, CH), 1.97-1.89 (m, 2H, CH), 1.89-1.79 (m, 1H, CH), 1.55-1.41 (m, 6H, CH_2), 1.30 (sextet, J = 7.5 Hz, 6H, CH_2Me), 1.25 (s, 9H, CMe_3), 0.92-0.79 (m, 6H, CH_2), 0.89 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2 (C=O), 50.1 (NCH), 48.0 (NCH_2), 38.7 (*C*Me_3), 29.2 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.8 (C*Me*$_3$), 27.6 (CH_2), 13.8 (Me), 9.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[48]

Lab Book Reference: GG3/35/1

Attempted synthesis of 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one 125



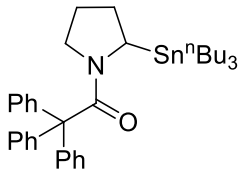
130 **125**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **130** (126 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, MeOH (13 mg, 16 μL, 0.4 mmol, 2.0 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated

$NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/41

2,2,2-Triphenyl-1-(2-(tributylstannyl)pyrrolidin-1-yl)ethanone 131

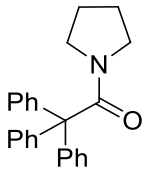


131

Oxalyl chloride (870 mg, 580 μL, 6.8 mmol, 1.6 eq.) was added to a stirred suspension of triphenylacetic acid (1.36 g, 4.7 mmol, 1.1 eq.) in CH_2Cl_2 (8 mL) at rt under Ar. Then, DMF (1 drop) was added and the reaction mixture was stirred and heated at 35 °C for 2 h until a brown solution was formed and effervescence ceased. Then, the solvent was evaporated under reduced pressure to give a light brown solid. The solid was dissolved in CH_2Cl_2 (8 mL) and added to a stirred solution of stannyl pyrrolidine **292** (1.54 g, 4.3 mmol, 1.0 eq.) and DMAP (52 mg, 0.4 mmol, 0.1 eq.) in CH_2Cl_2 (50 mL) at rt under Ar. Then, Et_3N (1.29 g, 1.79 mL, 12.8 mmol, 3.0 eq.) was added and the reaction mixture was stirred at rt for 60 h. Then, saturated $NaHCO_{3(aq)}$ (15 mL) and CH_2Cl_2 (15 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave stannyl pyrrolidine **131** (1.93 g, 71%) as a white solid, mp 121-123 °C; R_F (95:5 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2971, 2912, 1585 (C=O), 1470, 1424, 1379, 1196, 763, 731, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 6H, Ph), 7.23-7.16 (m, 9H, Ph), 3.69 (dd, J = 8.5, 8.5 Hz, 1H, NCH), 2.79 (ddd, J = 11.0, 7.0, 4.0 Hz, 1H, NCH), 2.29 (ddd, J = 11.0, 8.5, 6.5 Hz, 1H, NCH), 2.10-1.97 (m, 1H, CH), 1.80-1.69 (m, 1H, CH), 1.65-1.55 (m, 1H, CH), 1.55-1.40 (m, 7H, CH + CH_2), 1.31 (sextet, J = 7.5 Hz, 6H, CH_2Me), 1.00-0.82 (m, 6H, CH_2), 0.89 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.0 (C=O), 143.3 (*ipso*-Ph), 130.5 (Ph), 127.5 (Ph), 126.3 (Ph), 67.6

(*C*Ph_3), 49.6 (NCH), 48.7 (NCH_2), 29.3 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 13.8 (Me), 10.4 (CH_2); MS (ESI) *m/z* 654 [$(M + Na)^+$, 100], 632 [$(M + H)^+$, 80]; HRMS (ESI) *m/z* calcd for $C_{36}H_{49}NOSn$ $(M + H)^+$ 632.2916, found 632.2891 (+2.9 ppm error).
Lab Book Reference: GG3/34/1

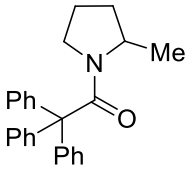
2,2,2-Triphenyl-1-(pyrrolidin-1-yl)ethanone 126



126

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **131** (126 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (13 mg, 16 μL, 0.4 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 petrol-EtOAc gave pyrrolidine **126** (54 mg, 79%) as a white solid, mp 175-177 °C (lit.,[136] 188.5 °C); R_F (70:30 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (m, 15H, Ph), 3.66 (t, J = 6.5 Hz, 2H, NCH_2), 2.44 (t, J = 6.5 Hz, 2H, NCH_2), 1.72 (quin, J = 6.5 Hz, 2H, CH_2), 1.57 (quin, J = 6.5 Hz, 2H, CH_2). Spectroscopic data consistent with those reported in the literature.[136]
Lab Book Reference: GG3/40/1

1-(2-Methylpyrrolidin-1-yl)-2,2,2-triphenylethanone 135



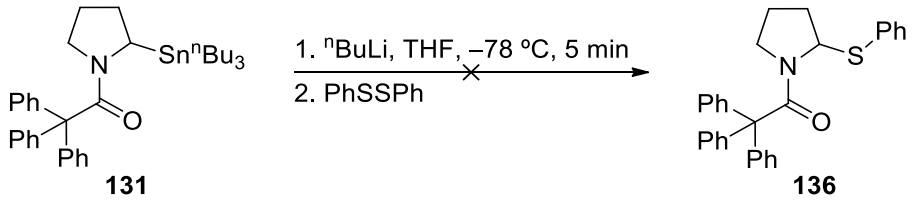
135

n-BuLi (260 μL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **131** (315 mg, 0.5 mmol, 1.0 eq.) in

THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, Me_2SO_4 (126 mg, 100 μL, 1.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O gave pyrrolidine **135** (155 mg, 87%) as a white solid, mp 178-180 °C; R_F (80:20 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2960, 2924, 2829, 1600 (C=O), 1470, 1432, 1371, 1160, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 6H, Ph), 7.26-7.20 (m, 9H, Ph), 4.45-4.35 (m, 1H, NCH), 2.84 (ddd, J = 11.0, 7.0, 4.5 Hz, 1H, NCH), 2.16 (ddd, J = 11.0, 8.0, 6.5 Hz, 1H, NCH), 2.05-1.95 (m, 1H, CH), 1.64-1.54 (m, 1H, CH), 1.53-1.41 (m, 1H, CH), 1.40-1.31 (m, 1H, CH), 1.29 (d, J = 6.5 Hz, 3H, Me). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 142.9 (*ipso*-Ph), 130.4 (Ph), 127.6 (Ph), 126.4 (Ph), 67.7 (*C*Ph_3), 54.7 (NCH), 47.9 (NCH_2), 31.7 (CH_2), 24.7 (CH_2), 19.2 (Me); MS (ESI) *m/z* 378 [$(M + Na)^+$, 100], 356 [$(M + H)^+$, 80]; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}NO$ $(M + H)^+$ 356.2009, found 356.2013 (−1.8 ppm error).

Lab Book Reference: GG3/49/1

Attempted synthesis of 2,2,2-triphenyl-1-(2-(phenylthio)pyrrolidin-1-yl)ethanone 136

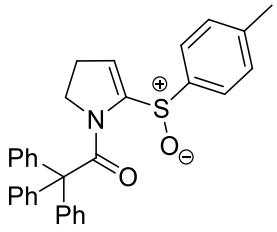


n-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **131** (315 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, diphenyl disulfide (327 mg, 1.5 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/50

2,2,2-Triphenyl-1-(5-(*p*-tolylsulfinyl)-2,3-dihydro-1H-pyrrol-1-yl)ethanone 137

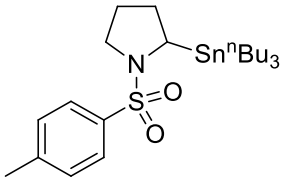


137

n-BuLi (260 μL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **131** (315 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, *p*-tolylsulfinate **92** (128 mg, 0.75 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (0.5 mL), saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 to 50:50 petrol-EtOAc with 0.5% of Et_3N gave pyrrolidine **126** (74 mg, 43%) as a white solid and sulfoxide **137** (50 mg, 21%) as a white solid, mp 160-163 °C; R_F (50:50 petrol-EtOAc with 0.5% of Et_3N) 0.3; IR ($CHCl_3$) 2962, 1612 (C=O), 1363, 1212, 1020, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H, Ar), 7.27 (d, J = 8.0 Hz, 2H, Ar), 7.22-7.15 (m, 9H, Ar), 6.93-6.87 (m, 6H, Ar), 6.30 (dd, J = 3.5, 2.0 Hz, 1H, C=CH), 3.45-3.37 (m, 1H, NCH), 2.67-2.42 (m, 2H, NCH and CH), 2.47 (s, 3H, Me), 2.41-2.29 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7 (C=O), 152.3 (*ipso*-Ar), 142.3 (*ipso*-Ar), 141.7 (=C), 141.5 (*ipso*-Ar), 130.0 (Ar), 129.4 (Ar), 127.8 (Ar), 127.4 (Ar), 126.7 (Ar), 116.3 (=CH), 66.7 (*C*Ph_3), 51.7 (NCH_2), 29.4 (CH_2), 21.5 (Me); MS (ESI) *m/z* 500 [$(M + Na)^+$, 100], 478 [$(M + H)^+$, 50]; HRMS (ESI) *m/z* calcd for $C_{31}H_{27}NO_2S$ $(M + H)^+$ 478.1835, found 478.1855 (−4.4 ppm error).

Lab Book Reference: GG3/43/2

***N*-4-Toluenesulfonyl-2-(tributylstannyl)pyrrolidine 139**

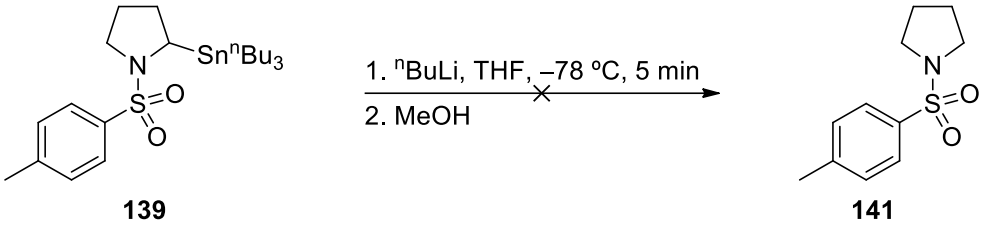


139

Et_3N (769 mg, 1.04 mL, 7.5 mmol, 3.0 eq.) was added to a stirred solution of stannyl pyrrolidine **292** (1.15 g, 2.5 mmol, 1.0 eq.), *p*-toluenesulfonyl chloride (524 mg, 2.75 mmol, 1.1 eq.) and DMAP (30 mg, 0.25 mmol, 0.1 eq.) in CH_2Cl_2 (29 mL) at rt under Ar. Then, the reaction mixture was stirred at rt for 20 h. Then, saturated $NaHCO_{3(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave tosyl pyrrolidine **139** (737 mg, 57%) as a colourless oil, R_F (90:10 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2911, 2879, 2826, 1437, 1320, 1139, 1076, 1031, 986, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 2H, *o*-$C_6H_4SO_2$), 7.31 (d, J = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 3.34-3.25 (m, 1H, NCH), 3.25-3.17 (m, 1H, NCH), 3.15-3.08 (m, 1H, NCH), 2.43 (s, 3H, C_6H_4*Me*), 1.96-1.71 (m, 3H, CH), 1.68-1.43 (m, 7H, CH + CH_2), 1.35 (sextet, J = 7.5 Hz, 6H, C*H*$_2$Me), 1.11-0.97 (m, 6H, CH_2), 0.92 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9 (*ipso*-Ar), 133.8 (*ipso*-Ar), 129.4 (Ar), 127.6 (Ar), 49.1 (NCH), 48.9 (NCH_2), 31.0 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 21.5 (Ar*Me*), 13.7 (Me), 9.8 (CH_2); MS (ESI) *m/z* 538 [$(M + Na)^+$, 25], 516 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{23}H_{41}NO_2SSn$ $(M + H)^+$ 516.1955, found 516.1956 (−1.6 ppm error).

Lab Book Reference: GG3/67/1

Attempted synthesis of *N*-4-toluenesulfonyl-pyrrolidine 141

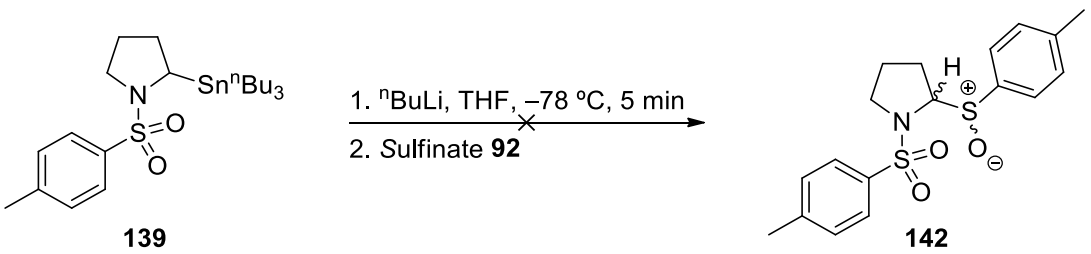


139 **141**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of tosyl pyrrolidine **139** (103 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, MeOH (13 mg, 16 μL, 0.4 mmol, 2.0 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave recovered tosyl pyrrolidine **139** (33 mg, 32%) as a colourless oil.

Lab Book Reference: GG3/71

Attempted synthesis of 2-(*p*-tolylsulfinyl) *N*-4-toluenesulfonyl-pyrrolidine 142

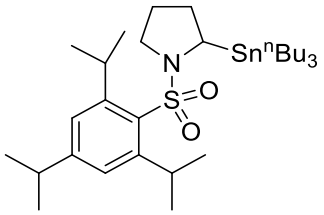


139 **142**

n-BuLi (260 μL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of tosyl pyrrolidine **139** (257 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, *p*-tolylsulfinate **92** (128 mg, 0.75 mmol, 2.0 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave recovered tosyl pyrrolidine **139** (55 mg, 21%) as a colourless oil.

Lab Book Reference: GG3/72

2-(Tributylstannyl) *N*-(2,4,6-triisopropylphenylsulfonyl)pyrrolidine 140

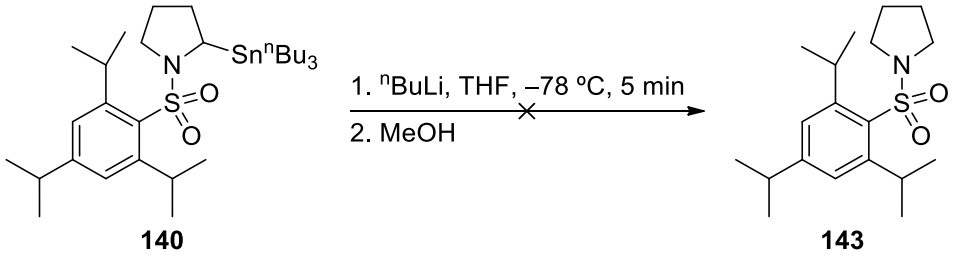


140

Et_3N (769 mg, 1.04 mL, 7.5 mmol, 3.0 eq.) was added to a stirred solution of stannyl pyrrolidine **292** (1.15 g, 2.5 mmol, 1.0 eq.), 2,4,6-triisopropylsulfonyl chloride (832 mg, 2.75 mmol, 1.1 eq.) and DMAP (30 mg, 0.25 mmol, 0.1 eq.) in CH_2Cl_2 (29 mL) at rt under Ar. Then, the reaction mixture was stirred at rt for 20 h. Then, saturated $NaHCO_{3(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 petrol-Et_2O as eluent gave sulfonyl pyrrolidine **140** (781 mg, 50%) as a colourless oil, R_F (98:2 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2913, 2882, 2827, 1575, 1439, 1272, 1128, 1055, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H, Ar), 4.25 (septet, J = 7.0 Hz, 2H, ArC*H*), 3.48 (dd, J = 7.5, 7.5 Hz, 1H, NCH), 3.13 (ddd, J = 10.0, 7.0, 7.0 Hz, 1H, NCH), 3.03 (ddd, J = 10.0, 7.0, 7.0 Hz, 1H, NCH), 2.90 (septet, J = 7.0 Hz, 1H, ArC*H*), 2.30-2.13 (m, 1H, CH), 1.99-1.80 (m, 3H, CH), 1.61-1.46 (m, 6H, CH_2), 1.33 (sextet, J = 7.5 Hz, 6H, CH_2), 1.26 (d, J = 7.0 Hz, 6H, CH*Me*$_2$), 1.25 (d, J = 7.0 Hz, 6H, CH*Me*$_2$), 1.24 (d, J = 7.0 Hz, 6H, CH*Me*$_2$), 1.00-0.93 (m, 6H, CH_2), 0.91 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.6 (*ipso*-Ar), 151.1 (*ipso*-Ar), 137.7 (*ipso*-Ar), 123.7 (Ar), 48.1 (NCH_2), 47.1 (NCH), 34.1 (Ar*C*H), 31.0 (CH_2), 29.4 (Me), 29.2 (CH_2), 27.6 (CH_2), 26.2 (CH_2), 25.0 (Me), 24.8 (Me), 23.6 (Me), 13.7 (Me), 10.0 (CH_2); MS (ESI) *m/z* 650 [(M + Na)$^+$, 40], 628 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{31}H_{57}NO_2SSn$ (M + H)$^+$ 628.3209, found 628.3206 (−0.5 ppm error).

Lab Book Reference: GG3/68/1

Attempted synthesis of *N*-(2,4,6-triisopropylphenylsulfonyl)pyrrolidine 143

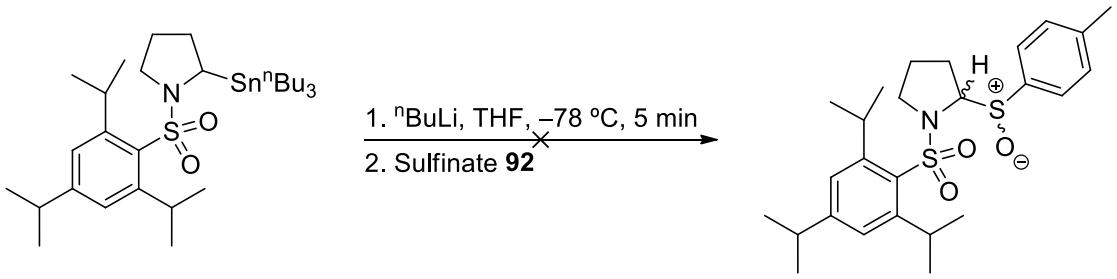


140 **143**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of tosyl pyrrolidine **140** (103 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (13 mg, 16 μL, 0.4 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/73

Attempted synthesis of 2-(*p*-tolylsulfinyl) *N*-(2,4,6-triisopropylphenylsulfonyl) pyrrolidine 145



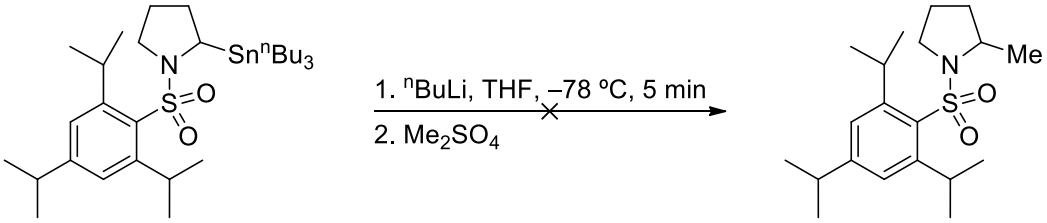
140 **145**

n-BuLi (260 μL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of tosyl pyrrolidine **140** (257 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, *p*-tolylsulfinate **92** (128 mg, 0.75 mmol, 2.0 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined

organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/74

Attempted synthesis of 2-methyl-1-(2,4,6-triisopropylphenylsulfonyl)pyrrolidine 144

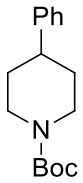


140 **144**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.25 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **140** (125 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, Me_2SO_4 (50 mg, 40 μL, 1.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^1H NMR spectrum of the crude product showed only starting material and therefore purification was not attempted.

Lab Book Reference: GG3/85

4-Phenylpiperidine-1-carboxylic acid *tert*-butyl ester 147



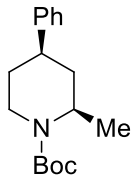
147

A solution of di-*tert*-butyl dicarbonate (7.1 g, 32.5 mmol, 1.05 eq.) in CH_2Cl_2 (20 mL) was added dropwise to a solution of 4-phenylpiperidine (5.0 g, 31.0 mmol, 1.0 eq.) in CH_2Cl_2 (33 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for 3 h. Then, 10% $NaHCO_{3(aq)}$ (30 mL) and CH_2Cl_2 (70 mL) were added. The

aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave 4-phenyl *N*-Boc piperidine **147** (8.0 g, 99%) as a colourless oil, bp 133-135 °C/0.5 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H, Ph), 7.25-7.19 (m, 3H, Ph), 4.24 (br s, 2H, NCH), 2.80 (br t, J = 11.5 Hz, 2H, NCH), 2.64 (tt, J = 12.0, 3.5 Hz, 1H, CHPh), 1.82 (br d, J = 13.0 Hz, 2H, CH), 1.69-1.56 (m, 2H, CH), 1.48 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[137]

Lab Book Reference: GG1/86/1

2-Methyl-4-phenylpiperidine-1-carboxylic acid *tert*-butyl ester *rac-syn*-148



rac-syn-**148**

(Table 3.2, Entry 1)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.5 mmol, 1.3 eq.) at –78 °C for 1 h and then Me_2SO_4 (290 mg, 210 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave 4-phenylpiperidine *rac-syn*-**148** (212 mg, 67%) as a colourless oil, R_F (95:5 hexane-EtOAc) 0.2; IR ($CHCl_3$) 2973, 2932, 1692 (C=O), 1478, 1453, 1413, 1365, 1250, 1171, 1142, 759, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H, Ph), 7.25-7.17 (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), 2.81-2-71 (m, 1H, CHPh), 2.22-2.10 (m, 1H, CH), 1.91 (dddd, J = 13.5, 6.5, 3.0, 1.5 Hz, 1H, CH), 1.68-1.56 (m, 2H, CH), 1.49 (s, 9H, CMe_3), 1.20 (d, J = 6.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 146.4 (*ipso*-Ph), 128.7 (Ph), 127.1 (Ph), 126.5 (Ph), 79.2 (*C*Me_3), 49.9 (NCH), 37.7 (*C*HPh), 37.4 (NCH_2), 36.9 (CH_2), 31.0 (CH_2), 28.3 (CMe_3), 19.5 (Me); MS (ESI) *m/z* 298 [(M + Na)$^+$, 60], 276 [(M + H)$^+$, 5], 220 (100), 176 (5); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ (M + H)$^+$ 276.1958, found 276.1953 (+1.9 ppm error) and starting material **147** (45 mg,

14%) as a colourless oil. Spectroscopic data consistent with those reported in the literature.[138]

Lab Book Reference: GG1/54/1

(Table 3.2, Entry 2)

s-BuLi (0.76 mL of a 1.3 M solution in hexanes, 1.0 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-phenyl *N*-Boc piperidine **147** (200 mg, 0.76 mmol, 1.0 eq.) and TMEDA (115 mg, 150 μL, 1.0 mmol, 1.3 eq.) in Et_2O (2.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, Me_2SO_4 (144 mg, 110 μL, 1.14 mmol, 1.5 eq.) was added. The resulting solution was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave 4-phenylpiperidine *rac-syn*-**148** (125 mg, 60%) as a colourless oil.

Lab Book Reference: GG1/49/1

(Table 3.2, Entry 3)

s-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) in THF (3.8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, Me_2SO_4 (290 mg, 210 μL, 2.3 mmol, 2.0 eq.) was added. The resulting solution was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave 4-phenylpiperidine *rac-syn*-**148** (120 mg, 38%) as a colourless oil and starting material **147** (72 mg, 24%) as a colourless oil.

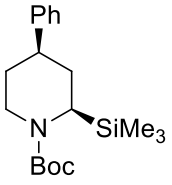
Lab Book Reference: GG1/56/1

(Table 3.2, Entry 4)

s-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) in THF (3.8 mL) at −30 °C under Ar. The resulting solution was stirred at −30 °C for 10 min. Then, Me_2SO_4 (290 mg, 210 μL, 2.3 mmol, 2.0 eq.) was added. The resulting solution was stirred at rt for 16 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave 4-phenylpiperidine *rac*-*syn*-**148** (63 mg, 20%) as a colourless oil.

Lab Book Reference: GG1/66/1

4-Phenyl-2-trimethylsilylpiperidine-1-carboxylic acid *tert*-butyl ester *rac*-*syn*-157



rac-syn-**157**

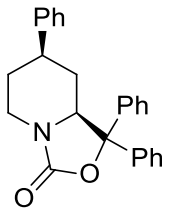
(Scheme 3.39)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.5 mmol, 1.3 eq.) at −78 °C for 1 h and then Me_3SiCl (250 mg, 290 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 97:3 petrol-EtOAc as eluent gave 4-phenylpiperidine *rac*-*syn*-**157** (327 mg, 86%) as a cloudy oil, R_F (97:3 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2935, 1691 (C=O), 1424, 1244, 1169, 839, 754, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H, Ph), 7.25-7.19 (m, 3H, Ph), 4.11 (br d, J = 12.5 Hz, 1H, NCH), 2.96 (br dd, J = 11.5, 11.5 Hz, 1H, NCH), 2.71 (dddd, J = 12.0, 12.0, 4.0, 4.0 Hz, 1H, CHPh), 2.41 (br d, J = 11.5 Hz, 1H, NCH), 1.87-1.77 (m, 2H, CH), 1.66-1.53 (m, 2H, CH), 1.47 (s, 9H, CMe_3), 0.07 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 146.6 (*ipso*-Ph), 128.7 (Ph), 127.1 (Ph), 126.5 (Ph), 79.0 (CMe_3), 50.9 (NCH), 47.8 (NCH_2), 44.7 (*C*HPh), 34.0 (CH_2), 33.3 (CH_2), 28.2 (CMe_3), −1.1 ($SiMe_3$); MS (ESI) *m/z* 356 [$(M + Na)^+$, 30], 334 [$(M + H)^+$, 15], 278 (80), 262 (100), 234 (5); HRMS

(ESI) *m/z* calcd for $C_{19}H_{31}NO_2Si$ $(M + H)^+$ 334.2197, found 334.2197 (–0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab Book Reference: GG1/63/1

1,1,7-Triphenyltetrahydro-oxazolo[3,4-α]pyridin-3-one *rac-syn*-158



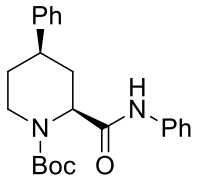
rac-syn-**158**

(Scheme 3.39)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.5 mmol, 1.3 eq.) in Et_2O (3.8 mL) at –78 °C for 1 h and then benzophenone (420 mg, 2.3 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product. Purification by flash column chromatography on silica with 6:4 petrol-Et_2O as eluent gave oxazolidinone *rac-syn*-**158** (100 mg, 23%) as a white solid, mp 226-228 °C; R_F (6:4 petrol-Et_2O) 0.1; IR ($CHCl_3$) 2948, 1748 (C=O), 1451, 1418, 1380, 909, 733, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.03 (m, 15H, Ph), 4.45 (dd, J = 12.0, 3.5 Hz, 1H, NCH), 4.09 (ddd, J = 13.5, 5.0, 1.5 Hz, 1H, NCH), 3.05 (ddd, J = 13.5, 13.5, 3.5 Hz, 1H, NCH), 2.77 (dddd, J = 12.0, 12.0, 3.0, 3.0 Hz, 1H, CHPh), 1.85-1.54 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6 (C=O), 144.7 (*ipso*-Ph), 142.9 (*ipso*-Ph), 139.4 (*ipso*-Ph), 128.9 (Ph), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.0 (Ph), 126.9 (Ph), 126.2 (Ph), 126.1 (Ph), 88.2 (Ph_2CO), 63.2 (NCH), 41.9 (NCH_2), 41.6 (*C*HPh), 35.6 (CH_2), 31.3 (CH_2); MS (ESI) *m/z* 370 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{23}NO_2$ $(M + H)^+$ 370.1802, found 370.1789 (+3.8 ppm error).

Lab Book Reference: GG1/67/1

4-Phenyl-2-phenylcarbamoylpiperidine-1-carboxylic acid *tert*-butyl ester *rac-syn*-159



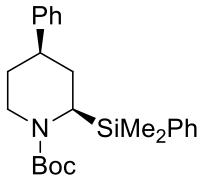
rac-syn-**159**

(Scheme 3.39)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.3 mmol, 1.3 eq.) in Et_2O (3.8 mL) at −78 °C for 1 h and then phenyl isocyanate (274 mg, 250 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-Et_2O as eluent gave 4-phenylpiperidine *rac-syn*-**159** (190 mg, 50%) as a white solid, mp 222-224 °C (lit.,[7] 225-226 °C); R_F (97:3 CH_2Cl_2-Et_2O) 0.2; IR ($CHCl_3$) 2982, 1692 (C=O), 1600, 1524, 1442, 1155, 905, 730, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H, NH), 7.53 (dd, J = 8.5, 1.0 Hz, 2H, Ph), 7.36-7.29 (m, 4H, Ph), 7.28-7.20 (m, 3H, Ph), 7.11 (tt, J = 7.5, 1.0 Hz, 1H, Ph), 4.38 (dd, J = 8.5, 8.5 Hz, 1H, NCH), 3.71-3.55 (m, 2H, NCH), 2.78 (dddd, J = 10.5, 10.5, 6.5, 6.5 Hz, 1H, CHPh), 2.31-2.19 (m, 2H, CH), 2.14 (dddd, J = 13.5, 6.5, 6.5, 6.5 Hz, 1H, CH), 1.75 (dddd, J = 13.5, 10.5, 6.0, 6.0 Hz, 1H, CH), 1.47 (s, 9H, CMe_3); MS (ESI) *m/z* 403 [$(M + Na)^+$, 100], 381 [$(M + H)^+$, 30], 325 (15), 281 (50); HRMS (ESI) *m/z* calcd for $C_{23}H_{28}N_2O_3$ $(M + H)^+$ 381.2173, found 381.2162 (+2.8 ppm error). Spectroscopic data consistent with those reported in the literature.[7]

Lab Book Reference: GG1/55/3

2-Dimethylphenylsilyl-4-phenylpiperidine-1-carboxylic acid *tert*-butyl ester *rac-syn*-160



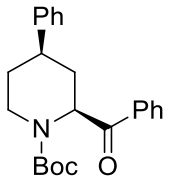
rac-syn-**160**

(Scheme 3.39)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.5 mmol, 1.3 eq.) at –78 °C for 1 h and then $PhMe_2SiCl$ (392 mg, 386 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave 4-phenylpiperidine *rac-syn*-**160** (407 mg, 90%) as a white solid, mp 144-145 °C; R_F (96:4 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3020, 1685 (C=O), 1425, 1218, 929, 782, 736, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 2H, Ph), 7.38-7.28 (m, 5H, Ph), 7.25-7.16 (m, 3H, Ph), 4.11 (br s, 1H, NCH), 3.09-2.91 (br m, 1H, NCH), 2.79-2.60 (br m, 1H, NCH), 2.67 (dddd, J = 12.0, 12.0, 4.0, 4.0 Hz, 1H, CHPh), 1.88-1.77 (m, 2H, CH), 1.73-1.54 (m, 2H, CH), 1.47 (s, 9H, CMe_3), 0.48 (s, 3H, SiMe), 0.44 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 146.4 (*ipso*-Ph), 142.1 (*ipso*-Ph), 134.3 (Ph), 128.7 (Ph), 128.5 (Ph), 127.7 (Ph), 127.1 (Ph), 126.5 (Ph), 79.3 (CMe_3), 50.1 (NCH), 47.8 (NCH_2), 44.4 (*C*HPh), 33.4 (CH_2), 28.1 (CMe_3), –2.7 (SiMe), –3.3 (SiMe); MS (ESI) *m/z* 418 $[(M + Na)^+, 70]$, 396 $[(M + H)^+, 80]$, 318 (100); HRMS (ESI) *m/z* calcd for $C_{24}H_{33}NO_2Si$ $(M + H)^+$ 396.2353, found 396.2348 (+1.1 ppm error).

Lab Book Reference: GG1/72/1

2-Benzoyl-4-phenylpiperidine-1-carboxylic acid *tert*-butyl ester *rac-syn*-161



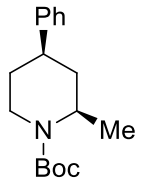
rac-syn-**161**

(Scheme 3.39)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and TMEDA (174 mg, 220 μL, 1.5 mmol, 1.3 eq.) at −78 °C for 1 h and then $PhCONMe_2$ (380 mg, 350 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1 to 8:2 petrol-EtOAc as eluent gave 4-phenylpiperidine *rac-syn*-**161** (192 mg, 45%) as a white solid, mp 155-157 °C; R_F (85:15 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3029, 2979, 1693 (C=O), 1450, 1408, 1250, 1157, 1016, 761, 731, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 2H, Ph), 7.54 (t, J = 7.5 Hz, 1H, Ph), 7.45 (t, J = 7.5 Hz, 2H, Ph), 7.33-7.28 (m, 2H, Ph), 7.24-7.18 (m, 3H, Ph), 4.80 (dd, J = 11.0, 4.5 Hz, 1H, NCH), 4.13-3.99 (m, 1H, NCH), 3.48 (ddd, J = 13.5, 9.0, 5.0 Hz, 1H, NCH), 2.87 (dddd, J = 11.5, 11.5, 4.0, 4.0 Hz, 1H, CHPh), 2.24 (dddd, J = 13.5, 5.0, 4.0, 1.5 Hz, 1H, CH), 2.12-2.03 (m, 1H, CH), 1.96-1.66 (m, 2H, CH), 1.28 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.9 (C=O), 145.2 (*ipso*-Ph), 136.0 (*ipso*-Ph), 133.1 (Ph), 128.8 (Ph), 128.7 (Ph), 128.5 (Ph), 127.0 (Ph), 126.8 (Ph), 81.1 (CMe_3), 60.5 (NCH), 43.7 (NCH_2), 40.0 ($CHPh$), 33.5 (CH_2), 31.3 (CH_2), 27.7 (CMe_3); MS (ESI) *m/z* 388 [$(M + Na)^+$, 95], 366 [$(M + H)^+$, 5], 310 (40), 266 (100); HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_3$ $(M + H)^+$ 366.2064, found 366.2062 (+0.8 ppm error).

Lab Book Reference: GG1/64/1

(2*R*,4*R*)-2-Methyl-4-phenylpiperidine-1-carboxylic acid *tert*-butyl ester (2*R*,4*R*)-148



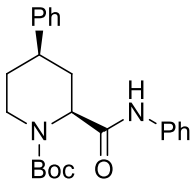
(2*R*,4*R*)-**148**

(Scheme 3.40)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (465 mg, 1.5 mmol, 1.3 eq.) at −78 °C for 1 h and then Me_2SO_4 (290 mg, 210 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave 4-phenylpiperidine (2*R*,4*R*)-**148** (70 mg, 22%, 91:9 er by CSP-HPLC)) as a colourless oil, $[\alpha]_D$ −68.8 (*c* 0.55 in $CHCl_3$) (lit.,[138] $[\alpha]_D$ −72.1 (*c* 0.6 in $CHCl_3$) for (2*R*,4*R*)-**148**); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (2*S*,4*S*)-**148** 15.9 min, (2*R*,4*R*)-**148** 17.3 and starting material **147** (152 mg, 50%) as a colourless oil.

Lab Book Reference: GG1/79/1

(2*R*,4*R*)-4-Phenyl-2-phenylcarbamoylpiperidine-1-carboxylic acid *tert*-butyl ester (2*R*,4*R*)-159



(2*R*,4*R*)-**159**

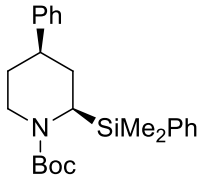
(Scheme 3.40)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (465 mg, 1.5 mmol, 1.3 eq.) in Et_2O (3.8 mL) at −78 °C under Ar for 1 h then, phenyl isocyanate (274 mg, 250 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-Et_2O as eluent gave 4-phenylpiperidine (2*R*,4*R*)-**159** (110 mg, 25%, 89:11 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −48.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (9:1 hexane-*i*-

PrOH, 1.0 mL min^{-1}) (2*S*,4*S*)-**159** 11.7 min, (2*R*,4*R*)-**159** 17.0 and starting material **47** (148 mg, 49%) as a colourless oil.

Lab Book Reference: GG1/74/1

(2*R*,4*R*)-2-Dimethylphenylsilyl-4-phenylpiperidine-1-carboxylic acid *tert*-butyl ester (2*R*,4*R*)-160



(2*R*,4*R*)-**160**

(Scheme 3.40)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.) 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (465 mg, 1.5 mmol, 1.3 eq.) at −78 °C for 1 h and then $PhMe_2SiCl$ (392 mg, 386 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave 4-phenylpiperidine (2*R*,4*R*)-**160** (138 mg, 31%, 90:10 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (2*S*,4*S*)-**160** 11.9 min, (2*R*,4*R*)-**160** 13.2 and starting material **147** (154 mg, 51%) as a colourless oil.

Lab Book Reference: GG1/77/1

(Table 3.3, Entry 2)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (465 mg, 1.5 mmol, 1.3 eq.) at −78 °C for 3 h and then $PhMe_2SiCl$ (392 mg, 386 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave 4-phenylpiperidine (2*R*,4*R*)-**160** (170 mg, 43%, 92:8 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −44.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (2*S*,4*S*)-**160** 12.0 min, (2*R*,4*R*)-**160** 13.2.

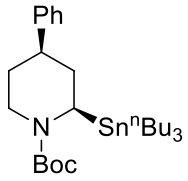
Lab Book Reference: GG1/84/1

(Table 3.3, Entry 3)

Using general procedure C: *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), 4-phenyl *N*-Boc piperidine **147** (300 mg, 1.15 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (465 mg, 1.5 mmol, 1.3 eq.) at –40 °C for 1 h and then $PhMe_2SiCl$ (392 mg, 386 μL, 2.3 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave 4-phenylpiperidine (2*R*,4*R*)-**160** (43 mg, 9%, 80:20 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (2*S*,4*S*)-**160** 11.8 min, (2*R*,4*R*)-**160** 13.0 and starting material **147** (193 mg, 64%) as a colourless oil.

Lab Book Reference: GG1/85/1

4-Phenyl-2-(tributylstannyl)piperidine-1-carboxylic acid *tert*-butyl ester *rac-syn*-162



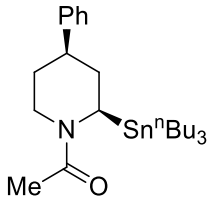
rac-syn-**162**

s-BuLi (4.0 mL of a 1.3 M solution in hexanes, 5.2 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-phenyl *N*-Boc piperidine **147** (1.04 g, 4.0 mmol, 1.0 eq.) and TMEDA (604 mg, 0.78 mL, 5.2 mmol, 1.3 eq.) in Et_2O (22 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 15 min. Then, Bu_3SnCl (1.63 mL, 6.0 mmol, 1.5 eq.) was added. The resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$) 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 stannyl piperidine *rac-syn*-**162** (1.52 g, 70%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2911, 2878, 1645 (C=O), 1405, 1217, 1148, 1125, 990, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H, Ph), 7.24-7.18 (m, 3H, Ph), 4.30-4.20 (m, 1H, NCH), 2.90 (td, J = 13.0, 2.5 Hz, 1H, NCH), 2.74-2.60 (m, 2H, NCH and CHPh), 1.93-1.86 (m, 1H, CH), 1.85-1.74 (m, 1H, CH), 1.77-1.58 (m, 2H, CH), 1.56-1.40 (m, 6H, CH_2), 1.45 (s, 9H, CMe_3), 1.29 (sextet, J = 7.5 Hz, 6H, CH_2Me), 0.88 (t, J = 7.5 Hz, 9H,

CH_2*Me*), 0.85-0.70 (m, 6H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 146.4 (*ipso*-Ph), 128.4 (Ph), 126.6 (Ph), 126.1 (Ph), 79.3 (*C*Me_3), 47.5 (NCH_2), 46.3 (NCH), 45.9 (*C*HPh), 38.4 (CH_2), 33.7 (CH_2), 29.2 (CH_2), 28.4 (C*Me*$_3$), 27.6 (CH_2), 13.8 (Me), 11.9 (CH_2); MS (ESI) *m/z* 552 [$(M + H)^+$, 100], 494 (30); HRMS (ESI) *m/z* calcd for $C_{28}H_{49}NO_2Sn$ $(M + H)^+$ 552.2863, found 552.2857 (–0.3 ppm error).

Lab Book Reference: GG3/83/1

4-Phenyl-2-(tributylstannyl)piperidin-1-yl ethanone *rac-syn*-163



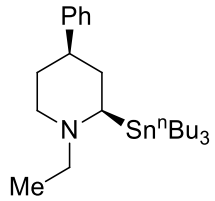
rac-syn-**163**

Me_3SiI (210 μL, 1.5 mmol, 1.3 eq.) was added to a stirred solution of stannyl piperidine *rac-syn*-**162** (630 mg, 1.14 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (2 mL) and CH_2Cl_2 (15 mL) were added and the layers were separated. The organic layer was washed with water (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (13 mL) and then DMAP (13 mg, 0.11 mmol, 0.1 eq.) and acetyl chloride (98 mg, 90 μL, 1.25 mmol, 1.1 eq.) were added at 0 °C under Ar. Then, Et_3N (346 mg, 480 μL, 3.42 mmol, 3.0 eq.) was added and the reaction mixture was stirred at rt for 16 h. Then, saturated $NaHCO_{3(aq)}$ (25 mL) and CH_2Cl_2 (25 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 petrol-EtOAc as eluent gave *N*-acetyl stannyl piperidine *rac-syn*-**163** (182 mg, 32%) as a colourless oil, R_F (90:10 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2911, 2878, 2827, 1593 (C=O), 1431, 888, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H, Ph), 7.26-7.18 (m, 3H, Ph), 4.01 (ddd, *J* = 13.5, 4.0, 2.5 Hz, 1H, NCH), 3.27 (ddd, *J* = 13.5, 13.5, 2.5 Hz, 1H, NCH), 2.78 (dddd, *J* = 12.0, 12.0, 4.0, 4.0 Hz, 1H, CHPh), 2.53 (dd, *J* = 13.5, 2.0 Hz, 1H, NCH), 2.13 (s, 3H, Me), 2.01-1.90 (m, 2H, CH), 1.81-1.63 (m, 2H, CH), 1.59-1.40 (m, 6H, CH_2), 1.30 (sextet, *J* = 7.5 Hz, 6H, CH_2Me), 0.89 (t, *J* = 7.5 Hz, 9H, CH_2*Me*), 0.86-0.77 (m, 6H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3 (C=O), 145.6 (*ipso*-Ph), 128.5 (Ph), 126.8 (Ph), 126.4

(Ph), 49.9 (NCH_2), 45.9 (*C*HPh), 44.7 (NCH), 38.3 (CH_2), 34.4 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 21.5 (Me), 13.8 (Me), 12.0 (CH_2); MS (ESI) *m/z* 494 [$(M + H)^+$, 100], 436 (20); HRMS (ESI) *m/z* calcd for $C_{25}H_{43}NOSn$ $(M + H)^+$ 492.2287, found 492.2251 (+6.5 ppm error).

Lab Book Reference: GG3/91/1

_N_-Ethyl-4-phenyl-2-(tributylstannyl)piperidine *rac-syn*-164

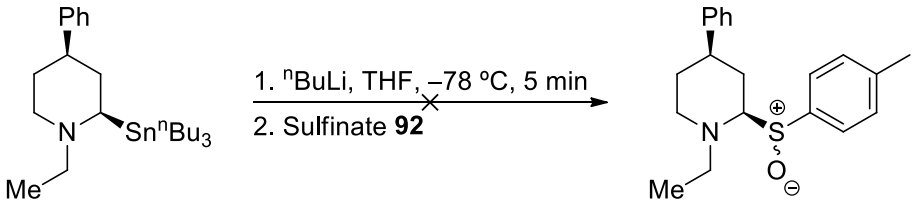


rac-syn-**164**

A solution of *N*-acetyl stannyl piperidine *rac-syn*-**163** (180 mg, 0.36 mmol, 1.0 eq.) in Et_2O (0.25 mL) was added to a stirred suspension of $LiAlH_4$ (29 mg, 0.77 mmol, 2.1 eq.) in Et_2O (0.9 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 20 min and then at rt for 1 h. Then, MeOH (0.5 mL) was carefully added followed by basic alumina and the solvent was evaporated under reduced pressure. Purification by flash column chromatography on basic alumina column with 98:2 petrol-EtOAc 98:2 as eluent gave *N*-ethyl stannyl piperidine *rac-syn*-**164** (128 mg, 74%) as a colourless oil, IR ($CHCl_3$) 2913, 2882, 2828, 1602, 1435, 1357, 1057, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H, Ph), 7.26-7.18 (m, 3H, Ph), 3.30-3.18 (m, 1H, NCH), 2.83-2.68 (m, 1H, CHPh), 2.60-2.50 (m, 1H, NCH), 2.48-2.35 (m, 1H, NCH), 2.34-2.20 (m, 1H, NCH), 2.05-1.90 (m, 3H, NCH and CH), 1.89-1.81 (m, 2H, CH), 1.58-1.39 (m, 6H, CH_2), 1.32 (sextet, J = 7.5 Hz, 6H, CH_2Me), 1.09 (t, J = 7.0 Hz, 3H, NCH_2*Me*), 0.97-0.79 (m, 6H, CH_2), 0.90 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.9 (*ipso*-Ph), 128.4 (Ph), 126.9 (Ph), 126.0 (Ph), 58.0 (NCH), 54.0 (NCH_2), 45.2 (*C*HPh), 39.7 (NCH_2), 33.2 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 27.5 (CH_2), 13.8 (Me), 11.8 (Me), 9.3 (CH_2); MS (ESI) *m/z* 480 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{45}NSn$ $(M + H)^+$ 480.2651, found 480.2651 (–0.2 ppm error).

Lab Book Reference: GG3/92/1

Attempted synthesis of *N*-ethyl-4-phenyl-2-(*p*-tolylsulfinyl)piperidine *rac-syn*-112

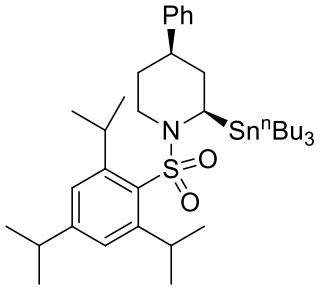


rac-syn-**164** *rac-syn*-**112**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.25 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-ethyl stannyl piperidine *rac-syn*-**164** (190 mg, 0.19 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, *p*-tolylsulfinate **92** (47 mg, 0.28 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (0.3 mL) and saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed no identifiable products and therefore purification was not attempted.

Lab Book Reference: GG3/96

4-Phenyl-2-(tributylstannyl)-1-(2,4,6-triisopropylphenylsulfonyl)piperidine *rac-syn*-165



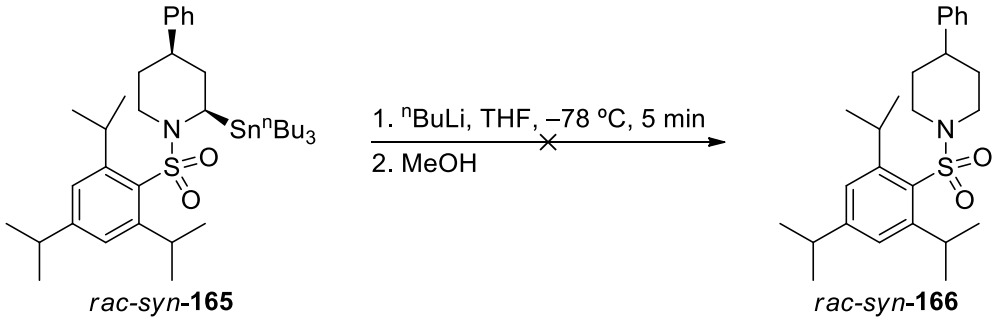
rac-syn-**165**

Me_3SiI (280 μL, 1.95 mmol, 1.3 eq.) was added to a stirred solution of stannyl piperidine *rac-syn*-**162** (825 mg, 1.5 mmol, 1.0 eq.) in CH_2Cl_2 (11 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (3 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The organic layer was washed with water (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (17 mL) and then, DMAP (18 mg, 0.15 mmol, 0.1 eq.) and 2,4,6-triisopropylsulfonyl chloride (500 mg, 1.65 mmol, 1.1 eq.)

were added at 0 °C under Ar. Then, Et_3N (455 mg, 630 μL, 4.5 mmol, 3.0 eq.) was added and the reaction mixture was stirred at rt for 24 h. Then, saturated $NaHCO_{3(aq)}$ (25 mL) and CH_2Cl_2 (25 mL) were added and the two layers separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (25 mL) and brine (25 mL), dried ($MgSO_4$) 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 stannyl piperidine *rac-syn*-**165** (452 mg, 42%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.1; IR ($CHCl_3$) 2914, 2882, 2826, 1439, 1270, 1127, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H, Ph), 7.25-7.18 (m, 3H, Ph), 7.16 (s, 2H, Ar), 4.28 (septet, *J* = 7.0 Hz, 2H, ArC*H*), 3.37 (ddd, *J* = 12.0, 3.5, 3.5 Hz, 1H, NCH), 2.90 (m, 2H, ArC*H* and PhC*H*), 2.84 (dd, *J* = 13.0, 2.0 Hz, 1H, NCH), 2.68-2.57 (m, 1H, NCH), 2.15-2.06 (m, 1H, CH), 1.93 (m, 1H, CH), 1.84-1.76 (m, 2H, CH), 1.64-1.43 (m, 6H, CH_2), 1.34 (sextet, *J* = 7.5 Hz, 6H, CH_2Me), 1.28 (d, *J* = 7.0 Hz, 6H, Me), 1.26 (d, *J* = 7.0 Hz, 12H, Me), 1.01 (m, 6H, CH_2), 0.91 (t, *J* = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.2 (*ipso*-Ar), 151.9 (*ipso*-Ar), 145.8 (*ipso*-Ar), 129.8 (*ipso*-Ar), 128.5 (Ar), 126.8 (Ar), 126.4 (Ar), 123.9 (Ar), 49.9 (NCH_2), 45.7 (*C*HPh), 44.6 (NCH), 38.4 (CH_2), 34.1 (Ar*C*H), 32.3 (CH_2), 29.2 (CH_2), 29.1 (Ar*C*H), 27.6 (CH_2), 25.0 (Me), 24.7 (Me), 23.5 (Me), 13.8 (Me), 11.6 (CH_2); MS (ESI) *m/z* 718 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{38}H_{63}NO_2SSn$ $(M + H)^+$ 718.3680, found 718.3667 (+1.5 ppm error).

Lab Book Reference: GG3/87/1

Attempted synthesis of 4-phenyl-1-(2,4,6-triisopropylphenylsulfonyl)piperidine *rac-syn*-166



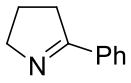
rac-syn-**165** *rac-syn*-**166**

n-BuLi (100 μL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl piperidine *rac-syn*-**165** (143 mg, 0.2 mmol, 1.0 eq.) in THF (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, MeOH (13 mg, 16 μL, 0.4 mmol, 2.0 eq.) was added. The resulting

solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) 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 stannyl piperidine *rac-syn*-**165** (74 mg, 52%) as a colourless oil.
Lab Book Reference: GG3/89

5.5 Experimental for Chapter Four

2-Phenylpyrroline 237

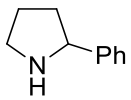


237

Et_3N (8.5 mL, 61.7 mmol, 1.05 eq.) was added to a stirred solution of pyrrolidin-2-one **236** (5.0 g, 58.7 mmol, 1.0 eq.) in Et_2O (150 mL) at rt under Ar. The mixture was cooled to 0 °C and Me_3SiCl (7.8 mL, 61.7 mmol, 1.05 eq.) was added dropwise. Then, the mixture was stirred and heated at reflux for 2 h. After being allowed to cool to rt, the solids were removed by filtration. Then, PhMgCl (29.3 mL of a 2.0 M THF, 58.7 mmol, 1.05 eq.) was added to the filtrate under Ar and the resulting mixture was stirred and heated at reflux for 3 h. After being allowed to cool to rt, 1 M $HCl_{(aq)}$ (30 mL) was added and the two layers were separated. The aqueous layer was basified to pH 10 by the addition of 2 M $NaOH_{(aq)}$ solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 petrol-EtOAc as eluent gave 2-phenylpyrroline **237** (1.55 g, 18%) as a colourless oil, R_F (50:50 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.83 (m, 2H, Ph), 7.49-7.38 (m, 3H, Ph), 4.08 (tt, J = 7.5, 2.0 Hz, 2H, NCH_2), 2.97 (tt, J = 8.0, 2.0 Hz, 2H, CH_2), 2.05 (tt, J = 8.0, 7.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=N), 134.5 (*ipso*-Ph), 130.3 (Ph), 128.4 (Ph), 127.6 (Ph), 61.4 (NCH_2), 34.9 (CH_2), 22.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[125]

Lab Book Reference: GG4/1/1

2-Phenylpyrrolidine *rac*-190



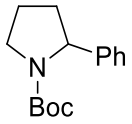
rac-**190**

$NaBH_4$ (325 mg, 8.6 mmol, 1.1 eq.) was added to a stirred solution of 2-phenylpyrroline **237** (1.14 g, 7.8 mmol, 1.0 eq.) in 4:1 MeOH-water (27 mL) at rt. The resulting mixture was stirred at rt for 16 h. Then, 2 M $HCl_{(aq)}$ was added until pH ~ 2 was obtained and the mixture was stirred for 30 min. Then, 2 M $NaOH_{(aq)}$ was added until pH ~ 13 was

obtained and the aqueous mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave 2-phenylpyrrolidine *rac*-**190** (1.1 g, 96%) as a colourless oil, bp 110-115 °C/4.0 mmHg (lit.,[139] 101-103 °C/0.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 4.12 (dd, J = 7.5, 7.5 Hz, 1H, NCH), 3.22 (ddd, J = 10.0, 8.0, 5.5 Hz, 1H, NCH), 3.02 (ddd, J = 10.0, 8.0, 7.0 Hz, 1H, NCH), 2.25-2.15 (m, 1H, CH), 1.99 (s, 1H, NH), 1.98-1.81 (m, 2H, CH), 1.74-1.63 (m, 1H, CH). Spectroscopic data consistent with those reported in the literature.[139]

Lab Book Reference: GG4/2/1

2-Phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-70

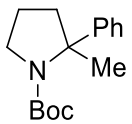


rac-**70**

A solution of di-*tert*-butyl dicarbonate (1.7 g, 7.8 mmol, 1.1 eq.) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of 2-phenylpyrrolidine *rac*-**190** (1.05 g, 7.1 mmol, 1.0 eq.) in CH_2Cl_2 (16 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, water (25 mL) and CH_2Cl_2 (12 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave phenyl pyrrolidine *rac*-**70** (1.6 g, 92%) as a white solid, mp 57-58 °C (lit.,[56] 61.9-62.7 °C); R_F (98:2 CH_2Cl_2-Et_2O) 0.4. Spectroscopic data consistent with those reported in the literature.[56]

Lab Book Reference: GG4/3/1

2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-232



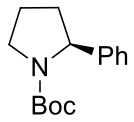
rac-**232**

n-BuLi (2.76 mL of a 2.5 M solution in hexanes, 6.9 mmol, 1.3 eq.) was added dropwise to a stirred solution of phenyl pyrrolidine *rac*-**70** (1.3 g, 5.3 mmol, 1.0 eq.) in

THF (29 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 min. Then, Me_2SO_4 (1.34 g, 1.0 mL, 1.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at 0 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine *rac*-**232** (1.37 g, 99%) as a colourless oil, R_F (80:20 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.33-7.15 (m, 5H, Ph), 3.75-3.56 (m, 2H, NCH), 2.12-1.99 (m, 2H, CH), 1.94-1.79 (m, 2H, CH), 1.76 (s, 3H, Me), 1.46 (s, 2.25H, CMe_3), 1.13 (s, 6.75H, CMe_3). Spectroscopic data consistent with those reported in the literature.[63]

Lab Book Reference: GG4/13/1

(*S*)-2-Phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-70



(S)-**70**

(Scheme 4.32)

s-BuLi (4.6 mL of a 1.3 M solution in hexanes, 6.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (856 mg, 5.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (1.17 g, 6.0 mmol, 1.2 eq.) in Et_2O (12 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 2 min. Then, $ZnCl_2$ (3.0 mL of a 1.0 M solution in Et_2O, 3.0 mmol, 0.6 eq.) was added and the resulting mixture was stirred at –30 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, bromobenzene (1.0 g, 680 μL, 6.5 mmol, 1.3 eq.) and a mixture of *t*-Bu_3PHBF_4 (94 mg, 0.325 mmol, 0.0625 eq.) and $Pd(OAc)_2$ (56 mg, 0.25 mmol, 0.05 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.5 mL) and Et_2O (10 mL) were added and mixture was stirred for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (15 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (15 mL) and water (2 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-Et_2O as eluent gave phenyl pyrrolidine (*S*)-**70** (608 mg, 50%, 90:10 er by

CSP-HPLC) as a white solid, mp 57-58 °C (lit.,[56] 61.9-62.7 °C); $[\alpha]_D$ −64.6 (*c* 1.0 in $CHCl_3$); $[\alpha]_D$ −62.0 (*c* 1.0 in acetone) (lit.,[13] $[\alpha]_D$ +83.2 (*c* 0.7 in acetone) for (*R*)-**70** of 95:5 er); R_F (99:1 CH_2Cl_2-Et_2O) 0.3; CSP-HPLC: Chiralcel AD-H (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**70** 11.8 min, (*S*)-**70** 12.8 min. Spectroscopic data consistent with those reported in the literature.[56]

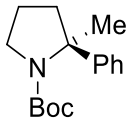
Lab Book Reference: GG4/33/1

(Scheme 4.31)

s-BuLi (3.38 mL of a 1.3 M solution in hexanes, 4.4 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (685 mg, 0.7 mL, 4.0 mmol, 1.0 eq.) and (+)-sparteine surrogate (855 mg, 4.4 mmol, 1.1 eq.) in Et_2O (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, $ZnCl_2$ (2.4 mL of a 1.0 M solution in Et_2O, 2.4 mmol, 0.6 eq.) was added and the resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, bromobenzene (753 mg, 500 μL, 4.8 mmol, 1.2 eq.) and a mixture of *t*-Bu_3PHBF_4 (58 mg, 0.2 mmol, 0.05 eq.) and $Pd(OAc)_2$ (36 mg, 0.16 mmol, 0.04 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.3 mL) and Et_2O (10 mL) were added and mixture was stirred for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (15 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (10 mL) and water (2 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-Et_2O as eluent gave phenyl pyrrolidine (*S*)-**70** (561 mg, 57%, 94:6 er by CSP-HPLC) as a white solid, R_F (99:1 CH_2Cl_2-Et_2O) 0.3; CSP-HPLC: Chiralcel AD-H (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**70** 14.1 min, (*S*)-**70** 15.6 min.

Lab Book Reference: GG5/94/1

(*S*)-2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-232



(*S*)-**232**

(Table 4.2, Entry 1)

Using general procedure D: *n*-BuLi (90 μL of a 2.5 M solution in hexanes, 0.22 mmol, 1.1 eq.), phenyl pyrrolidine (*S*)-**70** (49 mg, 0.2 mmol, 1.0 eq., 94:6 er) and TMEDA (25 mg, 33 μL, 0.22 mmol, 1.1 eq.) in Et_2O (2 mL) at –50 °C under Ar for 5 min. Then, Me_2SO_4 (38 mg, 28 μL, 0.3 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (12 mg, 23%, 93:7 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 7.0 min, (*R*)-**232** 7.9 min.

Lab Book Reference: GG5/97/1

(Table 4.2, Entry 2)

Using general procedure D: *n*-BuLi (620 μL of a 2.5 M solution in hexanes, 1.56 mmol, 1.1 eq.), phenyl pyrrolidine (*S*)-**70** (350 mg, 1.42 mmol, 1.0 eq., 94:6 er) and TMEDA (181 mg, 230 μL, 1.56 mmol, 1.1 eq.) in Et_2O (14 mL) at –50 °C under Ar for 30 min. Then, Me_2SO_4 (269 mg, 200 μL, 2.13 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (362 mg, 97%, 94:6 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 7.6 min, (*R*)-**232** 8.6 min.

Lab Book Reference: GG6/3/1

(Table 4.2, Entry 3)

Using general procedure D: *n*-BuLi (90 μL of a 2.5 M solution in hexanes, 0.22 mmol, 1.1 eq.), phenyl pyrrolidine (*S*)-**70** (49 mg, 0.2 mmol, 1.0 eq., 94:6 er) and TMEDA (25 mg, 33 μL, 0.22 mmol, 1.1 eq.) in Et_2O (2 mL) at –30 °C under Ar for 30 min. Then, Me_2SO_4 (38 mg, 28 μL, 0.3 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (49 mg, 94%, 91:9 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 6.9 min, (*R*)-**232** 7.9 min.

Lab Book Reference: GG5/98/1

(Table 4.2, Entry 4)

Using general procedure D: *n*-BuLi (90 μL of a 2.5 M solution in hexanes, 0.22 mmol, 1.1 eq.), phenyl pyrrolidine (*S*)-**70** (49 mg, 0.2 mmol, 1.0 eq., 94:6 er) and TMEDA (25 mg, 33 μL, 0.22 mmol, 1.1 eq.) in Et_2O (2 mL) at –30 °C under Ar for 1 h. Then, Me_2SO_4 (38 mg, 28 μL, 0.3 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (50 mg, 96%, 92:8 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 7.0 min, (*R*)-**232** 7.9 min.

Lab Book Reference: GG5/99/1

(Table 4.2, Entry 5)

Using general procedure D: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), phenyl pyrrolidine (*S*)-**70** (24 mg, 0.1 mmol, 1.0 eq., 94:6 er) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in THF (1 mL) at –50 °C under Ar for 30 min. Then, Me_2SO_4 (19 mg, 14 μL, 0.15 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (6 mg, 23%, 58:42 er by CSP-HPLC) as an off-white solid, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 6.6 min, (*R*)-**232** 7.5 min and recovered phenyl pyrrolidine (*S*)-**70** (13 mg, 53%).

Lab Book Reference: GG6/67/1

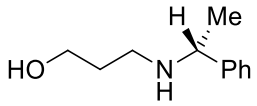
(Scheme 4.34)

n-BuLi (1.16 mL of a 2.5 M solution in hexanes, 2.9 mmol, 1.3 eq.) was added dropwise to a stirred solution of phenyl pyrrolidine (*S*)-**70** (550 mg, 2.24 mmol, 1.0 eq., 90:10 er) in THF (16 mL) at –50 °C under Ar. The resulting solution was stirred at –50 °C for 5 min. Then, Me_2SO_4 (565 mg, 420 μL, 4.5 mmol, 2.0 eq.) was added. The resulting solution was stirred at –50 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with

80:20 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (433 mg, 74%, 80:20 er by CSP-HPLC) as an off-white solid, $[\alpha]_D$ −49.6 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +54.0 (*c* 1.0 in $CHCl_3$) for (*R*)-**232** of 98:2 er); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 6.6 min, (*R*)-**232** 7.5 min.

Lab Book Reference: GG4/37/1

(*R*)-3-(1-Phenylethylamino)propan-1-ol (*R*)-239

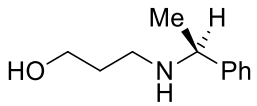


(*R*)-**239**

Using general procedure E: 3-Chloro-1-propanol (2.3 g, 2.0 mL, 23.9 mmol, 1.0 eq.), (*R*)-(+)-α-methylbenzylamine (*R*)-**238** (5.8 g, 6.1 mL, 47.9 mmol, 2.0 eq.) and water (0.7 mL) gave the crude product. Purification by Kügelrohr distillation gave amino alcohol (*R*)-**239** (4.1 g, 95%) as a colourless oil, bp 106-108 °C/0.6 mmHg; $[\alpha]_D$ +45.6 (*c* 0.65 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +51.6 (*c* 1.2 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H, Ph), 3.80-3.72 (m, 3H, CH_2OH + NCH), 2.96 (br s, 1H, NH), 2.83-2.75 (m, 1H), 2.71-2.63 (m, 1H), 1.79-1.68 (m, 1H), 1.67-1.57 (m, 1H), 1.39 (d, *J* = 6.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.8 (*ipso*-Ph), 128.5 (Ph), 127.0 (Ph), 126.4 (Ph), 64.1 (OCH_2), 58.6 (NCH), 47.7 (NCH_2), 31.2 (CH_2), 24.1 (Me). Spectroscopic data consistent with those reported in the literature.[63]

Lab Book Reference: GG4/26/1

(*S*)-3-(1-Phenylethylamino)propan-1-ol (*S*)-239

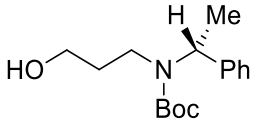


(*S*)-**239**

Using general procedure E: 3-chloro-1-propanol (2.3 g, 2.0 mL, 23.9 mmol, 1.0 eq.) and (*S*)-(+)-α-methylbenzylamine (*S*)-**238** (5.8 g, 6.1 mL, 47.9 mmol, 2.0 eq.) in water (0.7 mL) gave the crude product. Purification by Kügelrohr distillation gave the amino alcohol (*S*)-**239** (3.65 g, 85%) as a colourless oil, $[\alpha]_D$ –47.7 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +51.6 (*c* 1.2 in $CHCl_3$) for (*R*)-**239**).

Lab Book Reference: GG4/27/1

(*R*)-*tert*-Butyl 3-hydroxypropyl(1-phenylethyl)carbamate (*R*)-240

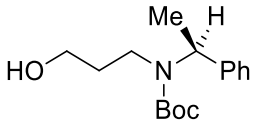


(*R*)-**240**

Using general procedure F: a solution of di-*tert*-butyl dicarbonate (5.0 g, 22.9 mmol, 1.0 eq.) in CH_2Cl_2 (14 mL) and amino alcohol (*R*)-**239** (4.1 g, 22.9 mmol, 1.0 eq.) in CH_2Cl_2 (57 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave *N*-Boc-amino alcohol (*R*)-**240** (5.83 g, 91%) as a colourless oil, R_F (80:20 petrol-Et_2O) 0.2; $[\alpha]_D$ +70.0 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +75.8 (*c* 1.0 in $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, Ph), 5.22 (br s, 1H, NCH), 3.57-3.45 (m, 2H, CH_2OH), 3.43-3.06 (br m, 2H), 2.62 (br s, 1H), 1.66-1.27 (br m, 2H), 1.56 (d, *J* = 7.0 Hz, 3H, Me), 1.46 (s, 9H, CMe_3).

Lab Book Reference: GG4/29/1

(*S*)-3-(1-Phenylethylamino)propan-1-ol (*S*)-240

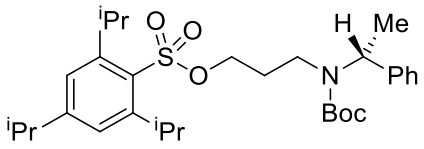


(*S*)-**240**

Using general procedure F: di-*tert*-butyl dicarbonate (4.45 g, 20.4 mmol, 1.0 eq.) in CH_2Cl_2 (11 mL) and amino alcohol (*S*)-**239** (3.65 g, 20.4 mmol, 1.0 eq.) in CH_2Cl_2 (45 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave *N*-Boc-amino alcohol (*S*)-**240** (5.5 g, 96%) as a colourless oil, $[\alpha]_D$ −72.3 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +75.8 (*c* 1.0 in $CHCl_3$) for (*R*)-**240**).

Lab Book Reference: GG4/30/1

(*R*)-3-(*tert*-Butoxycarbonyl(1-phenylethyl)amino)propyl 2,4,6-tri-*i*-propyl-benzenesulfonate (*R*)-241

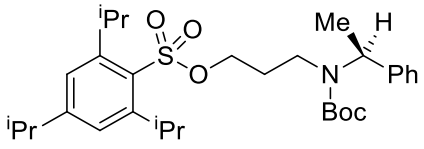


(*R*)-**241**

Using general procedure G: 2,4,6-Tri-*i*-propyl-benzenesulfonyl chloride (7.57 g, 21.9 mmol, 1.05 eq.), *N*-Boc amino alcohol (*R*)-**240** (5.83 g, 20.9 mmol, 1.0 eq.), Et_3N (2.5 g, 3.5 mL, 25.1 mmol, 1.2 eq.) and DMAP (256 mg, 2.1 mmol, 0.1 eq.) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10-80:20 petrol-Et_2O as eluent gave *N*-Boc amino sulfonate (*R*)-**241** (8.4 g, 74%) as a colourless oil, R_F (90:10 petrol-Et_2O) 0.1; $[\alpha]_D$ +44.4 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +41.7 (*c* 1.0 in $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H, Ph), 7.17 (s, 2H, Ar), 5.70-5.06 (br m, 1H, NCH), 4.08 (septet, *J* = 7.0 Hz, 2H, C*H*Me_2), 4.01-3.78 (br m, 2H), 3.03 (br s, 2H), 2.91 (septet, *J* = 7.0 Hz, 1H, C*H*Me_2), 1.93-1.57 (br m, 2H), 1.51 (d, *J* = 7.0 Hz, 3H, Me), 1.44 (s, 9H, CMe_3), 1.29-1.17 (m, 18H, CH*Me*$_2$). Spectroscopic data consistent with those reported in the literature.[63]

Lab Book Reference: GG4/31/1

(*S*)-3-(*tert*-Butoxycarbonyl(1-phenylethyl)amino)propyl 2,4,6-tri-*i*-propyl-benzenesulfonate (*S*)-241

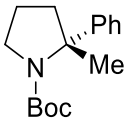


(*S*)-**241**

Using general procedure G: 2,4,6-tri-*i*-propyl-benzenesulfonyl chloride (6.27 g, 20.7 mmol, 1.05 eq.), *N*-Boc amino alcohol (*S*)-**240** (5.5 g, 19.7 mmol, 1.0 eq.), Et_3N (2.4 g, 3.3 mL, 23.6 mmol, 1.2 eq.) and DMAP (240 mg, 1.97 mmol, 0.1 eq.) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10-80:20 petrol-Et_2O as eluent gave *N*-Boc amino sulfonate (*S*)-**241** (8.5 g, 79%) as a colourless oil, $[\alpha]_D$ –43.4 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +41.7 (*c* 1.0 in $CHCl_3$) for (*R*)-**241**).

Lab Book Reference: GG4/32/1

(*R*)-2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-232

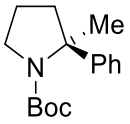


(*R*)-**232**

Using general procedure H: *s*-BuLi (8.0 mL of a 1.3 M solution in hexanes, 10.4 mmol, 1.3 eq.), *N*-Boc amino sulfonate (*R*)-**241** (4.36 g, 8.0 mmol, 1.0 eq.) and TMEDA (1.2 g, 1.56 mL, 10.4 mmol, 1.3 eq.) in Et_2O (56 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine (*R*)-**232** (1.81 g, 87%, 98:2 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +60.0 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +54.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 6.6 min, (*R*)-**232** 7.5 min.

Lab Book Reference: GG4/44/1

(*S*)-2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-232

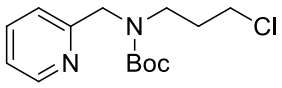


(*S*)-**232**

Using general procedure H: *s*-BuLi (8.0 mL of a 1.3 M solution in hexanes, 10.4 mmol, 1.3 eq.), *N*-Boc amino sulfonate (*S*)-**241** (4.36 g, 8.0 mmol, 1.0 eq.) and TMEDA (1.2 g, 1.56 mL, 10.4 mmol, 1.3 eq.) in Et_2O (56 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine (*S*)-**232** (1.87 g, 89%, 98:2 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –60.9 (*c* 1.0 in $CHCl_3$) (lit.,[63] $[\alpha]_D$ +54.0 (*c* 1.0 in $CHCl_3$) for (*R*)-**232**); CSP-HPLC: Chiralcel OD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**232** 6.5 min, (*R*)-**232** 7.8 min.

Lab Book Reference: GG4/45/1

***tert*-Butyl 3-chloropropyl-pyridin-2-ylmethyl-carbamate 245**



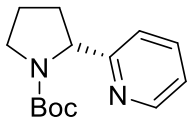
245

Using general procedure I: $NaBH(OAc)_3$ (5.9 g, 28 mmol, 1.4 eq.), 3-chloropropylamine hydrochloride **244** (2.6 g, 20 mmol, 1.0 eq.) and 2-pyridinecarboxaldehyde **243** (2.14 g, 1.9 mL, 20 mmol, 1.eq.) in 1,2-dichloroethane (80

mL), then di-*tert*-butylcarbonate (4.36 g, 20 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2-Et_2O as eluent gave *N*-Boc chloro-propylamine **245** (1.8 g, 32%) as a colourless oil, R_F (90:10 CH_2Cl_2-Et_2O) 0.2; IR (ATR) 2976, 1690 (C=O), 1409, 1366, 1245, 1159, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) 8.54 (s, 0.5H, Ar), 8.53 (s, 0.5H, Ar), 7.67 (dd, *J* = 7.5, 7.5 Hz, 0.5H, Ar), 7.66 (dd, *J* = 7.5, 7.5 Hz, 0.5H, Ar), 7.33-7.23 (m, 1H, Ar), 7.19 (d, *J* = 5.0 Hz, 0.5H, Ar), 7.18 (d, *J* = 5.0 Hz, 0.5H, Ar), 4.58 (s, 1H, NCH_2), 4.54 (s, 1H, NCH_2), 3.61-3.37 (m, 4H, NCH_2 + CH_2Cl), 2.11-1.91 (m, 2H, CH_2), 1.51 (s, 4.5H, CMe_3), 1.39 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 158.6 (*ipso*-Ar), 158.2 (*ipso*-Ar), 155.8 (C=O), 155.6 (C=O), 149.1 (Ar), 136.8 (Ar), 136.6 (Ar), 122.2 (Ar), 122.1 (Ar), 121.7 (Ar), 120.6 (Ar), 80.1 (*C*Me_3), 53.3 (NCH_2), 52.4 (NCH_2), 45.5 (NCH_2), 45.0 (NCH_2), 42.5 (CH_2Cl), 42.3 (CH_2Cl), 31.3 (CH_2), 28.4 (C*Me*$_3$); MS (ESI) *m/z* 285 [$(M + H)^+$, 20], 229 (100); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}{}^{35}ClN_2O_2$ $(M + H)^+$ 285.1364, found 285.1356 (+3.0 ppm error).

Lab Book Reference: GG6/44/1

2-Pyridin-2-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-211



(*R*)-**211**

(Table 4.3, Entry 3)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **245** (57 mg, 0.2 mmol, 1.0 eq.) and (+)-sparteine surrogate (50 mg, 0.26 mmol, 1.3 eq.) in toluene (2 mL) gave the crude product. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-Et_2O as eluent gave recovered starting material **245** (24 mg, 42%) and pyrrolidine (*R*)-**211** (29 mg, 58%, 60:40 er by CSP-HPLC) as a colourless oil, R_F (80:20 CH_2Cl_2-Et_2O) 0.1; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.58-8.50 (m, 1H, Ar), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 7.22-7.09 (m, 2H, Ar), 5.02 (br d, *J* = 5.5 Hz, 0.35H, NCH), 4.88 (dd, *J* = 8.0, 4.5 Hz, 0.65H, Ar), 3.72-3.45 (m, 2H, NCH), 2.47-2.22 (m, 1H, CH), 2.13-1.82 (m, 3H, CH), 1.46 (s, 3.15H, CMe_3), 1.20 (s, 5.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 163.7 (*ipso*-Ar), 154.5 (C=O), 149.2 (Ar), 148.9

(Ar), 136.4 (Ar), 136.2 (Ar), 121.5 (Ar), 120.1 (Ar), 119.6 (Ar), 79.3 (*C*Me_3), 62.8 (NCH), 62.1 (NCH), 47.4 (NCH_2), 47.0 (NCH_2), 34.2 (CH_2), 28.4 (C*Me*$_3$), 28.1 (C*Me*$_3$), 23.7 (CH_2), 23.2 (CH_2); CSP-HPLC: Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**211** 3.8 min, (*S*)-**211** 6.7 min. Spectroscopic data consistent with those reported in the literature.[30]

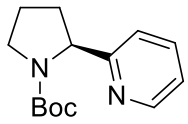
Lab Book Reference: GG6/46/1

(Table 4.3, Entry 4)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **245** (57 mg, 0.2 mmol, 1.0 eq.) and (+)-sparteine surrogate (50 mg, 0.26 mmol, 1.3 eq.) in Et_2O (2 mL) gave the crude product. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-Et_2O as eluent gave recovered starting material **245** (24 mg, 42%) and pyrrolidine (*R*)-**211** (29 mg, 58%, 62:38 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**211** 3.8 min, (*S*)-**211** 6.7 min.

Lab Book Reference: GG6/47/1

2-Pyridin-2-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-211



(*S*)-**211**

(Table 4.3, Entry 1)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **245** (57 mg, 0.2 mmol, 1.0 eq.) and (–)-sparteine (60 μL, 0.26 mmol, 1.3 eq.) in toluene (2 mL) gave the crude product. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-Et_2O as eluent gave pyrrolidine (*S*)-**211** (41 mg, 82%, 51:49 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**211** 3.8 min, (*S*)-**211** 6.6 min.

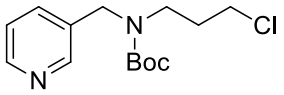
Lab Book Reference: GG6/48/1

(Table 4.3, Entry 2)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **245** (57 mg, 0.2 mmol, 1.0 eq.) and (–)-sparteine (60 μL, 0.26 mmol, 1.3 eq.) in Et_2O (2 mL) gave the crude product. Purification by flash column chromatography on silica with 50:50 CH_2Cl_2-Et_2O as eluent gave recovered starting material **245** (24 mg, 42%) and pyrrolidine (*S*)-**211** (28 mg, 56%, 50:50 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**211** 3.8 min, (*S*)-**211** 6.6 min.

Lab Book Reference: GG6/49/1

tert-Butyl 3-chloropropyl-pyridin-3-ylmethyl-carbamate 246

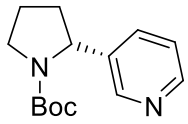


246

Using general procedure I: $NaBH(OAc)_3$ (5.9 g, 28 mmol, 1.4 eq.), 3-chloropropylamine hydrochloride **244** (2.6 g, 20 mmol, 1.0 eq.) and 3-pyridinecarboxaldehyde (2.14 g, 1.9 mL, 20 mmol, 1.eq.) in 1,2-dichloroethane (80 mL), then di-*tert*-butylcarbonate (4.36 g, 20 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 CH_2Cl_2-Et_2O as eluent gave N-Boc propylamine **246** (2.2 g, 39%) as a colourless oil, R_F (70:30 CH_2Cl_2-Et_2O) 0.2; IR (ATR) 2975, 1685 (C=O), 1411, 1365, 1248, 1158, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.60-8.47 (m, 2H, Ar), 7.68-.7.51 (m, 1H, Ar), 7.32-7.26 (m, 1H, Ar), 4.46 (s, 2H, NCH_2), 3.54 (br s, 2H, NCH_2), 3.44-3.24 (m, 2H, CH_2Cl), 2.08-1.88 (m, 2H, CH_2), 1.49 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 155.8 (C=O), 155.3 (C=O), 149.0 (Ar), 148.8 (Ar), 135.4 (Ar), 134.7 (Ar), 133.8 (*ipso*-Ar), 123.4 (Ar), 80.4 (CMe_3), 48.9 (NCH_2), 48.0 (NCH_2), 44.7 (NCH_2), 44.1 (NCH_2), 42.2 (CH_2Cl), 31.1 (CH_2), 28.3 (CMe_3); MS (ESI) *m/z* 285 [$(M + H)^+$, 100], 229 (500); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}ClN_2O_2$ $(M + H)^+$ 285.1364, found 285.1361 (+1.0 ppm error).

Lab Book Reference: GG6/58/1

2-Pyridin-3-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-247



(*R*)-**247**

(Table 4.4, Entry 3)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **246** (57 mg, 0.2 mmol, 1.0 eq.) and (+)-sparteine surrogate (50 mg, 0.26 mmol, 1.3 eq.) in toluene (2 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 CH_2Cl_2-Et_2O as eluent gave pyrrolidine (*R*)-**247** (15 mg, 30%, 65:35 er by CSP-HPLC) as a colourless oil, R_F (70:30 CH_2Cl_2-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.51-8.41 (m, 2H, Ar), 7.49 (d, J = 8.0 Hz, 1H, Ar), 7.23 (dd, J = 8.0, 5.0Hz, 1H, Ar), 4.95 (br s, 0.35H, NCH), 4.77 (br s, 0.65H, Ar), 3.68-3.44 (m, 2H, NCH), 2.44-2.23 (m, 1H, CH), 1.98-1.75 (m, 3H, CH), 1.44 (s, 3.15H, CMe_3), 1.18 (s, 5.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.2 (C=O), 148.0 (Ar), 147.7 (Ar), 147.2 (Ar), 140.3 (Ar), 133.2 (*ipso*-Ar), 133.0 (*ipso*-Ar), 123.2 (Ar), 79.6 (*C*Me_3), 59.1 (NCH), 58.7 (NCH), 47.2 (NCH_2), 47.0 (NCH_2), 35.8 (CH_2), 34.5 (CH_2), 28.4 (C*Me*$_3$), 28.1 (C*Me*$_3$), 23.5 (CH_2), 23.2 (CH_2); CSP-HPLC: Chiralcel AD-H (80:20 hexane:*i*-PrOH, 0.7 mL min^{-1}) (*S*)-**247** 5.8 min, (*R*)-**247** 6.6 min and recovered starting material **246** (31 mg, 54%). Spectroscopic data consistent with those reported in the literature.[56]

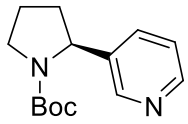
Lab Book Reference: GG6/59/1

(Table 4.4, Entry 4)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **246** (57 mg, 0.2 mmol, 1.0 eq.) and (+)-sparteine surrogate (50 mg, 0.26 mmol, 1.3 eq.) in Et_2O (2 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 CH_2Cl_2-Et_2O as eluent gave pyrrolidine (*R*)-**247** (25 mg, 50%, 64:36 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (80:20 hexane:*i*-PrOH, 0.7 mL min^{-1}) (*S*)-**247** 5.8 min, (*R*)-**247** 6.6 min and recovered starting material **246** (13 mg, 23%).

Lab Book Reference: GG6/60/1

2-Pyridin-3-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-247



(*S*)-**247**

(Table 4.3, Entry 1)

Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **246** (57 mg, 0.2 mmol, 1.0 eq.) and (–)-sparteine (60 μL, 0.26 mmol, 1.3 eq.) in toluene (2 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 CH_2Cl_2-Et_2O as eluent gave pyrrolidine (*S*)-**247** (18 mg, 36%, 53:47 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (80:20 hexane:*i*-PrOH, 0.7 mL min^{-1}) (*S*)-**247** 5.8 min, (*R*)-**247** 6.6 min and recovered starting material **246** (23 mg, 40%).

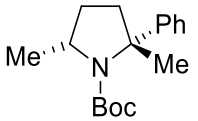
Lab Book Reference: GG6/63/1

(Table 4.4, Entry 2)

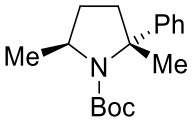
Using general procedure J: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), *N*-Boc chloro-propylamine **246** (57 mg, 0.2 mmol, 1.0 eq.) and (–)-sparteine (60 μL, 0.26 mmol, 1.3 eq.) in Et_2O (2 mL) gave the crude product. Purification by flash column chromatography on silica with 70:30 CH_2Cl_2-Et_2O as eluent gave pyrrolidine (*S*)-**247** (35 mg, 70%, 51:49 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (80:20 hexane:*i*-PrOH, 0.7 mL min^{-1}) (*S*)-**247** 5.8 min, (*R*)-**247** 6.6 min and recovered starting material **246** (13 mg, 23%).

Lab Book Reference: GG6/64/1

2,5-Dimethyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-249 and (2*R*,5*S*)-250



(2*R*,5*R*)-**249**



(2*R*,5*S*)-**250**

(Table 4.6, Entry 2)

Using general procedure K: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), pyrrolidine (*R*)-**232** (131 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at –40 °C under Ar for 30 min.

Then, Me_2SO_4 (126 mg, 100 μL, 1.0 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (5 mL), Et_2O (5 mL) and extraction with Et_2O (3 × 5 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave an 81:19 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** (114 mg, 82%) as a colourless oil, IR ($CHCl_3$) 2928, 1648 (C=O), 1369, 1147, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.38-7.27 (m, 3.5H, Ph), 7.24-7.13 (m, 1.5H, Ph), 4.36-4.08 (m, 1H, NCH), 2.29-2.02 (m, 2H, CH), 1.97-1.88 (m, 1H, CH), 1.84 (s, 0.3H, Me), 1.81-1.67 (m, 2.4H, Me), 1.64-1.51 (m, 2H, Me + CH), 1.50-1.37 (m, 4H, Me + CMe_3), 1.37-1.21 (m, 1.6H, Me), 1.14 (s, 0.7H, CMe_3), 1.09 (s, 5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.2 (C=O $_{2R,5S}$), 153.8 (C=O $_{2R,5R}$), 153.1 (C=O$_{2R,5R}$), 148.4 (*ipso*-Ph $_{2R,5R}$), 148.2 (*ipso*-Ph $_{2R,5S}$), 147.5 (*ipso*-Ph $_{2R,5R}$), 128.1 (Ph $_{2R,5R}$), 128.0 (Ph $_{2R,5S}$), 127.8 (Ph $_{2R,5R}$), 127.7 (Ph $_{2R,5S}$), 125.9 (Ph $_{2R,5S}$), 125.8 (Ph $_{2R,5S}$), 125.7 (Ph $_{2R,5R}$), 125.0 (Ph $_{2R,5R}$), 124.7 (Ph $_{2R,5R}$), 78.9 (*C*Me$_3$ $_{2R,5S}$), 78.8 (*C*Me$_3$ $_{2R,5R}$), 66.6 (NC $_{2R,5R}$), 66.4 (NC $_{2R,5S}$), 66.1 (NC $_{2R,5R}$), 65.8 (NC $_{2R,5S}$), 55.8 (NCH $_{2R,5S}$), 55.6 (NCH $_{2R,5S}$), 54.8 (NCH $_{2R,5R}$), 54.7 (NCH $_{2R,5R}$), 43.4 (CH$_2$ $_{2R,5R}$), 42.8 (CH$_2$ $_{2R,5S}$), 42.6 (CH$_2$ $_{2R,5R}$), 42.0 (CH$_2$ $_{2R,5S}$), 30.3 (CH$_2$ $_{2R,5R}$), 29.9 (CH$_2$ $_{2R,5R}$), 28.6 (C*Me*$_3$ $_{2R,5S}$), 28.5 (C*Me*$_3$ $_{2R,5R}$), 28.4 (CH$_2$ $_{2R,5S}$), 28.2 (CH$_2$ $_{2R,5S}$), 28.1 (C*Me*$_3$ $_{2R,5S}$), 28.0 (C*Me*$_3$ $_{2R,5R}$), 23.7 (Me $_{2R,5R}$), 23.6 (Me $_{2R,5R}$), 21.5 (Me $_{2R,5S}$), 21.2 (Me $_{2R,5R}$), 20.9 (Me $_{2R,5S}$), 20.3 (Me $_{2R,5R}$); MS (ESI) *m/z* 298 [(M + Na)$^+$, 80], 276 [(M + H)$^+$, 30], 220 (100); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ (M + H)$^+$ 276.1958, found 276.1945 (+4.9 ppm error).

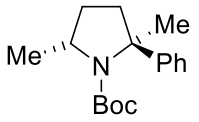
Lab Book Reference: GG4/15/1

(Table 4.6, Entry 1)

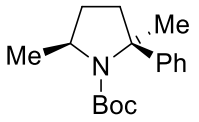
Using general procedure K: *s*-BuLi (0.4 mL of a 1.3 M solution in hexanes, 0.52 mmol, 1.3 eq.), pyrrolidine (*R*)-**232** (104 mg, 0.4 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (101 mg, 0.52 mmol, 1.3 eq.) in Et_2O (2.8 mL) at –78 °C under Ar for 1 h. Then, Me_2SO_4 (101 mg, 76 μL, 0.8 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (4 mL), Et_2O (4 mL) and extraction with Et_2O (3 × 4 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave an 87:13 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** (49 mg, 45%) as a colourless oil and recovered starting material (*R*)-**232** (45 mg, 43%) as a white solid.

Lab Book Reference: GG4/65/1

2,5-Dimethyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*S*,5*R*)-250 and (2*S*,5*S*)-249



(2*S*,5*R*)-**250**



(2*S*,5*S*)-**249**

(Table 4.7, Entry 2)

Using general procedure K: *s*-BuLi (0.4 mL of a 1.3 M solution in hexanes, 0.52 mmol, 1.3 eq.), pyrrolidine (*S*)-**232** (104 mg, 0.4 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (101 mg, 0.52 mmol, 1.3 eq.) in Et_2O (2.8 mL) at –40 °C under Ar for 30 min. Then, Me_2SO_4 (101 mg, 76 μL, 0.8 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (4 mL), Et_2O (4 mL) and extraction with Et_2O (3 × 4 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave a 94:6 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*S*,5*R*)-**250** and (2*S*,5*S*)-**249** (94 mg, 85%) as a colourless oil, $[\alpha]_D$ –103.0 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2961, 2928, 1649 (C=O), 1367, 1146, 1071, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.32-7.25 (m, 2H, Ph), 7.22-7.13 (m, 3H, Ph), 4.37-4.27 (m, 0.65H, NCH), 4.25-4.14 (m, 0.35H, NCH), 2.31-2.16 (m, 1H, CH), 2.05-1.86 (m, 2H, CH), 1.95 (s, 1H, Me), 1.84 (s, 2H, Me), 1.48 (s, 3.15H, CMe_3), 1.46-1.35 (m, 1H, Me), 1.33 (d, *J* = 6.0 Hz, 2H, Me), 1.28 (d, *J* = 6.0 Hz, 1H, Me), 1.31-1.17 (m, 1H, CH), 1.14 (s, 5.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.2 (C=O), 153.5 (C=O), 148.2 (*ipso*-Ph), 146.5 (*ipso*-Ph), 128.0 (Ph), 127.7 (Ph), 125.9 (Ph), 125.8 (Ph), 124.7 (Ph), 78.9 (CMe_3), 78.8 ($CMe_{3\ 2S,5S}$), 66.4 (NC), 65.8 (NC), 55.8 (NCH), 55.7 (NCH), 42.8 (CH_2), 42.6 (CH_2), 42.0 (CH_2), 28.6 (CMe_3), 28.4 (CH_2), 28.2 (CH_2), 28.1 (CMe_3), 21.5 (Me), 20.9 (Me); MS (ESI) *m/z* 298 [$(M + Na)^+$, 80], 276 [$(M + H)^+$, 30], 220 (100); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ $(M + H)^+$ 276.1958, found 276.1950 (+3.0 ppm error) and recovered starting material (*S*)-**232** (15 mg, 14%) as a white solid.

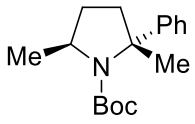
Lab Book Reference: GG4/68/1

(Table 4.6, Entry 1)

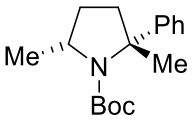
Using general procedure K: *s*-BuLi (0.4 mL of a 1.3 M solution in hexanes, 0.52 mmol, 1.3 eq.), pyrrolidine (*S*)-**232** (104 mg, 0.4 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (101 mg, 0.52 mmol, 1.3 eq.) in Et_2O (2.8 mL) at −78 °C under Ar for 1 h. Then, Me_2SO_4 (101 mg, 76 μL, 0.8 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (4 mL), Et_2O (4 mL) and extraction with Et_2O (3 × 4 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave a 92:8 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*S*,5*R*)-**250** and (2*S*,5*S*)-**249** (56 mg, 51%) as a colourless oil and recovered starting material (*S*)-**232** (42 mg, 40%) as a white solid.

Lab Book Reference: GG4/67/1

2,5-Dimethyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*S*)-250 and (2*R*,5*R*)-249



(2*R*,5*S*)-**250**



(2*R*,5*R*)-**249**

(Table 4.6, Entry 3)

Using general procedure K: *s*-BuLi (0.4 mL of a 1.3 M solution in hexanes, 0.52 mmol, 1.3 eq.), pyrrolidine (*R*)-**232** (104 mg, 0.4 mmol, 1.0 eq., 98:2 er) and (−)-sparteine (122 mg, 0.52 mmol, 1.3 eq.) in Et_2O (2.8 mL) at −78 °C under Ar for 1 h. Then, Me_2SO_4 (101 mg, 76 μL, 0.8 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (4 mL), Et_2O (4 mL) and extraction with Et_2O (3 × 4 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave a 98:2 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (50 mg, 45%) as a colourless oil, $[\alpha]_D$ +86.0 (*c* 1.0 in $CHCl_3$) and recovered starting material (*R*)-**232** (55 mg, 53%) as a white solid.

Lab Book Reference: GG4/92/1

(Table 4.6, Entry 4)

Using general procedure K: *s*-BuLi (0.2 mL of a 1.3 M solution in hexanes, 0.26 mmol, 1.3 eq.), pyrrolidine (*R*)-**232** (52 mg, 0.2 mmol, 1.0 eq., 98:2 er) and (−)-sparteine (61 mg, 0.26 mmol, 1.3 eq.) in Et_2O (1.4 mL) at −40 °C under Ar for 30 min. Then, Me_2SO_4

(50 mg, 40 μL, 0.4 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (2 mL), Et_2O (2 mL) and extraction with Et_2O (3 × 2 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave a 91:9 mixture (by ^1H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (53 mg, 96%) as a colourless oil.

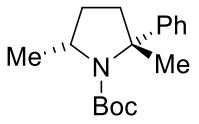
Lab Book Reference: GG4/50/1

(Scheme 4.48)

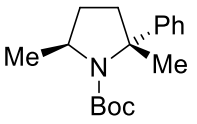
Using general procedure K: *s*-BuLi (0.37 mL of a 1.3 M solution in hexanes, 0.48 mmol, 1.3 eq.), pyrrolidine (*R*)-**232** (96 mg, 0.37 mmol, 1.0 eq., 98:2 er) and TMEDA (56 mg, 70 μL, 0.48 mmol, 1.3 eq.) in Et_2O (2.6 mL) at −78 °C under Ar for 30 min. Then, Me_2SO_4 (91 mg, 70 μL, 0.74 mmol, 2.0 eq.), saturated $NH_4Cl_{(aq)}$ (4 mL), Et_2O (4 mL) and extraction with Et_2O (3 × 4 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave a 60:40 mixture (by ^1H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (52 mg, 51%) as a colourless oil and recovered starting material (*R*)-**232** (40 mg, 42%) as a white solid.

Lab Book Reference: GG3/97/1

2,5-Dimethyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R,5*R**)-249 and (2*R**,5*S**)-250**



(2*R**,5*R**)-**249**



(2*R**,5*S**)-**250**

(Table 4.5, Entry 1)

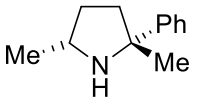
s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of pyrrolidine *rac*-**232** (131 mg, 0.5 mmol, 1.0 eq.) in THF (3.5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, Me_2SO_4 (126 mg, 100 μL, 1.0 mmol, 1.0 eq.) was added. The resulting solution was stirred at −40 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave an undetermined mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (112 mg, 81%) as a colourless oil, R_F (90:10 petrol-Et_2O) 0.2.
Lab Book Reference: GG4/7/1

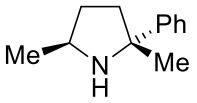
(Table 4.5, Entry 2)
Using general procedure K: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), pyrrolidine *rac*-**232** (131 mg, 0.5 mmol, 1.0 eq.) and TMEDA (75 mg, 100 μL, 0.65 mmol, 1.3 eq.) in THF (3.5 mL) at −40 °C under Ar for 30 min. Then, Me_2SO_4 (126 mg, 100 μL, 1.0 mmol, 1.0 eq.), saturated $NH_4Cl_{(aq)}$ (5 mL), Et_2O (5 mL) and extraction with Et_2O (3 × 5 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave an undetermined mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (128 mg, 93%) as a colourless oil.
Lab Book Reference: GG4/8/1

(Table 4.5, Entry 3)
Using general procedure K: *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), pyrrolidine *rac*-**232** (131 mg, 0.5 mmol, 1.0 eq.) and TMEDA (75 mg, 100 μL, 0.65 mmol, 1.3 eq.) in Et_2O (3.5 mL) at −40 °C under Ar for 30 min. Then, Me_2SO_4 (126 mg, 100 μL, 1.0 mmol, 1.0 eq.), saturated $NH_4Cl_{(aq)}$ (5 mL), Et_2O (5 mL) and extraction with Et_2O (3 × 5 mL) gave the crude product. Purification by flash column chromatography on silica with 90:10 petrol-Et_2O as eluent gave an undetermined mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (124 mg, 90%) as a colourless oil.
Lab Book Reference: GG4/14/1

(2*R*,5*R*)-2,5-Dimethyl-2-phenylpyrrolidine (2*R*,5*R*)-251 and (2*R*,5*S*)-252



(2*R*,5*R*)-**251**



(2*R*,5*S*)-**252**

(from reaction in Table 4.6, Entry 1)

Using general procedure L: TFA (114 mg, 76 μL, 1.0 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** (27 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave an 87:13 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**251** and (2*R*,5*S*)-**252** (13 mg, 74%) as a yellow oil, IR ($CHCl_3$) 3361 (NH), 2917, 2882, 1425, 1354, 1241, 1120, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.48 (m, 2H, Ph), 7.36-7.30 (m, 2H, Ph), 7.24-7.19 (m, 1H, Ph), 3.52 (ddq, J = 6.5, 6.5, 6.5 Hz, 0.87H, NCH $_{2R,5R}$), 3.23 (ddq, J = 6.5, 6.5, 6.5 Hz, 0.13H, NCH $_{2R,5S}$), 2.22-1.82 (m, 4H, CH + NH), 1.50 (s, 0.39H, Me), 1.44 (s, 2.61H, Me), 1.43-1.35 (m, 1H, CH), 1.25 (d, J = 6.5 Hz, 0.39H, Me), 1.23 (d, J = 6.5 Hz, 2.61H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.0 (*ipso*-Ph $_{2R,5R}$), 128.1 (Ph $_{2R,5R}$), 126.1 (Ph $_{2R,5R}$), 126.0 (Ph $_{2R,5R}$), 125.3 (Ph $_{2R,5S}$), 65.5 (NC $_{2R,5R}$), 54.0 (NCH $_{2R,5S}$), 53.2 (NCH $_{2R,5R}$), 40.5 (CH_2 $_{2R,5S}$), 40.0 (CH_2 $_{2R,5R}$), 34.2 (CH_2 $_{2R,5S}$), 33.5 (CH_2 $_{2R,5R}$), 32.0 (Me $_{2R,5S}$), 30.4 (Me $_{2R,5R}$), 21.9 (Me $_{2R,5R}$); MS (ESI) *m/z* 176 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}N$ $(M + H)^+$ 176.1434, found 176.1438 (–2.1 ppm error).

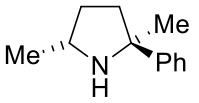
Lab Book Reference: GG4/71/1

(from reaction in Table 4.6, Entry 2)

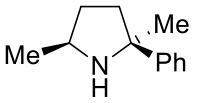
Using general procedure L: TFA (114 mg, 76 μL, 1.0 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**249** and (2*R*,5*S*)-**250** (27 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave an 81:19 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**251** and (2*R*,5*S*)-**252** (13 mg, 74%) as a yellow oil.

Lab Book Reference: GG4/86/1

(2*S*,5*R*)-2,5-Dimethyl-2-phenylpyrrolidine (2*S*,5*R*)-252 and (2*S*,5*S*)-251



(2*S*,5*R*)-**252**



(2*S*,5*S*)-**251**

(from reaction in Table 4.7, Entry 2)

Using general procedure L: TFA (114 mg, 76 μL, 1.0 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*S*,5*R*)-**249** and (2*S*,5*S*)-**250** (27 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave a 94:6 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*S*,5*R*)-**252** and (2*S*,5*S*)-**251** (11 mg, 63%), IR ($CHCl_3$) 3290 (NH), 2915, 1425, 1353, 1240, 1121, 1012, 745, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (for (2*S*,5*R*)-**252**) δ 7.54-7.48 (m, 2H, Ph), 7.36-7.30 (m, 2H, Ph), 7.24-7.19 (m, 1H, Ph), 3.52 (ddq, J = 6.5, 6.5, 6.5 Hz, 0.06H, NCH $_{2S,5S}$), 3.23 (ddq, J = 6.5, 6.5, 6.5 Hz, 0.94H, NCH $_{2S,5R}$), 2.22 (dt, J = 12.5, 7.5 Hz, 1H, CH), 2.14-2.01 (m, 1H, CH + NH), 2.01-1.82 (m, 2H, CH_2), 1.50 (s, 2.82H, Me), 1.49-1.39 (m, 1.18H, CH + Me), 1.25 (d, J = 6.5 Hz, 2.82H, Me), 1.23 (d, J = 6.5 Hz, 0.18H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.1 (*ipso*-Ph), 128.1 (Ph), 126.0 (Ph), 125.3 (Ph), 65.7 (NC), 54.0 (NCH), 40.5 (CH_2), 34.2 (CH_2), 32.0 (Me), 21.9 (Me); MS (ESI) *m/z* 176 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}N$ (M + H)$^+$ 176.1434, found 176.1438 (–2.1 ppm error).

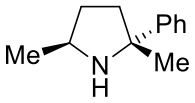
Lab Book Reference: GG4/74/1

(from reaction in Table 4.7, Entry 1)

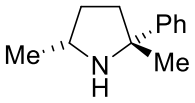
Using general procedure L: TFA (114 mg, 76 μL, 1.0 mmol, 10.0 eq.) and an unknown a mixture of pyrrolidines (2*S*,5*R*)-**250** and (2*S*,5*S*)-**249** (27 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave a 92:8 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*S*,5*R*)-**252** and (2*S*,5*S*)-**251** (5 mg, 28%).

Lab Book Reference: GG4/73/1

(2*R*,5*S*)-2,5-Dimethyl-2-phenylpyrrolidine (2*R*,5*S*)-252 and (2*R*,5*R*)-251



(2*R*,5*S*)-**252**



(2*R*,5*R*)-**251**

(from reaction in Table 4.6, Entry 3)

Using general procedure L: TFA (114 mg, 76 μL, 1.0 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (27 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave a 98:2 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*S*)-**252** and (2*R*,5*R*)-**251** (12 mg, 74%).

Lab Book Reference: GG4/95/1

(from reaction in Table 4.6, Entry 4)

Using general procedure L: TFA (148 mg, 48 μL, 1.3 mmol, 10.0 eq.) and a mixture of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (35 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave a 91:9 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*S*)-**252** and (2*R*,5*R*)-**251** (13 mg, 57%).

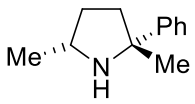
Lab Book Reference: GG4/53/1

(Scheme 4.48)

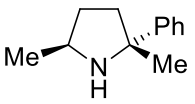
Using general procedure L: TFA (74 mg, 48 μL, 0.64 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*S*)-**250** and (2*R*,5*R*)-**249** (18 mg, 0.065 mmol, 1.0 eq.) in CH_2Cl_2 (0.65 mL) gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*S*)-**252** and (2*R*,5*R*)-**251** (10 mg, 83%).

Lab Book Reference: GG4/70/1

2,5-Dimethyl-2-phenylpyrrolidine (2*R,5*R**)-251 and (2*R**,5*S**)-252**



(2*R**,5*R**)-**251**



(2*R**,5*S**)-**252**

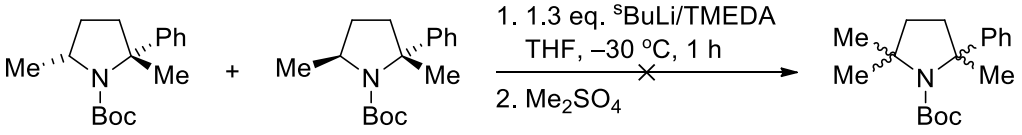
(Scheme 4.46)

Using general procedure L: TFA (114 mg, 76 μL, 0.64 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (30 mg, 0.11 mmol, 1.0 eq.)

in CH_2Cl_2 (0.3 mL) gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R**,5*R**)-**251** and (2*R**,5*S**)-**252** (10 mg, 92%).

Lab Book Reference: GG4/47/1

Attempted synthesis of 2,2,5-trimethyl-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester 255



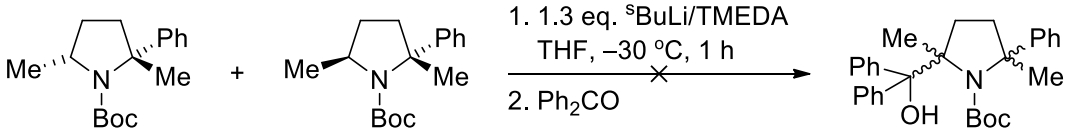
(2*R**,5*R**)-**249** (2*R**,5*S**)-**250** **255**

(Scheme 4.53)

s-BuLi (0.24 mL of a 1.3 M solution in hexanes, 0.31 mmol, 1.3 eq.) was added dropwise to a stirred solution of an undetermined mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (62 mg, 0.24 mmol, 1.0 eq.) and TMEDA (36 mg, 50 μL, 0.31 mmol, 1.3 eq.) in THF (1.7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 1 h. Then, Me_2SO_4 (60 mg, 45 μL, 0.48 mmol, 2.0 eq.) was added. The resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed only starting material and therefore purification was not attempted.

Lab Book Reference: GG4/21/1

Attempted synthesis of 2-(hydroxydiphenylmethyl)-2,5-dimethyl-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester 256



(2*R**,5*R**)-**249** (2*R**,5*S**)-**250** **256**

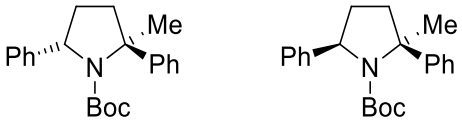
(Scheme 4.53)

s-BuLi (0.3 mL of a 1.3 M solution in hexanes, 0.39 mmol, 1.3 eq.) was added dropwise to a stirred solution of an undetermined mixture of pyrrolidines (2*R**,5*R**)-**249** and (2*R**,5*S**)-**250** (75 mg, 0.24 mmol, 1.0 eq.) and TMEDA (45 mg, 60 μL, 0.39 mmol, 1.3

eq.) in THF (2.1 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 1 h. Then, a solution of benzophenone (109 mg, 0.6 mmol, 2.0 eq.) in THF (1 mL) was added. The resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The ^{1}H NMR spectrum of the crude product showed only starting material and therefore purification was not attempted.

Lab Book Reference: GG4/25/1

2-Methyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*S*,5*S*)-253 and (2*S*,5*R*)-254



(2*S*,5*S*)-**253** (2*S*,5*R*)-**254**

(Table 4.8, Entry 1)

Using general procedure M: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), pyrrolidine (*S*)-**232** (261 mg, 1.0 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL), then $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 eq.), bromobenzene (204 mg, 140 μL, 1.3 mmol, 1.3 eq.), *t*-Bu_3PHBF_4 (14.5 mg, 0.05 mmol, 0.05 eq.) and $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 96:4 mixture (by CSP-HPLC) of pyrrolidines (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (190 mg, 56%, >99:1 er for (2*S*,5*S*)-**253** and 98:2 er for (2*S*,5*R*)-**254** by CSP-HPLC) as a colourless oil, IR ($CHCl_3$) 2929, 2889, 1668 (C=O), 1427, 1343, 1228, 1144, 1104, 1013, 749, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.38-7.20 (m, 10H, Ph), 5.33 (dd, J = 8.0, 2.5 Hz, 0.55H, NCH), 5.16 (dd, J = 8.0, 2.5 Hz, 0.45H, NCH), 2.36-2.16 (m, 2H, CH), 2.14 (s, 1.35H, Me), 2.04 (s, 1.65H, Me), 1.97-1.90 (m, 1H, CH), 1.75-1.63 (m, 1H, CH), 1.18 (s, 4.05H, CMe_3), 1.16 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.5 (C=O), 153.7 (C=O), 147.9 (*ipso*-Ph), 146.5 (*ipso*-Ph), 145.4 (*ipso*-Ph), 144.2 (*ipso*-Ph), 128.4 (Ph), 128.2 (Ph), 128.1 (Ph), 127.9 (Ph), 126.5 (Ph), 126.3 (Ph), 126.2 (Ph), 126.1 (Ph), 125.5 (Ph), 125.4 (Ph), 125.0 (Ph), 124.9 (Ph), 79.5 (*C*Me_3), 79.1

(*C*Me_3), 67.2 (NC), 66.6 (NC), 64.3 (NCH), 64.1 (NCH), 42.5 (CH_2), 41.7 (CH_2), 31.05 (CH_2), 31.00 (CH_2), 28.1 (C*Me*$_3$), 27.4 (Me), 26.9 (Me); MS (ESI) *m/z* 360 [$(M + Na)^+$, 50], 338 [$(M + H)^+$, 45], 282 (100); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}NO_2$ $(M + H)^+$ 338.2115, found 338.2115 (+0.7 ppm error); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 5.7 min, (2*R*,5*S*)-**254** 7.6 min, (2*R*,5*R*)-**253** 9.0 min, (2*S*,5*S*)-**253** 11.8 min.

Lab Book Reference: GG5/95/1

(Table 4.8, Entry 2)

Using general procedure M: *s*-BuLi (0.42 mL of a 1.3 M solution in hexanes, 0.55 mmol, 1.1 eq.), pyrrolidine (*S*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 94:6 er) and (+)-sparteine surrogate (107 mg, 0.55 mmol, 1.1 eq.) in Et_2O (1.4 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), bromobenzene (94 mg, 63 μL, 0.6 mmol, 1.2 eq.), *t*-Bu_3PHBF_4 (7.2 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 94:6 mixture (by CSP-HPLC) of pyrrolidines (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (65 mg, 38%, >99:1 er for (2*S*,5*S*)-**253** and 76:24 er for (2*S*,5*R*)-**254** by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 5.4 min, (2*R*,5*S*)-**254** 7.1 min, (2*R*,5*R*)-**253** 8.2 min, (2*S*,5*S*)-**253** 11.1 min.

Lab Book Reference: GG6/7/1

(Table 4.8, Entry 3)

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 pyrrolidine (*S*)-**232** (261 mg, 1.0 mmol, 1.0 eq., 80:20 er) and (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL) at –40 °C under Ar. The resulting solution was stirred at –40 °C for 30 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 eq.) was added and the resulting mixture was stirred at –40 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, bromobenzene (204 mg, 140 μL, 1.3 mmol, 1.3 eq.) and a mixture of *t*-Bu_3PHBF_4 (19 mg, 0.0625 mmol, 0.0625 eq.) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.1 mL) and Et_2O (5 mL) were added and mixture stirred for 1 h. The solids were removed by filtration through a

pad of Celite® and washed with Et_2O (10 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (10 mL) and water (2 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave an 86:14 mixture (by CSP-HPLC) of pyrrolidines (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (197 mg, 58%, 98:2 er for (2*S*,5*S*)-**253** and 18:82 er for (2*S*,5*R*)-**254** by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 4.9 min, (2*R*,5*S*)-**254** 5.4 min, (2*R*,5*R*)-**253** 6.1 min, (2*S*,5*S*)-**253** 8.4 min and recovered starting material (*S*)-**232** (95 mg, 36%) as a white solid.

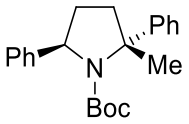
Lab Book Reference: GG4/61/1

(Scheme 4.56)

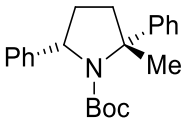
Using general procedure M: *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), pyrrolidine (*S*)-**232** (261 mg, 1.0 mmol, 1.0 eq., 98:2 er) and (–)-sparteine (234 mg, 1.3 mmol, 1.3 eq.) in Et_2O (7 mL), then $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 eq.), bromobenzene (204 mg, 140 μL, 1.3 mmol, 1.3 eq.), *t*-Bu_3PHBF_4 (19 mg, 0.065 mmol, 0.065 eq.) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 19:81 mixture (by CSP-HPLC) of pyrrolidines (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (190 mg, 56%, 94:6 er for (2*S*,5*S*)-**253** and >99:1 er for (2*S*,5*R*)-**254** by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 5.7 min, (2*R*,5*S*)-**254** 7.6 min, (2*R*,5*R*)-**253** 9.0 min, (2*S*,5*S*)-**253** 10.8 min.

Lab Book Reference: GG4/93/1

2-Methyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-253 and (2*R*,5*S*)-254



(2*R*,5*R*)-**253**



(2*R*,5*S*)-**254**

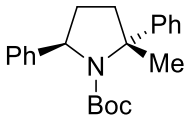
(Scheme 4.55)

Using general procedure M: *s*-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 1.1 eq.), pyrrolidine (*R*)-**232** (653 mg, 2.5 mmol, 1.0 eq., 98:2 er) and (–)-

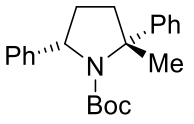
sparteine (644 mg, 2.75 mmol, 1.1 eq.) in Et_2O (7 mL), then $ZnCl_2$ (1.5 mL of a 1.0 M solution in Et_2O, 1.5 mmol, 0.6 eq.), bromobenzene (471 mg, 310 μL, 3.0 mmol, 1.2 eq.), *t*-Bu_3PHBF_4 (36 mg, 0.125 mmol, 0.05 eq.) and $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 95:5 mixture (by CSP-HPLC) of pyrrolidines (2*R*,5*R*)-**253** and (2*R*,5*S*)-**254** (502 mg, 60%, >99:1 er for (2*R*,5*R*)-**253** and 99:1 er for (2*R*,5*S*)-**254** by CSP-HPLC), as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 4.0 min, (2*R*,5*S*)-**254** 5.3 min, (2*R*,5*R*)-**253** 6.7 min, (2*S*,5*S*)-**253** 11.1 min and recovered starting material (*R*)-**232** (208 mg, 32%) as a white solid.

Lab Book Reference: GG6/5/1

2-Methyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R,5*R**)-253 and (2*R**,5*S**)-254**



(2*R**,5*R**)-**253**



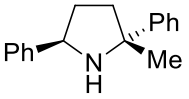
(2*R**,5*S**)-**254**

(Scheme 4.47)

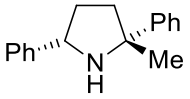
s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine *rac*-**232** (261 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 eq.) was added and the resulting mixture was stirred at −40 °C for 30 min. The reaction mixture was allowed to warm to rt over 30 min. Then, bromobenzene (204 mg, 140 μL, 1.3 mmol, 1.3 eq.) and a mixture of $^tBu_3PHBF_4$ (19 mg, 0.0625 mmol, 0.0625 eq.) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 eq.) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.1 mL) and Et_2O (5 mL) were added and mixture stirred for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (10 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (10 mL) and water (2 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 64:36 mixture (by CSP-HPLC) of pyrrolidines (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254** (140 mg, 42%) as a

colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*S*,5*R*)-**254** 4.6 min, (2*R*,5*S*)-**254** 5.3 min, (2*R*,5*R*)-**253** 6.2 min, (2*S*,5*S*)-**253** 8.5 min.
Lab Book Reference: GG4/46/1

2-Methyl-2,5-diphenylpyrrolidine (2*R,5*R**)-293 and (2*R**,5*S**)-294**



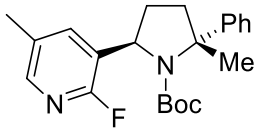
(2*R**,5*R**)-**293**



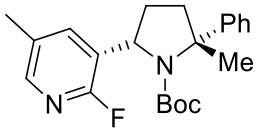
(2*R**,5*S**)-**294**

Using general procedure L: TFA (205 mg, 137 μL, 1.8 mmol, 10.0 eq.), a 64:36 mixture (by CSP-HPLC) of pyrrolidines (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254** (65 mg, 0.2 mmol, 1.0 eq.) in CH_2Cl_2 (0.55 mL) gave a 64:36 mixture (by ^1H NMR spectroscopy) of pyrrolidines (2*R**,5*R**)-**293** and (2*R**,5*S**)-**294** (44 mg, 93%) as a colourless oil, ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.59 (m, 2H, Ph), 7.57-7.46 (m, 2H, Ph), 7.44-7.33 (m, 4H, Ph), 7.33-7.25 (m, 2H, Ph), 4.59 (dd, *J* = 7.5, 7.5 Hz, 0.36H, NCH), 4.31 (dd, *J* = 7.5, 7.5 Hz, 0.64H, NCH $_{2R^*,5R^*}$), 2.43-2.12 (m, 4H, CH_2), 1.63 (s, 1.92H, Me $_{2R^*,5R^*}$), 1.62 (s, 1.08H, Me $_{2R^*,5S^*}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.5 (*ipso*-Ph $_{2R^*,5S^*}$), 149.5 (*ipso*-Ph $_{2R^*,5R^*}$), 143.4 (*ipso*-Ph $_{2R^*,5S^*}$), 145.5 (*ipso*-Ph $_{2R^*,5R^*}$), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 128.0 (Ph), 127.8 (Ph), 126.8 (Ph), 126.7 (Ph), 126.6 (Ph), 126.0 (Ph), 125.9 (Ph), 125.3 (Ph), 65.3 (NC $_{2R^*,5R^*}$), 64.4 (NC $_{2R^*,5S^*}$), 62.0 (NCH $_{2R^*,5R^*}$), 61.4 (NCH $_{2R^*,5S^*}$), 40.8 (CH_2 $_{2R^*,5S^*}$), 40.6 (CH_2 $_{2R^*,5R^*}$), 34.7 (CH_2 $_{2R^*,5S^*}$), 34.6 (CH_2 $_{2R^*,5R^*}$), 32.0 (Me $_{2R^*,5R^*}$), 30.7 (Me $_{2R^*,5S^*}$).
Lab Book Reference: GG4/48/1

5-(2-Fluoro-5-methylpyridin-3-yl)-2-methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-257 and (2*R*,5*S*)-295



(2*R*,5*R*)-**257**



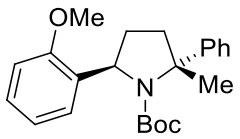
(2*R*,5*S*)-**295**

(Scheme 4.58)
Using general procedure M: *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (−)-sparteine (140 mg, 0.6 mmol, 1.2 eq.) in Et_2O (1 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), 3-bromo-2-fluoro-5-methylpyridine (190 mg, 0.41 mmol, 0.83 eq.),

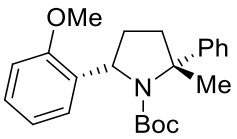
t-Bu_3PHBF_4 (7.25 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1-95:5 CH_2Cl_2-Et_2O as eluent gave 97:3 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*R*)-**257** and (2*R*,5*S*)-**295** (100 mg, 66%) as a white solid, mp 109-113 °C; R_F (99:1 CH_2Cl_2-Et_2O) 0.3; IR (ATR) 2971, 2933, 1695 (C=O), 1444, 1364, 1165, 1110, 1027, 761, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.91 (br s, 0.45H, Ar), 7.88 (br s, 0.55H, Ar), 7.53 (d, $^4J_{HF}$ = 9.5 Hz, d, *J* = 2.0 Hz, 0.45H, Ar), 7.45 (d, $^4J_{HF}$ = 9.5 Hz, d, *J* = 2.5 Hz, 0.55H, Ar), 7.39-7.31 (m, 2H, Ph), 7.27-7.21 (m, 3H, Ph), 5.44 (d, *J* = 8.0 Hz, 0.55H, NCH), 5.34 (d, *J* = 8.0 Hz, 0.45H, NCH), 2.35 (s, 3H, Ar*Me*), 2.34-2.26 (m, 0.55H, CH), 2.23-2.15 (m, 0.45H, CH), 2.14 (s, 1.35H, Me), 2.13-2.05 (m, 1H, CH), 2.03 (s, 1.65H, Me), 1.77-1.63 (m, 1H, CH), 1.23 CMe_3), 1.18 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 159.0 (d, $^1J_{CF}$ = 235.5 Hz, *ipso*-Ar), 158.9 (d, $^1J_{CF}$ = 235.5 Hz, *ipso*-Ar), 154.4 (C=O), 153.3 (C=O), 147.1 (*ipso*-Ph), 145.6 (*ipso*-Ph), 144.9 (d, $^3J_{CF}$ = 14.5 Hz, Ar), 144.8 (d, $^3J_{CF}$ = 14.5 Hz, Ar), 137.9 (d, $^3J_{CF}$ = 5.0 Hz, Ar), 137.7 (d, $^3J_{CF}$ = 5.0 Hz, Ar), 130.6 (d, $^4J_{CF}$ = 4.0 Hz, *ipso*-Ar), 130.5 (d, $^4J_{CF}$ = 4.0 Hz, *ipso*-Ar), 128.3 (Ph), 128.0 (Ph), 126.5 (Ph), 126.3 (Ph), 125.9 (d, $^2J_{CF}$ = 27.5 Hz, *ipso*-Ar), 124.9 (Ph), 124.8 (d, $^2J_{CF}$ = 27.5 Hz, *ipso*-Ar), 124.8 (Ph), 80.1 (*C*Me_3), 79.7 (*C*Me_3), 67.3 (NC), 66.8 (NC), 58.6 (d, $^3J_{CF}$ = 2.5 Hz, NCH), 57.8 (d, $^3J_{CF}$ = 1.5 Hz, NCH), 42.4 (CH_2), 41.6 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.2 (C*Me*$_3$), 28.0 (C*Me*$_3$), 27.6 (Me), 27.2 (Me), 17.8 (Me), 17.7 (Me); MS (ESI) *m/z* 393 [$(M + Na)^+$, 100], 371 [$(M + H)^+$, 20], 315 (10); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}FN_2O_2$ $(M + H)^+$ 371.2129, found 371.2117 (+3.0 ppm error).

Lab Book Reference: GG6/28/1

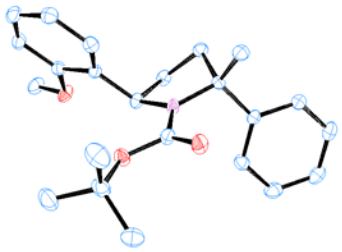
5-(2-Methoxyphenyl)-2-methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-258 and (2*R*,5*S*)-296



(2*R*,5*R*)-**258**



(2*R*,5*S*)-**296**



X-ray structure of (2*R*,5*R*)-258

(Scheme 4.58)

Using general procedure M: *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (–)-sparteine (140 mg, 0.6 mmol, 1.2 eq.) in Et_2O (1 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), 2-bromo-anisole (77 mg, 0.05 μL, 0.41 mmol, 0.83 eq.), *t*-Bu_3PHBF_4 (7.25 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 85:15 petrol-Et_2O as eluent gave a 96:4 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*R*)-**258** and (2*R*,5*S*)-**296** (104 mg, 70%) as a white solid, mp 136-139 °C; R_F (85:15 petrol-Et_2O) 0.3; IR (ATR) 2977, 2942, 1691 (C=O), 1488, 1372, 1239, 1027, 1027, 756, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.38-7.19 (m, 7H, Ar), 6.98 (dd, J = 7.5, 7.5 Hz, 0.45H, Ar), 6.97 (dd, J = 7.5, 7.5 Hz, 0.55H, Ar), 6.90 (br d, J = 8.0 Hz, 0.45H, Ar), 6.89 (br d, J = 8.0 Hz, 0.55H, Ar), 5.63 (d, J = 7.5 Hz, 0.55H, NCH), 5.49 (d, J = 7.5 Hz, 0.45H, NCH), 3.87 (s, 1.35H, OMe), 3.86 (s, 1.65H, OMe), 2.31-2.02 (m, 2H, CH), 2.17 (s, 1.35H, Me), 2.08 (s, 1.65H, Me), 1.93-1.80 (m, 1H, CH), 1.66-1.57 (m, 1H,CH), 1.20 (s, 4.05H, CMe_3), 1.19 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 156.1 (*ipso*-Ar), 156.0 (*ipso*-Ar), 154.4 (C=O), 153.7 (C=O), 147.8 (*ipso*-Ar), 146.5 (*ipso*-Ar), 133.2 (*ipso*-Ar), 132.0 (*ipso*-Ar), 128.1 (Ar), 127.8 (Ar), 127.5 (Ar), 127.2 (Ar), 126.1 (Ar), 126.0 (Ar), 125.8 (Ar), 125.2 (Ar), 125.1 (Ar), 125.0 (Ar), 120.1 (Ar), 120.0 (Ar), 110.3 (Ar), 110.1 (Ar), 79.4 (*C*Me_3), 78.8 (*C*Me_3), 67.0 (NC), 66.6 (NC), 59.5 (NCH), 58.8 (NCH), 55.3 (OMe), 55.2 (OMe), 42.3 (CH_2), 41.7 (CH_2), 29.0 (CH_2),

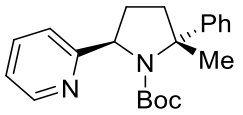
28.9 (CH_2), 28.1 (C*Me*$_3$), 28.0 (C*Me*$_3$), 27.6 (Me), 27.0 (Me); MS (ESI) *m/z* 390 [(M + Na)$^+$, 100], 368 [(M + H)$^+$, 25], 312 (25); HRMS (ESI) *m/z* calcd for $C_{23}H_{29}NO_3$ (M + H)$^+$ 368.2220, found 368.2216 (+0.7 ppm error).

Crystal structure determination of (2*R*,5*R*)-258

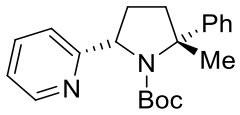
$C_{23}H_{29}NO_3$, M = 367.47, monoclinic, a = 9.88187(15), b = 7.96489(14), c = 13.5877(3) Å, β = 98.7072(16)°, U = 1057.14(3) Å^3, T = 110.05(10) K, space group $P2_1$, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, 10412 reflection measured, 5412 unique (R_{int} = 0.0280) which were used in calculation. The final R1 was 0.0424 (I≥2σ) and wR2 was 0.0974 (all data).

Lab Book Reference: GG6/30/1

2-Methyl-2-phenyl-5-(pyridin-2-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-259 and (2*R*,5*S*)-297



(2*R*,5*R*)-**259**



(2*R*,5*S*)-**297**

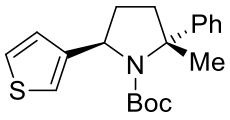
(Scheme 4.58)

Using general procedure M: *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (−)-sparteine (140 mg, 0.6 mmol, 1.2 eq.) in Et_2O (1 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), 2-bromo-pyridine (65 mg, 0.04 μL, 0.41 mmol, 0.83 eq.), *t*-Bu_3PHBF_4 (7.25 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 90:10-80:20 CH_2Cl_2-Et_2O as eluent gave a 97:3 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines of (2*R*,5*R*)-**259** and (2*R*,5*S*)-**297** (62 mg, 45%) as a white solid, mp 72-74 °C; R_F (85:15 CH_2Cl_2-Et_2O) 0.3; IR (ATR) 2975, 2946, 1691 (C=O), 1363, 1154, 1044, 765, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 8.60-8.54 (m, 1H, Ar), 7.72-7.64 (m, 1H, Ar), 7.38-7.31 (m, 3H, Ph), 7.31-7.20 (m, 3H, Ar), 7.19-7.12 (m, 1H, Ar), 5.38 (dd, J = 8.5, 2.0 Hz, 0.55H, NCH), 5.23 (dd, J = 8.5, 2.0 Hz, 0.45H, NCH), 2.38-2.26 (m, 0.55H, CH), 2.25-2.10 (m, 1.45H, CH), 2.14 (s, 1.35H, Me), 2.02 (s, 1.65H, Me), 2.01-1.90 (m, 1.55H, CH), 1.89-1.81 (m, 0.45H, CH), 1.21 (s, 4.05H, CMe_3), 1.16 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 163.9 (*ipso*-Ar), 162.5 (*ipso*-Ar), 154.5 (C=O), 153.5

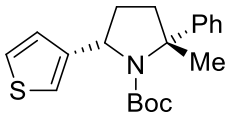
(C=O), 149.2 (Ar), 149.0 (Ar), 147.8 (*ipso*-Ar), 146.2 (*ipso*-Ar), 136.4 (Ar), 136.1 (Ar), 128.2 (Ar), 127.9 (Ar), 126.1 (Ar), 124.9 (Ar), 124.8 (Ar), 121.5 (Ar), 121.4 (Ar), 119.9 (Ar), 119.6 (Ar), 79.6 (*C*Me_3), 79.3 (*C*Me_3), 67.4 (NC), 66.8 (NC), 65.7 (NCH), 65.4 (NCH), 42.8 (CH_2), 41.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.2 (C*Me*$_3$), 28.1 (C*Me*$_3$), 27.5 (Me), 27.0 (Me); MS (ESI) *m/z* 361 [$(M + Na)^+$, 30], 339 [$(M + H)^+$, 100], 283 (10); HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O_2$ $(M + H)^+$ 339.2067, found 339.2067 (0.0 ppm error).

Lab Book Reference: GG6/84/1

2-Methyl-2-phenyl-5-(thiophen-3-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-260 and (2*R*,5*S*)-298



(2*R*,5*R*)-**260**



(2*R*,5*S*)-**298**

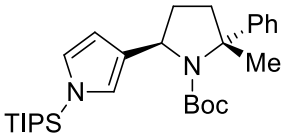
(Scheme 4.58)

Using general procedure M: *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (–)-sparteine (140 mg, 0.6 mmol, 1.2 eq.) in Et_2O (1 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), 2-bromo-thiophene (67 mg, 0.04 μL, 0.41 mmol, 0.83 eq.), *t*-Bu_3PHBF_4 (7.25 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave a 95:5 mixture (by ^{1}H NMR spectroscopy of the amines) of pyrrolidines (2*R*,5*R*)-**260** and (2*R*,5*S*)-**298** (107 mg, 76%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.2; IR (ATR) 2974, 2932, 1686 (C=O), 1361, 1162, 1080, 1029, 760, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.37-7.31 (m, 2H, Ar), 7.30 (d, *J* = 3.0 Hz, 0.45H, Ar), 7.28 (d, *J* = 3.0 Hz, 0.55H, Ar), 7.26-7.19 (m, 3H, Ar), 7.14-7.10 (m, 0.55H, Ar), 7.09-7.06 (m, 0.45H, Ar), 7.05 (dd, *J* = 5.0, 1.0 Hz, 0.55H Ar), 7.02 (dd, *J* = 5.0, 1.0 Hz, 0.45H Ar), 5.43 (d, *J* = 7.5 Hz, 0.55H, NCH), 5.26 (d, *J* = 7.5 Hz, 0.45H, NCH), 2.27-2.16 (m, 1.45H, CH), 2.15-2.04 (m, 0.55H, CH), 2.10 (s, 1.35H, Me), 2.01-1.91 (m, 1H, CH), 1.98 (s, 1.65H, Me), 1.28 (s, 4.05H, CMe_3), 1.18 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.5 (C=O), 153.6 (C=O), 147.8 (*ipso*-Ar), 146.6 (*ipso*-Ar), 146.3 (*ipso*-Ar), 145.5 (*ipso*-Ar), 128.2 (Ar), 127.9 (Ar), 126.2 (Ar), 126.1 (Ar), 126.0 (Ar), 125.7 (Ar), 125.4

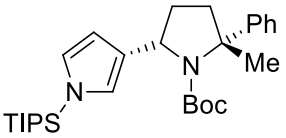
(Ar), 124.9 (Ar), 119.8 (Ar), 119.4 (Ar), 79.5 (*C*Me_3), 79.2 (*C*Me_3), 66.8 (NC), 66.2 (NC), 60.2 (NCH), 60.0 (NCH), 42.8 (CH_2), 42.0 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 28.2 (C*Me*$_3$), 28.1 (C*Me*$_3$), 27.9 (Me), 27.4 (Me); MS (ESI) *m/z* 366 [$(M + Na)^+$, 100], 288 (10); HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NO_2S$ $(M + Na)^+$ 366.1498, found 366.1488 (+2.3 ppm error).

Lab Book Reference: GG6/81/1

2-Methyl-2-phenyl-5-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-261 and (2*R*,5*S*)-270



(2*R*,5*R*)-**261**



(2*R*,5*S*)-**270**

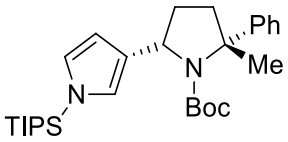
(Scheme 4.58)

Using general procedure M: *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (392 mg, 1.5 mmol, 1.0 eq., 98:2 er) and (–)-sparteine (530 mg, 1.8 mmol, 1.2 eq.) in Et_2O (3 mL), then $ZnCl_2$ (0.9 mL of a 1.0 M solution in Et_2O, 0.9 mmol, 0.6 eq.), 3-bromo-*N*-triisopropylsilyl-pyrrole (363 mg, 0.32 μL, 1.2 mmol, 0.83 eq.), *t*-Bu_3PHBF_4 (22 mg, 0.075 mmol, 0.05 eq.) and $Pd(OAc)_2$ (13 mg, 0.06 mmol, 0.04 eq.) gave the crude product as a 94:6 mixture (by ^{1}H NMR spectroscopy) of (2*R*,5*R*)-**261** and (2*R*,5*S*)-**270**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 94:6 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**261** and (2*R*,5*S*)-**270** (411 mg, 71%) as an orange oil, R_F (95:5 petrol-Et_2O) 0.1; IR (ATR) 2952, 2874, 1693 (C=O), 1362, 1160, 1099, 1082, 761, 697, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers for (2*R*,5*R*)-**261** and 75:25 mixture of rotamers for (2*R*,5*S*)-**270**) δ 7.35-7.16 (m, 5H, Ar), 6.74-6.68 (m, 1.5H, Ar), 6.64 (br s, 0.5H, Ar), 6.24 (dd, *J* = 2.5, 1.5 Hz, 0.5H, Ar), 6.19 (dd, *J* = 2.5, 1.5 Hz, 0.5H, Ar), 5.38 (d, *J* = 7.5 Hz, 0.47H, NCH), 5.32 (d, *J* = 6.0 Hz, 0.045H, NCH), 5.22 (d, *J* = 7.5 Hz, 0.47H, NCH), 5.16 (d, *J* = 6.0 Hz, 0.015H, NCH), 2.35-1.97 (m, 2H, CH), 2.02 (s, 1.5H, Me), 1.96-1.80 (m, 1.5H, CH), 1.87 (s, 1.5H, Me), 1.70 (dd, *J* = 12.0 6.0 Hz, 0.5H, CH), 1.44 (septet, *J* = 7.5 Hz, 1.5H, C*H*Me_2), 1.43 (septet, *J* = 7.5 Hz, 1.5H, C*H*Me_2), 1.36 (s, 4.5H, CMe_3), 1.15 (s, 4.5H, CMe_3), 1.14-1.07 (m, 18H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.1 (C=O), 153.9 (C=O), 148.6 (*ipso*-Ar), 147.0 (*ipso*- Ar), 129.9 (*ipso*-Ar), 128.8 (*ipso*-Ar), 128.0 (Ar),

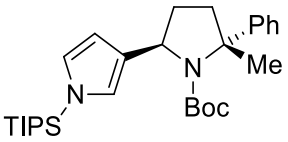
127.7 (Ar), 125.9 (Ar), 125.7 (Ar), 124.9 (Ar), 124.8 (Ar), 123.8 (Ar), 123.7 (Ar), 121.6 (Ar), 120.8 (Ar), 108.9 (Ar), 108.7 (Ar), 78.7 (*C*Me_3), 78.6 (*C*Me_3), 66.3 (NC), 65.5 (NC), 58.0 (NCH), 57.4 (NCH), 43.5 (CH_2), 43.4 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 28.4 (C*Me*$_3$), 28.1 (C*Me*$_3$), 27.4 (Me), 23.8 (Me), 17.8 (Me), 11.7 (SiCH), 11.6 (SiCH); MS (ESI) *m/z* 505 [(M + Na)$^+$, 100], 483 [(M + H) $^+$, 60], 427 (5); HRMS (ESI) *m/z* calcd for $C_{29}H_{46}N_2O_2Si$ (M + H)$^+$ 483.3401, found 483.3389 (+2.4 ppm error) and recovered starting material (*R*)-**232** (115 mg, 29%) as a white solid.

Lab Book Reference: GG6/56/1

2-Methyl-2-phenyl-5-(1-triisopropylsilyl-pyrrol-3-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*S*)-270 and (2*R*,5*R*)-261



(2*R*,5*S*)-**270**



(2*R*,5*R*)-**261**

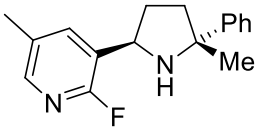
(Scheme 4.61)

Using general procedure M: *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), pyrrolidine (*R*)-**232** (130 mg, 0.5 mmol, 1.0 eq., 98:2 er) and (+)-sparteine surrogate (116 mg, 0.6 mmol, 1.2 eq.) in Et_2O (1 mL), then $ZnCl_2$ (0.3 mL of a 1.0 M solution in Et_2O, 0.3 mmol, 0.6 eq.), 3-bromo-*N*-triisopropylsilyl-pyrrole (124 mg, 0.11 µL, 0.41 mmol, 0.83 eq.), *t*-Bu_3PHBF_4 (7.25 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.04 eq.) gave the crude product as a 74:26 mixture (by ^{1}H NMR spectroscopy) of (2*R*,5*S*)-**270** and (2*R*,5*R*)-**261**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*S*)-**270** and (2*R*,5*R*)-**261** (111 mg, 56%) as an orange oil, R_F (95:5 petrol-Et_2O) 0.1; IR (ATR) 2947, 2868, 1684 (C=O), 1363, 1158, 1098, 883, 761, 691, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers for (2*R*,5*S*)-**270** and 50:50 mixture of rotamers for (2*R*,5*R*)-**261**) δ 7.34-6.98 (m, 6H, Ar), 6.79-6.62 (m, 1H, Ar), 6.36 (br s, 0.52H, Ar), 6.29 (br s, 0.18H, Ar), 6.24 (dd, *J* = 2.5, 1.5 Hz, 0.15H, Ar), 6.19 (dd, *J* = 2.5, 1.5 Hz, 0.15H, Ar), 5.38 (d, *J* = 7.5 Hz, 0.15H, NCH), 5.32 (d, *J* = 6.0 Hz, 0.52H, NCH), 5.22 (d, *J* = 7.5 Hz, 0.15H, NCH), 5.16 (d, *J* = 6.0 Hz, 0.18H, NCH), 2.40-1.67 (m, 7H, CH_2 + Me), 1.50-1.34 (m, 3H, C*H*Me_2), 1.36 (s, 1.35H, CMe_3), 1.29-1.03 (m, 25.65H, CH*Me*$_2$ + CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 154.1 (C=O $_{2R,5R}$), 154.0 (C=O $_{2R,5S}$), 153.9

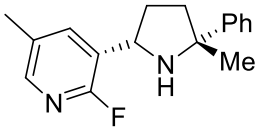
(C=O $_{2R,5S}$), 148.9 (*ipso*-Ar $_{2R,5S}$), 148.6 (*ipso*-Ar $_{2R,5R}$), 147.0 (*ipso*-Ar $_{2R,5R}$), 129.9 (*ipso*-Ar $_{2R,5R}$), 128.8 (*ipso*-Ar $_{2R,5R}$), 128.0 (Ar $_{2R,5R}$), 127.9 (Ar $_{2R,5S}$), 127.7 (Ar $_{2R,5R}$), 127.5 (Ph $_{2R,5S}$), 125.9 (Ar $_{2R,5R}$), 125.7 (Ar $_{2R,5R}$), 125.6 (Ar $_{2R,5S}$), 125.5 (Ar $_{2R,5S}$), 124.9 (Ar $_{2R,5R}$), 124.8 (Ar $_{2R,5R}$), 123.8 (Ar $_{2R,5R}$), 123.7 (Ar $_{2R,5R}$), 123.3 (*ipso*-Ar $_{2R,5S}$), 123.2 (*ipso*-Ar $_{2R,5S}$), 121.7 (Ar $_{2R,5S}$), 121.6 (Ar $_{2R,5R}$), 120.8 (Ar $_{2R,5R}$), 109.9 (Ar $_{2R,5S}$), 109.7 (Ar $_{2R,5S}$), 108.9 (Ar $_{2R,5R}$), 108.7 (Ar $_{2R,5R}$), 78.8 (*C*Me$_3$ $_{2R,5S}$), 78.7 (*C*Me$_3$ $_{2R,5R}$), 78.6 (*C*Me$_3$ $_{2R,5R}$), 78.5 (*C*Me$_3$ $_{2R,5S}$), 66.7 (NC $_{2R,5S}$), 66.3 (NC $_{2R,5R}$), 66.0 (NC $_{2R,5S}$), 65.5 (NC $_{2R,5R}$), 58.0 (NCH $_{2R,5R}$), 57.4 (NCH $_{2R,5R}$), 56.8 (NCH $_{2R,5S}$), 55.9 (NCH $_{2R,5S}$), 45.1 (CH$_2$ $_{2R,5S}$), 43.5 (CH$_2$ $_{2R,5R}$), 43.4 (CH$_2$ $_{2R,5R}$), 40.8 (CH$_2$ $_{2R,5S}$), 29.8 (CH$_2$ $_{2R,5R}$), 29.7 (CH$_2$ $_{2R,5S}$), 29.6 (CH$_2$ $_{2R,5S}$), 29.0 (CH$_2$ $_{2R,5R}$), 28.5 (C*Me*$_3$ $_{2R,5S}$) 28.4 (C*Me*$_3$ $_{2R,5R}$), 28.1 (C*Me*$_3$ $_{2R,5R}$), 28.0 (C*Me*$_3$ $_{2R,5S}$) 27.4 (Me $_{2R,5R}$), 24.0 (Me $_{2R,5S}$), 23.8 (Me $_{2R,5S}$), 20.8 (Me $_{2R,5S}$), 17.8 (Me $_{2R,5S}$), 11.7 (SiCH $_{2R,5R}$), 11.6 (SiCH $_{2R,5S}$); MS (ESI) *m/z* 505 [(M + Na)$^+$, 100], 483 [(M + H) $^+$, 20]; HRMS (ESI) *m/z* calcd for $C_{29}H_{46}N_2O_2Si$ (M + H)$^+$ 483.3401, found 483.3388 (2.5 ppm error) and recovered starting material (*R*)-**232** (51 mg, 39%) as a white solid.

Lab Book Reference: GG6/57/1

2-Fluoro-5-methyl-3-(5-methyl-5-phenylpyrrolidin-2-yl)pyridine (2*R*,5*R*)-262 and (2*S*,5*R*)-299



(2*R*,5*R*)-**262**



(2*S*,5*R*)-**299**

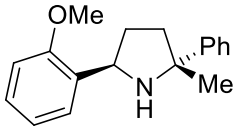
(Scheme 4.59)

Using general procedure L: TFA (57 mg, 38 μL, 0.5 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**257** and (2*R*,5*S*)-**295** (18 mg, 0.05 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) gave a 97:3 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**262** and (2*S*,5*R*)-**299** (12 mg, 89%) as a yellow oil, IR (ATR) 3348 (NH), 2965, 2928, 2870, 1445, 1235, 762, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.84 (m, 2H, Ar), 7.49 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar), 7.37 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar), 7.25 (tt, *J* = 7.5, 1.5 Hz, 1H, Ph), 4.74 (dd, *J* = 7.5, 7.5 Hz, 0.03H, NCH), 4.46 (dd, *J* = 7.5, 7.5 Hz, 0.97H, NCH), 2.35 (s, 3H, Ar*Me*), 2.32-2.23 (m, 2H, CH), 2.19-1.98 (m, 2H, CH + NH), 1.85-1.65 (m, 1H, CH), 1.57 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.7 (d, $^1J_{CF}$ = 237.0 Hz, *ipso*-Ar), 149.9 (*ipso*-Ph), 144.7 (d, $^3J_{CF}$ = 14.5 Hz, Ar), 139.1 (d,

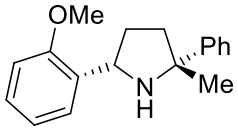
$^{3}J_{CF}$ = 6.0 Hz, Ar), 130.1 (d, $^{4}J_{CF}$ = 4.0 Hz, *ipso*-Ar), 128.4 (Ph), 126.5 (d, $^{2}J_{CF}$ = 29.0 Hz, *ipso*-Ar), 126.3 (Ph), 125.0 (Ph), 65.2 (NC), 54.9 (d, $^{3}J_{CF}$ = 3.0 Hz, NCH), 39.7 (CH_2), 32.9 (CH_2), 31.7 (Me), 17.6 (Me); MS (ESI) *m/z* 271 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}FN_2$ $(M + H)^+$ 271.1605, found 271.1608 (–0.9 ppm error).

Lab Book Reference: GG6/34/1

5-(2-Methoxyphenyl)-2-methyl-2-phenylpyrrolidine (2*R*,5*R*)-263 and (2*R*,5*S*)-300



(2*R*,5*R*)-**263**



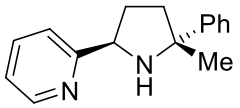
(2*R*,5*S*)-**300**

(Scheme 4.59)

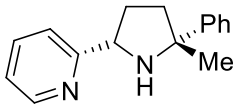
Using general procedure L: TFA (57 mg, 38 μL, 0.5 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**258** and (2*R*,5*S*)-**296** (18 mg, 0.05 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) gave a 96:4 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**263** and (2*R*,5*S*)-**300** (13 mg, 97%) as a yellow oil, IR (ATR) 3358 (NH), 2962, 1488, 1462, 1236, 1027, 751, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.0 Hz, 2H, Ar), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.40-7.34 (m, 2H, Ar), 7.27-7.22 (m, 2H, Ar), 6.98 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.89 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar), 4.83 (dd, *J* = 7.5, 7.5 Hz, 0.04H, NCH), 4.48 (dd, *J* = 7.5, 7.5 Hz, 0.96H, NCH), 3.85 (s, 2.88H, OMe), 3.84 (s, 0.12H, OMe), 2.37-2.20 (m, 2H, CH + NH), 2.20-2.04 (m, 2H, CH), 1.94-1.84 (m, 1H, CH), 1.59 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.2 (*ipso*-Ar), 149.7 (*ipso*-Ar), 132.6 (*ipso*-Ar), 128.2 (Ar), 127.7 (Ar), 127.1 (Ar), 125.9 (Ar), 125.3 (Ar), 120.5 (Ar), 110.4 (Ar), 65.2 (NC), 57.2 (NCH), 55.2 (OMe), 40.5 (CH_2), 32.8 (CH_2), 32.0 (Me); MS (ESI) *m/z* 268 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO$ $(M + H)^+$ 268.1696, found 268.1695 (+0.7 ppm error).

Lab Book Reference: GG6/36/1

2-(5-Methyl-5-phenylpyrrolidin-2-yl)pyridine (2*R*,5*R*)-264 and (2*S*,5*R*)-301



(2*R*,5*R*)-**264**



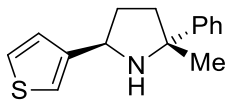
(2*S*,5*R*)-**301**

(Scheme 4.59)

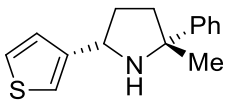
Using general procedure L: TFA (57 mg, 38 μL, 0.5 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**259** and (2*R*,5*S*)-**297** (16 mg, 0.05 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) gave an 97:3 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**264** and (2*S*,5*R*)-**301** (11 mg, 92%) as a yellow oil, IR (ATR) 3304 (NH), 2960, 2927, 2867, 1443, 1259, 1027, 763, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar), 7.65 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, Ar), 7.62-7.59 (m, 1H, Ar), 7.39-7.29 (m, 3H, Ar), 7.23 (tt, *J* = 7.5. 1.5 Hz, 1H, Ar), 7.17 (ddd, *J* = 7.5, 5.0, 1.5 Hz, 1H, Ar), 4.34 (dd, *J* = 7.5, 7.5 Hz, 0.95H, NCH), 4.23 (dd, *J* = 7.5, 7.5 Hz, 0.05H, NCH), 2.53 (br s, 1H, NH), 2.34 (ddd, *J* = 12.0, 7.5, 6.0 Hz, 1H, CH), 2.16 (dddd, *J* = 12.0, 7.5, 7.5, 7.5 Hz, 1H, CH), 2.04 (ddd, *J* = 12.0, 7.5, 7.0 Hz, 1H, CH), 1.93-1.83 (m, 1H, CH), 1.62 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9 (*ipso*-Ar), 149.0 (*ipso*-Ar), 148.9 (Ar), 136.4 (Ar), 128.1 (Ar), 126.1 (Ar), 125.5 (Ar), 121.9 (Ar), 121.8 (Ar), 66.2 (NC), 63.0 (NCH), 40.6 (CH_2), 34.4 (CH_2), 31.3 (Me); MS (ESI) *m/z* 239 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N_2$ (M + H)$^+$ 239.1543, found 239.1543 (–0.5 ppm error).

Lab Book Reference: GG6/85/1

2-Methyl-2-phenyl-5-(thiophen-3-yl)pyrrolidine (2*R*,5*R*)-265 and (2*R*,5*S*)-302



(2*R*,5*R*)-**265**



(2*R*,5*S*)-**302**

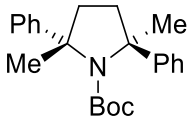
(Scheme 4.59)

Using general procedure L: TFA (57 mg, 38 μL, 0.5 mmol, 10.0 eq.) and an unknown mixture of pyrrolidines (2*R*,5*R*)-**260** and (2*R*,5*S*)-**298** (16 mg, 0.05 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) gave a 95:5 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**265** and (2*R*,5*S*)-**302** (12 mg, 99%) as a yellow oil, IR (ATR) 3357 (NH), 2960, 2865, 1444, 1074, 780, 762, 700, 645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.5 Hz, 2H, Ar), 7.36 (dd, *J* = 8.0, 8.0 Hz, 2H, Ar), 7.32 (dd, *J* = 5.0, 3.0 Hz, 1H,

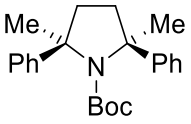
Ar), 7.24 (t, *J* = 8.0 Hz, 1H, Ph), 7.21-7.19 (m, 1H, Ar), 7.14 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar), 4.62 (dd, *J* = 7.5, 7.5 Hz, 0.05H, NCH), 4.30 (dd, *J* = 7.5, 7.5 Hz, 0.95H, NCH), 2.38-2.28 (m, 1H, CH), 2.21-2.06 (m, 2H, CH), 1.97-1.82 (m, 2H, CH + NH), 1.56 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.4 (*ipso*-Ar), 146.2 (*ipso*-Ar), 128.2 (Ar), 126.4 (Ar), 126.0 (Ar), 125.9 (Ar), 125.3 (Ar), 120.0 (Ar), 65.3 (NC), 58.0 (NCH), 40.6 (CH_2), 34.0 (CH_2), 32.0 (Me); MS (ESI) *m/z* 244 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}NS$ $(M + H)^+$ 244.1154, found 244.1156 (−0.7 ppm error).

Lab Book Reference: GG6/82/1

2,5-Dimethyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*S*,5*S*)-272 and *meso*-273



(2*S*,5*S*)-**272**



meso-**273**

(Table 4.9, Entry 2)

General procedure N: *n*-BuLi (110 μL of a 2.5 M solution in hexanes, 0.27 mmol, 1.3 eq.), an 86:14 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (98:2 er) and (2*S*,5*R*)-**254** (82:18 er) (70 mg, 0.21 mmol, 1.0 eq.) in THF (4 mL) at –50 °C under Ar for 3 min. Then, Me_2SO_4 (53 mg, 40 μL, 0.42 mmol, 2.0 eq.) gave the crude product which contained a 70:30 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *meso*-**273** (7 mg, 10%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.2; IR (ATR) 2973, 2928, 1687 (C=O), 1351, 1165, 1061, 760, 696, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.60-7.46 (m, 4H, Ph), 7.43-7.28 (m, 4H, Ph), 7.26-7.16 (m, 2H, Ph), 2.44-2.22 (m, 2H, CH), 2.17-2.02 (m, 1H, CH), 1.96 (br s, 4H, Me + CH), 1.89 (br s, 3H, Me), 1.12 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.6 (C=O), 148.4 (*ipso*-Ph), 146.9 (*ipso*-Ph), 127.9 (Ph), 127.7 (Ph), 126.0 (Ph), 125.9 (Ph), 79.2 (*C*Me_3), 68.2 (NC), 67.5 (NC), 42.0 (CH_2), 41.6 (CH_2), 28.6 (Me), 28.1 (C*Me*$_3$), 25.4 (Me); MS (ESI) *m/z* 374 [$(M + Na)^+$, 100], 352 [$(M + H)^+$, 10], 296 (15); HRMS (ESI) *m/z* calcd for $C_{23}H_{29}NO_2$ $(M + H)^+$ 352.2271, found 352.2267 (+0.7 ppm error) and pyrrolidine (2*S*,5*S*)-**272** (25 mg, 34%, 97:3 er by CSP-HPLC) as a white solid, mp 101-103 °C; R_F (95:5 petrol-Et_2O) 0.2; $[\alpha]_D$ –61.9 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2931, 1658 (C=O), 1425, 1343, 1243, 1149, 1039, 843, 689 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.44-7.31 (m, 8H, Ph), 7.26-7.19 (m, 2H, Ph), 2.13-2.02 (m, 2H, CH), 2.07 (s, 3H, Me), 2.00-1.87 (m, 2H, CH), 1.97 (s, 3H, Me), 1.12 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.1 (C=O), 148.4 (*ips*o-Ph), 147.2 (*ips*o-Ph), 128.2 (Ph), 127.9 (Ph), 126.0 (Ph), 125.9 (Ph), 125.3 (Ph), 125.0 (Ph), 79.0 (CMe_3), 68.5 (NC), 67.9 (NC), 42.2 (CH_2), 41.6 (CH_2), 28.1 (CMe_3), 26.0 (Me), 25.4 (Me); MS (ESI) *m/z* 374 [$(M + Na)^+$, 80], 352 [$(M + H)^+$, 100], 296 (80); HRMS (ESI) *m/z* calcd for $C_{23}H_{29}NO_2$ $(M + H)^+$ 352.2271, found 352.2257 (+3.3 ppm error); CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.2 min, (2*S*,5*S*)-**272** 8.7 min and recovered starting material (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (40 mg, 56%) as a colourless oil.

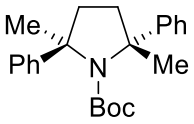
Lab Book Reference: GG4/63

(Table 4.9, Entry 1)

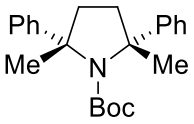
General procedure N: *n*-BuLi (90 μL of a 2.5 M solution in hexanes, 0.21 mmol, 1.3 eq.), an 86:14 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (98:2 er) and (2*S*,5*R*)-**254** (82:18 er) (55 mg, 0.16 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under Ar for 1 h. Then, Me_2SO_4 (40 mg, 30 μL, 0.32 mmol, 2.0 eq.) gave the crude product which contained a 78:22 mixture (by ^1H NMR spectroscopy) of (2*S*,5*S*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *meso*-**273** (4.5 mg, 8%) as a colourless oil, pyrrolidine (2*S*,5*S*)-**272** (20 mg, 35%, 97:3 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.1 min, (2*S*,5*S*)-**272** 8.7 min and recovered starting material (2*S*,5*S*)-**253** and (2*S*,5*R*)-**254** (30 mg, 56%) as a colourless oil.

Lab Book Reference: GG4/64

2,5-Dimethyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R,5*R**)-272 and *meso*-273**



(2*R**,5*R**)-**272**



meso-**273**

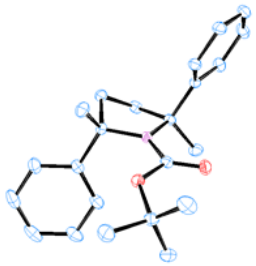
(Scheme 4.65)

General procedure N: *n*-BuLi (0.33 mL of a 2.5 M solution in hexanes, 0.83 mmol, 1.3 eq.), a 64:36 mixture of (2*R**,5*R**)-**253** and (2*R**,5*S**)-**254** (215 mg, 0.64 mmol, 1.0

eq.) in THF (4.5 mL) at 0 °C under Ar for 5 min. Then, Me_2SO_4 (161 mg, 120 μL, 1.3 mmol, 2.0 eq.) gave the crude product which contained a 55:45 mixture (by ^{1}H NMR spectroscopy) of (2*R**,5*R**)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of (2*R**,5*R**)-**272** and *meso*-**273** (64 mg, 29%) as a colourless oil.
Lab Book Reference: GG4/28/2

2,5-Dimethyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*S*,5*S*)-272 and *meso*-273

(2*S*,5*S*)-**272** *meso*-**273**



X-ray structure of (2*S*,5*S*)-272

(Table 4.10, Entry 1)
General procedure O: *n*-BuLi (70 μL of a 2.5 M solution in hexanes, 0.18 mmol, 1.1 eq.), a 96:4 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*R*)-**254** (92:8 er) (54 mg, 0.16 mmol, 1.0 eq.) and TMEDA (20 mg, 25 μL, 0.18 mmol, 1.1 eq.) in Et_2O (1.6 mL) at −30 °C under Ar for 30 min. Then, Me_2SO_4 (30 mg, 22 μL, 0.24 mmol, 1.5 eq.) gave the crude product which contained a 91:9 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *meso*-**273** (1 mg, 2%) as a colourless oil, pyrrolidine (2*S*,5*S*)-**272** (48 mg, 85%, 99:1 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.0 min, (2*S*,5*S*)-**272** 8.2 min and recovered starting material (5 mg, 9%) as a colourless oil.

Crystal structure determination of (2*S*,5*S*)-272

$C_{23}H_{29}NO_2$, M = 351.47, orthorhombic, a = 8.54159(14), b = 9.92093(16), c = 23.6875(4) Å, β = 90.00°, U = 2007.30(6) Å^3, T = 110.00(10) K, space group $P2_12_12_1$, Z

= 4, μ(Mo-Kα) = 0.073 mm^{-1}, 28011 reflection measured, 5855 unique (R_{int} = 0.0353) which were used in calculation. The final R1 was 0.0354 (I≥2σ) and wR2 was 0.0933 (all data).

Lab Book Reference: GG6/1

(Table 4.10, Entry 2)

General procedure O: *n*-BuLi (90 μL of a 2.5 M solution in hexanes, 0.22 mmol, 1.1 eq.), a 96:4 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*R*)-**254** (92:8 er) (67 mg, 0.2 mmol, 1.0 eq.) and TMEDA (25 mg, 33 μL, 0.22 mmol, 1.1 eq.) in Et_2O (2 mL) at −30 °C under Ar for 1 h. Then, Me_2SO_4 (38 mg, 28 μL, 0.3 mmol, 1.5 eq.) gave the crude product which contained a 90:10 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *meso*-**273** (2.5 mg, 3%) as a colourless oil and pyrrolidine (2*S*,5*S*)-**272** (61 mg, 87%, 99:1 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.0 min, (2*S*,5*S*)-**272** 8.5 min.

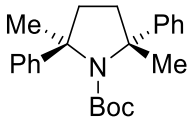
Lab Book Reference: GG6/2

(Scheme 4.68)

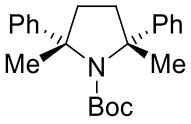
General procedure XO: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 94:6 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*R*)-**254** (76:24 er) (33 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL) at −30 °C under Ar for 1 h. Then, Me_2SO_4 (19 mg, 14 μL, 0.15 mmol, 1.5 eq.) gave the crude product which contained a 89:11 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine (2*S*,5*S*)-**272** (31 mg, 88%, 99:1 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.3 min, (2*S*,5*S*)-**272** 9.8 min.

Lab Book Reference: GG6/11

2,5-Dimethyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (2*R*,5*R*)-272 and *meso*-273



(2*R*,5*R*)-**272**



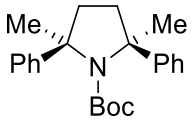
meso-**273**

(Scheme 4.69)

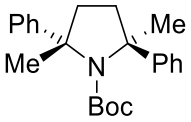
General procedure O: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 95:5 mixture of phenyl pyrrolidines (2*R*,5*R*)-**253** (>99:1 er) and (2*R*,5*S*)-**254** (99:1 er) (33 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL) at 0 °C under Ar for 1 min. Then, Me_2SO_4 (19 mg, 14 μL, 0.15 mmol, 1.5 eq.) gave the crude product which contained a 89:11 mixture (by ^1H NMR spectroscopy) of (2*R*,5*R*)-**272** and *meso*-**273**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine (2*R*,5*R*)-**272** (30 mg, 85%, 99:1 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +60.1 (*c* 1.8 in $CHCl_3$); CSP-HPLC: Chiralcel AD-H (99.5:0.5 hexane:*i*-PrOH, 0.7 mL min^{-1}) (2*R*,5*R*)-**272** 5.2 min, (2*S*,5*S*)-**272** 10.8 min.

Lab Book Reference: GG6/16

2,5-Dimethyl-2,5-diphenylpyrrolidine-1-carboxylic acid *tert*-butyl ester *meso*-273 and (2*S*,5*S*)-272



meso-**273**



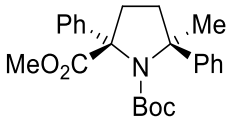
(2*S*,5*S*)-**272**

(Scheme 4.70)

General procedure O: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 81:19 mixture of phenyl pyrrolidines (2*S*,5*R*)-**254** (>99:1 er) and (2*S*,5*S*)-**253** (94:6 er) (33 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL) at −30 °C under Ar for 1 h. Then, Me_2SO_4 (19 mg, 14 μL, 0.15 mmol, 1.5 eq.) gave the crude product which contained an 81:19 mixture (by ^1H NMR spectroscopy) of *meso*-**273** and (2*S*,5*S*)-**272**. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *meso*-**273** (14 mg, 40%) as colourless oil and pyrrolidine (2*S*,5*S*)-**272** (3 mg, 8%) as a white solid.

Lab Book Reference: GG6/17

1-*tert*-Butyl 2-methyl 5-methyl-2,5-diphenylpyrrolidine-1,2-dicarboxylate (2*S*,5*S*)-274



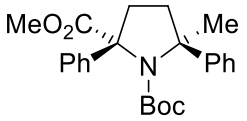
(2*S*,5*S*)-**274**

(Scheme 4.73)

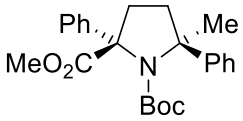
General procedure O: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 94:6 mixture of phenyl pyrrolidines (2*S*,5*S*)-**253** (>99:1 er) and (2*S*,5*S*)-**254** (76:24 er) (33 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL) at –30 °C under Ar for 1 h. Then, methyl chloroformate (14 mg, 11 μL, 0.15 mmol, 1.5 eq.) gave the crude product which contained a 91:9 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**274** and (2*R*,5*S*)-**275**. Purification by flash column chromatography on silica with 70:30 petrol-Et_2O as eluent gave pyrrolidine (2*S*,5*S*)-**274** (35 mg, 88%) as white solid, mp 91-93 °C; R_F (70:30 petrol-Et_2O) 0.2; IR (ATR) 2970, 2950, 1733 (C=O, CO_2Me), 1686 (C=O, Boc), 1387, 1369, 1255, 1161, 1007, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.73 (dd, J = 8.5, 1.0 Hz, 1.1H, Ph), 7.66 (dd, J = 8.5, 1.0 Hz, 0.9H, Ph), 7.43 (t, J = 7.0 Hz, 1H, Ph), 7.40-7.33 (m, 5H, Ph), 7.32-7.28 (m, 1H, Ph), 7.27-7.20 (m, 1H, Ph), 3.85 (s, 1.35H, OMe), 3.81 (s, 1.65H, OMe), 2.66 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.55H, CH), 2.49 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.45H, CH), 2.29 (ddd, J = 12.5, 6.5, 2.0 Hz, 0.55H, CH), 2.20 (ddd, J = 12.5, 6.5, 2.0 Hz, 0.45H, CH), 2.04 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.45H, CH), 2.03 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.55H, CH), 2.01 (s, 1.35H, Me), 1.93-1.77 (m, 1H, CH), 1.89 (s, 1.65H, Me), 1.32 (s, 4.05H, CMe_3), 1.22 (s, 4.95H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 173.3 (C=O, CO_2Me), 154.0 (C=O, Boc), 152.7 (C=O, Boc), 147.4 (*ipso*-Ph), 146.0 (*ipso*-Ph), 139.7 (*ipso*-Ph), 139.5 (*ipso*-Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 127.5 (Ph), 127.2 (Ph), 127.1 (Ph), 127.0 (Ph), 126.1 (Ph), 126.0 (Ph), 125.8 (Ph), 125.7 (Ph), 80.5 (CMe_3), 80.3 (CMe_3), 74.5 (NC), 74.3 (NC), 68.3 (NC), 67.1 (NC), 52.6 (OMe), 52.4 (OMe), 42.7 (CH_2), 41.8 (CH_2), 38.2 (CH_2), 37.0 (CH_2), 28.1 (CMe_3), 28.0 (CMe_3), 27.7 (Me), 27.1 (Me); MS (ESI) *m/z* 418 [$(M + Na)^+$, 100], 396 [$(M + H)^+$, 20], 340 (10); HRMS (ESI) *m/z* calcd for $C_{24}H_{29}NO_4$ $(M + H)^+$ 396.2169, found 396.2169 (–0.1 ppm error).

Lab Book Reference: GG6/53/1

1-*tert*-Butyl 2-methyl 5-methyl-2,5-diphenylpyrrolidine-1,2-dicarboxylate (2*R*,5*S*)-275 and (2*S*,5*S*)-274



(2*R*,5*S*)-**275**



(2*S*,5*S*)-**274**

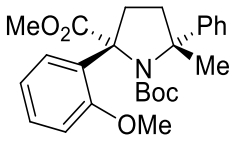
(Scheme 4.74)

General procedure O: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 81:19 mixture of phenyl pyrrolidines (2*S*,5*R*)-**254** (>99:1 er) and (2*S*,5*S*)-**253** (94:6 er) (33 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL) at −30 °C under Ar for 1 h. Then, methyl chloroformate (14 mg, 11 μL, 0.15 mmol, 1.5 eq.) gave the crude product as a 86:14 mixture (by ^{1}H NMR spectroscopy) of (2*R*,5*S*)-**275** and (2*S*,5*S*)-**274**. Purification by flash column chromatography on silica with 70:30 petrol-Et_2O as eluent gave an 86:14 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*S*)-**275** and (2*S*,5*S*)-**274** (28 mg, 57%) as white solid, mp 108-112 °C; R_F (70:30 petrol-Et_2O) 0.2; IR (ATR) 2985, 2948, 1740 (C=O), 1679 (C=O), 1362, 1250, 1156, 755, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers for (2*R*,5*S*)-**275** and 55:45 mixture of rotamers for (2*S*,5*S*)-**274**) δ 7.73 (dd, J = 8.5, 1.0 Hz, 0.15H, Ph), 7.66 (dd, J = 8.5, 1.0 Hz, 0.13H, Ph), 7.54 (d, J = 8.0 Hz, 1.12H, Ph), 7.50 (d, J = 8.0 Hz, 0.6H, Ph), 7.48-7.35 (m, 4H, Ph), 7.35-7.24 (m, 3H, Ph), 7.23-7.17 (m, 1H, Ph), 3.85 (s, 0.2H, OMe), 3.84-3.69 (s, 1.12H, OMe), 3.75 (s, 1.68H, OMe), 2.93-2.73 (m, 1H, CH), 2.66 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.08H, CH), 2.60 (dd, J = 12.5, 5.5 Hz, 0.56H, CH), 2.54-2.42 (m, 0.36H, CH), 2.14-1.96 (m, 4.61H, CH + Me), 1.93-1.77 (m, 0.42H, CH + Me), 1.32 (s, 0.58H, CMe_3), 1.25-1.19 (m, 3.38H, CMe_3), 1.15 (s, 5.04H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 173.8 (C=O, CO_2Me $_{2R,5S}$), 173.7 (C=O, CO_2Me $_{2R,5S}$), 173.3 (C=O, CO_2Me $_{2S,5S}$), 154.4 (C=O, Boc $_{2R,5S}$), 154.0 (C=O, Boc $_{2S,5S}$), 152.7 (C=O, Boc $_{2S,5S}$), 147.4 (*ipso*-Ph $_{2S,5S}$), 147.2 (*ipso*-Ph $_{2R,5S}$), 146.3 (*ipso*-Ph $_{2R,5S}$), 146.0 (*ipso*-Ph $_{2S,5S}$), 139.6 (*ipso*-Ph $_{2R,5S}$), 139.5 (*ipso*-Ph $_{2R,5S}$), 128.4 (Ph $_{2R,5S}$), 128.3 (Ph $_{2R,5S}$), 128.0 (Ph $_{2R,5S}$), 127.9 (Ph $_{2S,5S}$), 127.8 (Ph $_{2S,5S}$), 127.7 (Ph $_{2R,5S}$), 127.6 (Ph $_{2S,5S}$), 127.5 (Ph $_{2R,5S}$), 127.2 (Ph $_{2R,5S}$), 127.1 (Ph $_{2R,5S}$), 126.3 (Ph $_{2R,5S}$), 126.2 (Ph $_{2R,5S}$), 126.0 (Ph $_{2R,5S}$), 125.9 (Ph $_{2R,5S}$), 125.8 (Ph $_{2S,5S}$), 125.7 (Ph $_{2S,5S}$), 125.5 (Ph $_{2R,5S}$), 80.5 (*C*Me_3 $_{2S,5S}$), 80.3 (*C*Me_3 $_{2S,5S}$), 80.2 (*C*Me_3 $_{2R,5S}$), 80.1 (*C*Me_3 $_{2R,5S}$), 74.5 (NC $_{2S,5S}$), 74.4 (br, NC $_{2R,5S}$), 74.3 (NC $_{2S,5S}$), 68.4 (NC $_{2R,5S}$), 68.3 (NC $_{2S,5S}$), 67.6 (NC $_{2R,5S}$), 67.1 (NC $_{2S,5S}$), 52.7 (OMe

$_{2R,5S}$), 52.5 (OMe $_{2R,5S}$), 52.4 (OMe $_{2S,5S}$), 43.1 ($CH_{2\ 2R,5S}$), 42.7 ($CH_{2\ 2S,5S}$), 41.8 ($CH_{2\ 2S,5S}$), 41.7 ($CH_{2\ 2R,5S}$), 39.6 ($CH_{2\ 2R,5S}$), 38.2 ($CH_{2\ 2S,5S}$), 38.1 ($CH_{2\ 2R,5S}$), 37.0 ($CH_{2\ 2S,5S}$), 30.3 (Me $_{2R,5S}$), 29.7 (Me $_{2R,5S}$), 28.1 (C*Me*$_{3\ 2S,5S}$), 28.0 (C*Me*$_{3\ 2S,5S}$), 27.9 (br, C*Me*$_{3\ 2R,5S}$), 27.7 (Me $_{2S,5S}$), 27.1 (Me $_{2S,5S}$); MS (ESI) *m/z* 418 [$(M + Na)^+$, 100], 396 [$(M + H)^+$, 5], 340 (5); HRMS (ESI) *m/z* calcd for $C_{24}H_{29}NO_4$ $(M + H)^+$ 396.2169, found 396.2175 (–1.4 ppm error).

Lab Book Reference: GG6/52/1

1-*tert*-Butyl 2-methyl 2-(2-methoxyphenyl)-5-methyl-5-phenylpyrrolidine-1,2-dicarboxylate (2*R*,5*R*)-276



(2*R*,5*R*)-**276**

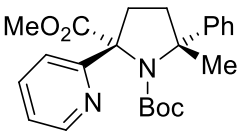
(Scheme 4.75)

General procedure P: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 96:4 mixture of phenyl pyrrolidines (2*R*,5*R*)-**258** and (2*R*,5*S*)-**296** (37 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL), then methyl chloroformate (14 mg, 11 μL, 0.15 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 70:30 petrol-Et_2O as eluent gave pyrrolidine (2*R*,5*R*)-**276** (16 mg, 38%) as a white solid, mp 131-134 °C; R_F (70:30 petrol-Et_2O) 0.2; IR (ATR) 2945, 1731 (C=O, CO_2Me), 1697 (C=O, Boc), 1363, 1249, 1156, 1027, 756, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.71 (d, J = 7.5 Hz, 1.4H, Ar), 7.63 (d, J = 7.5 Hz, 0.6H, Ar), 7.37 (dd, J = 7.5, 7.5 Hz, 2H, Ar), 7.34-7.27 (m, 1H, Ar), 7.26-7.18 (m, 2H, Ar), 7.00 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 6.94 (d, J = 8.0 Hz, 1H, Ar), 3.82 (s, 3H, OMe), 3.77 (s, 3H, OMe), 2.77 (ddd, J = 12.5, 12.5, 6.5 Hz, 0.7H, CH), 2.66-2.52 (m, 1.3H, CH), 2.09-2.02 (m, 1H, CH), 2.00 (s, 0.9H, Me), 1.93 (s, 2.1H, Me), 1.85 (td, J = 12.5, 6.5 Hz, 1H, CH), 1.31 (s, 2.7H, CMe_3), 1.17 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 174.8 (C=O, CO_2Me), 173.4 (C=O, CO_2Me), 157.4 (*ipso*-Ar), 157.3 (*ipso*-Ar), 153.8 (C=O, Boc), 147.9 (*ipso*-Ar), 146.4 (*ipso*-Ar), 128.7 (Ar), 128.4 (*ipso*-Ar), 128.0 (Ar), 127.7 (Ar), 125.9 (Ar), 125.7 (Ar), 120.3 (Ar), 111.9 (Ar), 80.2 (*C*Me_3), 73.5 (NC), 67.3 (NC), 55.5 (OMe), 52.4 (OMe), 52.1 (OMe), 42.8 (CH_2), 42.2 (CH_2), 35.0 (CH_2), 34.5 (CH_2), 28.1 (C*Me*$_3$), 28.0 (C*Me*$_3$), 27.9 (Me), 27.3 (Me); MS (ESI) *m/z* 448 [$(M + Na)^+$,

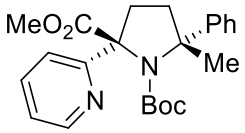
60], 426 [(M + H)$^+$, 100], 370 (20), 326 (10); HRMS (ESI) *m/z* calcd for $C_{25}H_{31}NO_5$ (M + H)$^+$ 426.2275, found 426.2269 (+1.1 ppm error) and recovered starting material (14 mg, 38%).

Lab Book Reference: GG6/40/1

1-*tert*-Butyl 2-methyl 5-methyl-5-phenyl-2-(pyridin-2-yl)pyrrolidine-1,2-dicarboxylate (2*R*,5*R*)-277 and (2*S*,5*R*)-303



(2*R*,5*R*)-**277**



(2*S*,5*R*)-**303**

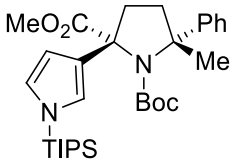
(Scheme 4.75)

General procedure P: *n*-BuLi (70 μL of a 2.5 M solution in hexanes, 0.165 mmol, 1.1 eq.), a 95:5 mixture of phenyl pyrrolidines (2*R*,5*R*)-**259** and (2*R*,5*S*)-**297** (51 mg, 0.15 mmol, 1.0 eq.) and TMEDA (20 mg, 26 μL, 0.165 mmol, 1.1 eq.) in Et_2O (1.5 mL), then methyl chloroformate (21 mg, 17 μL, 0.225 mmol, 1.5 eq.) gave the crude product which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of (2*S*,5*S*)-**277** and (2*S*,5*R*)-**303**. Purification by flash column chromatography on silica with 90:10 CH_2Cl_2-Et_2O as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines (2*R*,5*R*)-**277** and (2*S*,5*R*)-**303** (18 mg, 35%) as a yellow oil, R_F (90:10 CH_2Cl_2-Et_2O) 0.2; IR (ATR) 2977, 1740 (C=O, CO_2Me), 1683 (C=O, Boc), 1361, 1249, 1159, 757, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers for (2*R*,5*R*)-**277** and 60:40 mixture of rotamers for (2*S*,5*R*)-**303**) δ 8.69-8.70 (m, 1H, Ar), 7.84-7.69 (m, 2H, Ar), 7.69-7.46 (m, 1H, Ar), 7.40-7.28 (m, 2H, Ar), 7.26-7.13 (m, 3H, Ar), 3.85 (s, 0.3H, OMe), 3.82 (s, 0.45H, OMe), 3.80 (s, 0.57H, OMe), 3.75 (s, 1.68H, OMe), 2.34 (dd, *J* = 12.5, 5.5 Hz, 0.65H, CH), 3.05-2.94 (m, 0.35H, CH), 2.79-2.47 (m, 1H, CH), 2.13-1.94 (m, 4H, Me + CH), 1.87-1.66 (m, 1H, CH), 1.32 (s, 0.9H, CMe_3), 1.26 (s, 1.35H, CMe_3), 1.19 (s, 1.71H, CMe_3), 1.11 (s, 5.04H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 173.4 (C=O, CO_2Me), 172.9 (C=O, CO_2Me), 158.9 (*ipso*-Ar), 158.6 (*ipso*-Ar), 154.4 (C=O, Boc), 154.1 (C=O, Boc), 148.3 (Ar), 148.0 (Ar), 147.6 (*ipso*-Ar), 136.2 (Ar), 136.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 126.0 (Ar), 125.6 (Ar), 125.4 (Ar), 124.1 (Ar), 122.6 (Ar), 122.4 (Ar), 122.2 (Ar), 80.4 (CMe_3), 80.2 (CMe_3), 75.5 (NC), 75.4 (NC), 68.2 (NC), 67.3 (NC), 52.8 (OMe), 52.7 (OMe), 43.9 (CH_2), 42.9 (CH_2), 42.2 (CH_2), 36.6 (CH_2), 35.7 (CH_2), 34.8 (CH_2), 28.1 (CMe_3), 28.0

(C*Me*$_3$), 27.9 (C*Me*$_3$), 23.1 (Me), 22.8 (Me); MS (ESI) *m/z* 419 [(M + Na)$^+$, 60], 397 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}N_2O_4$ (M + H)$^+$ 397.2122, found 397.2121 (+0.8 ppm error) and recovered starting material (17 mg, 33%).

Lab Book Reference: GG6/95/1

1-*tert*-Butyl 2-methyl 5-methyl-5-phenyl-2-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)pyrrolidine-1,2-dicarboxylate (2*R*,5*R*)-278



(2*R*,5*R*)-**278**

(Scheme 4.75)

General procedure P: *n*-BuLi (44 μL of a 2.5 M solution in hexanes, 0.11 mmol, 1.1 eq.), a 94:6 mixture of phenyl pyrrolidines (2*R*,5*R*)-**261** and (2*R*,5*S*)-**270** (48 mg, 0.1 mmol, 1.0 eq.) and TMEDA (13 mg, 16 μL, 0.11 mmol, 1.1 eq.) in Et_2O (1 mL), then methyl chloroformate (14 mg, 11 μL, 0.15 mmol, 1.5 eq.) gave the crude product which contained a 98:2 mixture (by ^{1}H NMR spectroscopy) of (2*R*,5*R*)-**278** and diastereoisomer (2*R*,5*S*). Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine (2*R*,5*R*)-**278** (28 mg, 52%) as a yellow oil, R_F (80:20 petrol-Et_2O) 0.2; IR (ATR) 2947, 2868, 1739 (C=O, CO_2Me), 1698 (C=O, Boc), 1361, 1161, 1107, 1088, 691, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.71 (d, *J* = 7.5 Hz, 0.9H, Ar), 7.66 (d, *J* = 7.5 Hz, 1.1H, Ar), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar), 7.24-7.17 (m, 1H, Ar), 6.77 (dd, *J* = 2.0, 2.0 Hz, 0.45H, Ar), 6.73 (d, *J* = 2.5 Hz, 1H, Ar), 6.70 (dd, *J* = 2.5, 2.5 Hz, 0.55H, Ar), 6.33 (dd, *J* = 2.5, 1.5 Hz, 0.45H, Ar), 6.31 (dd, *J* = 2.5, 2.5 Hz, 0.55H, Ar), 3.83 (s, 1.65H, OMe), 3.81 (s, 1.35H, OMe), 2.45-2.34 (m, 0.45H, CH), 2.30-2.00 (m, 3.55H, CH), 1.95 (s, 1.65H, Me), 1.81 (s, 1.35H, Me), 1.45 (septet, *J* = 7.5 Hz, 1.35H, C*H*Me$_2$), 1.43 (septet, *J* = 7.5 Hz, 1.65H, C*H*Me$_2$), 1.35 (s, 4.95H, CMe$_3$), 1.19 (s, 4.05H, CMe$_3$), 1.16-1.08 (m, 18H, CH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 174.3 (C=O, CO_2Me), 174.1 (C=O, CO_2Me), 153.4 (C=O, Boc), 152.7 (C=O, Boc), 148.0 (*ipso*-Ar), 146.5 (*ipso*-Ar), 127.8 (Ar), 127.6 (Ar), 126.4 (*ipso*-Ar), 126.1 (Ar), 125.9 (*ipso*-Ar), 125.8 (Ar), 125.7 (Ar), 123.4 (Ar), 123.1 (Ar), 123.0 (Ar), 122.8 (Ar), 110.7 (Ar), 110.5 (Ar), 79.8 (*C*Me$_3$), 79.4 (*C*Me$_3$), 70.6 (NC), 69.9 (NC), 67.9 (NC), 66.7 (NC), 52.4

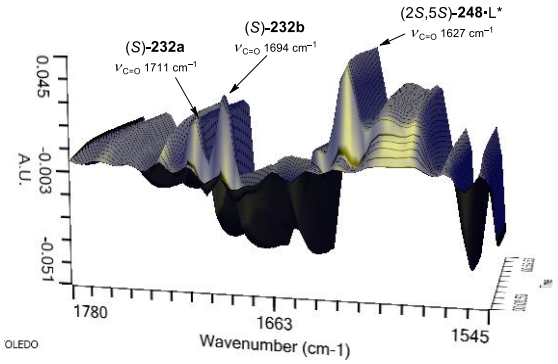
(OMe), 52.1 (OMe), 43.3 (CH_2), 42.2 (CH_2), 37.7 (CH_2), 36.3 (CH_2), 28.2 (C*Me*$_3$), 28.0 (C*Me*$_3$), 27.9 (Me), 27.5 (Me), 17.9 (CH*Me*$_2$), 17.8 (CH*Me*$_2$), 11.7 (SiCH); MS (ESI) *m/z* 563 [(M + Na)$^+$, 90], 541 [(M + H)$^+$, 100], 485 (15); HRMS (ESI) *m/z* calcd for $C_{31}H_{48}N_2O_4Si$ (M + H)$^+$ 541.3456, found 541.3456 (+2.4 ppm error) and recovered starting material (22 mg, 45%).

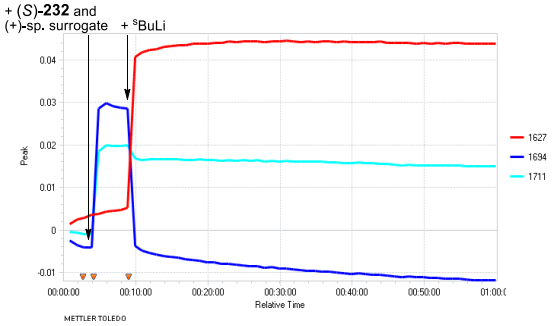
Lab Book Reference: GG6/39/1

ReactIR™ monitoring of the lithiation of di-substituted *N*-Boc pyrrolidine (*S*)-232 at –78 °C

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 (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of di-substituted *N*-Boc pyrrolidine (*S*)-**232** (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 the 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 50 min. For di-substituted *N*-Boc pyrrolidine (*S*)-**232**, two peaks at 1711 cm^{-1} and 1694 cm^{-1} were observed and assigned to $\nu_{C=O}$ in the two rotamers (*S*)-**232a** and (*S*)-**232b**. After addition of *s*-BuLi, a new peak at 1627 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 di-substituted *N*-Boc pyrrolidine (*S*)-**232b** to give the lithiated intermediate and di-substituted *N*-Boc pyrrolidine (*S*)-**232a** was observed.

Lab Book Reference: GG6/14

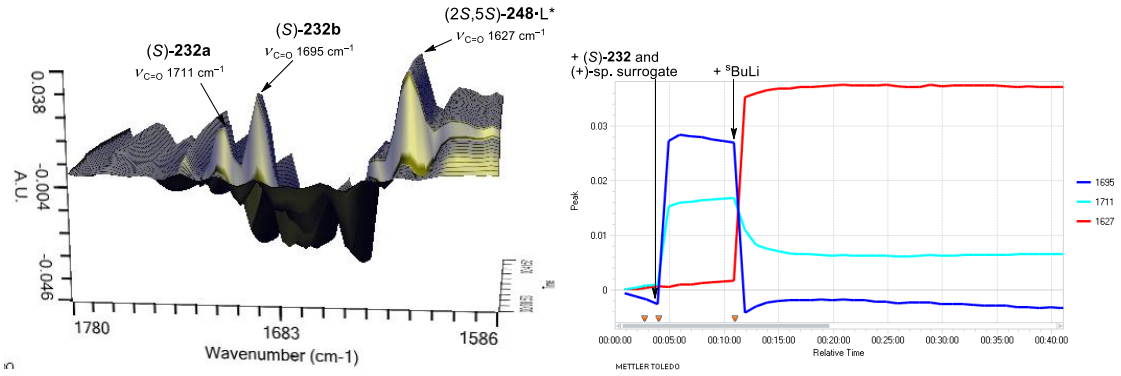




ReactIR™ monitoring of the lithiation of di-substituted *N*-Boc pyrrolidine (*S*)-232 at –40 °C

Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –40 °C, a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of di-substituted *N*-Boc pyrrolidine (*S*)-**232** (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 the 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 –40 °C for 40 min. For di-substituted *N*-Boc pyrrolidine (*S*)-**232**, two peaks at 1711 cm^{-1} and 1695 cm^{-1} were observed and assigned to $\nu_{C=O}$ in the two rotamers (*S*)-**232a** and (*S*)-**232b**. After addition of *s*-BuLi, a new peak at 1627 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 di-substituted *N*-Boc pyrrolidine (*S*)-**232a** and (*S*)-**232b** to give the lithiated intermediate was observed.

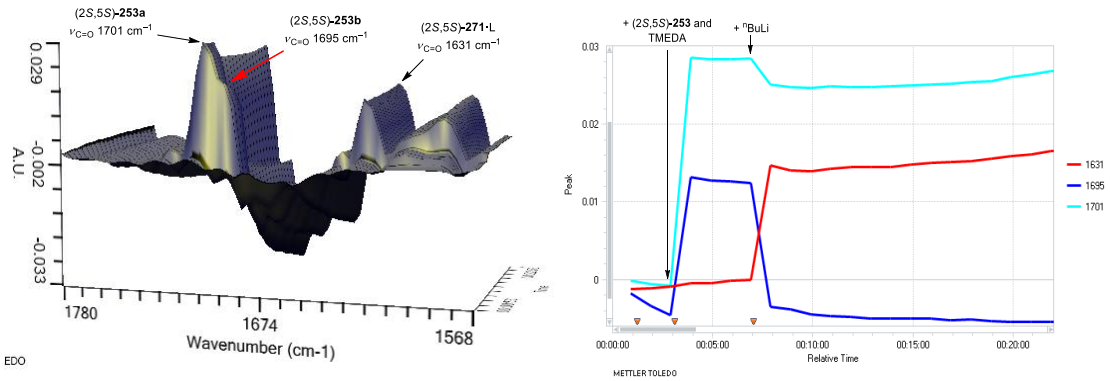
Lab Book Reference: GG6/13



ReactIR™ monitoring of the lithiation of tri-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-253 at –78 °C

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 TMEDA (128 mg, 160 µL, 1.1 mmol, 1.1 eq.) was added followed by a solution of tri-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253** (337 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of the readout on ReactIR™). Then, *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol, 1.1 eq.) was added dropwise. The solution was stirred at –78 °C for 15 min. For di-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253**, two peaks at 1701 cm^{-1} and 1695 cm^{-1} were observed and assigned to $\nu_{C=O}$ in the two rotamers (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b**. After addition of *n*-BuLi, a new peak at 1631 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 di-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253b** to give the lithiated intermediate and di-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253a** was observed.

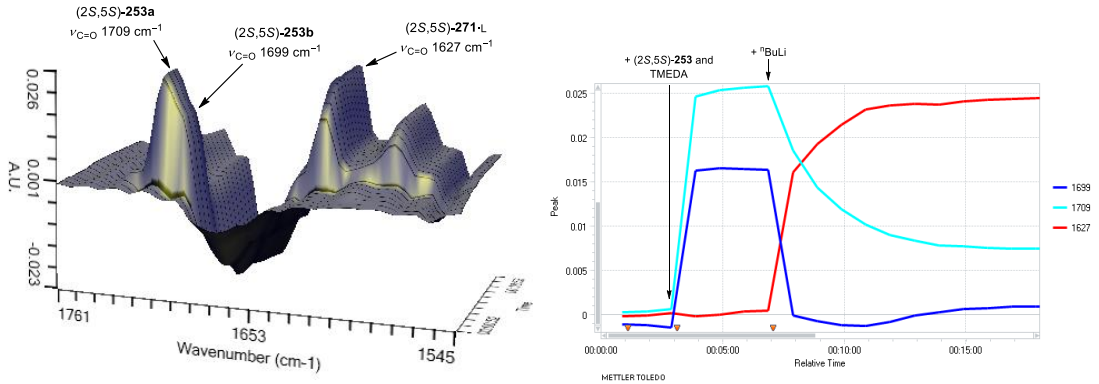
Lab Book Reference: GG6/12



ReactIR™ monitoring of the lithiation of tri-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-253 at –30 °C

Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –30 °C, a solution of TMEDA (89 mg, 110 µL, 0.77 mmol, 1.1 eq.) was added followed by a solution of tri-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253** (240 mg, 0.7 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of the readout on ReactIR™). Then, *n*-BuLi (0.31 mL of a 2.5 M solution in hexanes, 0.77 mmol, 1.1 eq.) was added dropwise. The solution was stirred at –78 °C for 11 min. For di-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253**, two peaks at 1709 cm^{-1} and 1699 cm^{-1} were observed and assigned to $\nu_{C=O}$ in the two rotamers (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b**. After addition of *n*-BuLi, a new peak at 1627 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 7 min, complete lithiation of di-substituted *N*-Boc pyrrolidine (2*S*,5*S*)-**253a** and (2*S*,5*S*)-**253b** to give the lithiated intermediate was observed.

Lab Book Reference: GG6/15



Abbreviations

aq.	Aqueous
Boc	*t*-Butoxycarbonyl
bp	Boiling point
br	Broad
cm^{-1}	Wavenumber
CSP	Chiral Stationary Phase
δ	Chemical shift
d	Doublet
dd	Doublet doublet
ddd	Doublet doublet doublet
dddd	Doublet doublet doublet doublet
ddddd	Doublet doublet doublet doublet doublet
dq	Double quartet
dr	Diastereomeric ratio
er	Enantiomeric ratio
E^+	Electrophile
ESI	Electrospray ionisation
eq.	Equivalent(s)
Et	Ethyl
Et_2O	Diethyl ether

g	Gram(s)
h	Hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infra-red
J	Coupling constant in Hz
µL	Microlitres
m	Multiplet
M	Molar
M^+	Molecular ion
Me	Methyl
mg	Milligrams
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mp	Melting point
MS	Mass spectrometry
m/*z*	Mass to charge ratio
NMR	Nuclear Magnetic Resonance
Petrol	Petroleum ether (fraction which boils at 40-60 °C)

Ph	Phenyl
ppm	Parts per million
q	Quartet
quin	Quintet
R_F	Retention factor
rt	Room temperature
s	Singlet
(+)-sp. surr.	(+)-Sparteine surrogate
t	Triplet
tt	Triplet triplet
TBME	*tert*-Butyl methyl ether
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine

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