Abstract

This thesis describes the development of methodologies for lithiation-trapping and lithiation-arylation of *N*-Boc heterocycles in the position α to nitrogen as well as *in situ* infra-red spectroscopic monitoring of lithiation reactions and the application of lithiation-arylation in total synthesis.

Chapter 2 details the use of *in situ* infra-red spectroscopy to monitor the lithiation of *N*-Boc pyrrolidine, *N*-Boc piperidine, *N*-Boc homopiperidine, an *N*-Boc acetal piperidine, *N*-Boc-*N*′-benzyl piperazine, *N*-Boc-*N*′-*i*-Pr imidazolidine and an *O*-alkyl carbamate in diethyl ether using *s*-BuLi and the diamines TMEDA, (–)-sparteine, or the (+)-sparteine surrogate.

Chapter 3 describes the expansion of a previously reported two-ligand catalytic lithiation-trapping procedure for *N*-Boc pyrrolidine, discussing the optimisation of catalytic lithiation conditions, the use of new bispidine-derived diamine ligands and examples of two-ligand catalytic lithiation-arylation of *N*-Boc pyrrolidine.

The application of stoichiometric and catalytic lithiation-arylation of *N*-Boc pyrrolidine in total synthesis is presented in chapter 4. Lithiation-arylation is used to complete the shortest and most efficient synthesis of (*S*)-nicotine to date, as well as the shortest synthesis of SIB1508Y and to attempt the first asymmetric synthesis of (*R*)-dihydroshihunine. Additionally, a protocol for the lithiation-vinylation of *N*-Boc pyrrolidine is developed and used to carry out the first asymmetric synthesis of (*R*)-maackiamine.

Chapter 5 details the development of a new diamine-free racemic lithiation procedure for the lithiation-trapping and lithiation-arylation of *N*-Boc pyrrolidine, *N*-Boc-*N*′-*i*-Pr imidazolidine and *N*-Boc-*N*′-benzyl piperazine. Additionally, diamine-free lithiations are monitored using *in situ* infra-red spectroscopy.

In chapter 6, benzylic lithiation-trapping of *N*-Boc-2-phenyl pyrrolidine is described. Lithiation-trapping of *rac*-*N*-Boc-2-phenyl pyrrolidine is first discussed, followed by lithiation-trapping of enantioenriched (*R*)-*N*-Boc-2-phenyl pyrrolidine, giving access to products bearing enantioenriched quaternary stereocentres. The use of *in situ* infra-red spectroscopic monitoring was integral to the development of this methodology.

Contents

Acknowledgements

Firstly, I would like to thank Prof. Peter O'Brien for the opportunity to work in his group. Without his help and encouragement, this research would not have been possible. I would also like to thank Prof. Richard Taylor for his assistance and advice as my independent panel member.

Next, I would like to thank the inhabitants of lab D215 during my time at York for making my days so enjoyable. In no particular order: Jonny, Canipa, Julia, Johan, Giorgio, Francesco, Melissa, Rayner, Xiao, Nah, Dave, Palframan, Birch, "Donald" and Giacomo as well as temporary members: Phil, Annika, Greg, Kenny, Boris, Toby, Eeva, Charline, Alastair and Anaïs. Thanks also to the Taylor, Clarke and Fairlamb groups for good times, advice and "loans" of chemicals. I would particularly like to thank Dr. Mike Edwards for several pointers integral to obtaining the results in this thesis.

This research would not have been possible without considerable support from the York technical staff, in particular Steve, Mike and Val from stores, Heather and Amanda for their excellent NMR service and Trevor and Karl for mass spectrometry assistance. Additionally, thanks must go to Prof. Ian Fairlamb for his invaluable assistance with the ReactIR machine, and Prof. Iain Coldham and Dr. Nadeem Sheikh for help with GC.

Finally, special thanks to my family for their support and encouragement over the past four years and especially to Amanda for love and support whenever I needed it.

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.

Graeme Barker

Abbreviations

Ac	acetyl
ADHD	attention deficit hyperactivity disorder
aq	aqueous
Ar	argon
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
CAN	ceric ammonium nitrate
Cb	*N*,*N*-di-*i*-propyl carbamoyl
CIPE	complex induced proximity effect
cm^{-1}	wavenumber
CNS	central nervous system
COD	cyclooctadiene
CSP	chiral stationary phase
CDR	catalytic dynamic resolution
d	doublet
dba	dibenzylidene acetone
dd	double doublet
ddd	double double doublet
DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	di-*i*-butylaluminium hydride
DKR	dynamic kinetic resolution
DMAE	dimethylaminoethanol
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide

DMP	Dess-Martin periodinane
DMPU	*N*,*N'*-dimethylpropylideneurea
dppf	bis-diphenylphosphinoferrocene
dr	diastereomeric ratio
DTR	dynamic thermodynamic resolution
er	enantiomeric ratio
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
g	grams
h	hours
HMPA	*N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high reolution mass spectrometry
Hsp90	heat shock protein 90
Hz	Hertz
Ipc	*iso*-pinocamphenyl
IR	infra-red
KHMDS	potassium hexamethyldisilazide
LC-MS	liquid chromatography-mass spectrometry
LiDMAE	lithium dimethylaminoethoxide
M	molar
m	multiplet
Me	methyl
min	minutes
mp	melting point
MS	mass spectrometry

NAChR	nicotinic acetylcholine receptor
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
PMDTA	*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
q	quartet
R_F	retention factor
rt	room temperature
s	singlet
(–)-sp	(–)-sparteine
t	triplet
TBAF	tetrabutyl ammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS	*t*-butyl trimethylsilyl
TBME	*t*-butyl methyl ether
Tf	trifluoromethyl sulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri-*i*-propyl silyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMPDA	*N*,*N*,*N*′,*N*′-tetramethylpropylenediameine
TMS	trimethylsilyl
Ts	*para*-toluene sulfonyl
UV	ultraviolet

Chapter One: Introduction

1.1 Organolithium Reagents in Modern Organic Synthesis

It is an understatement to say that organolithiums are of great importance to modern organic chemistry. It is a rare total synthesis that proceeds without their use. For example, Suzuki's recently reported synthesis of seragakinone A begins with a *n*-BuLi-mediated bromine-lithium exchange.[1] We confidently expect an undergraduate chemist to be familiar with the structures and reactivity of the common reagents. While most chemists will primarily associate organolithium reagents with deprotonation chemistry, their reactivity is broader then this, encompassing a wealth of transformations fundamental to organic synthesis. The vast range of organolithium chemistry and the ubiquity of their use in total syntheses of natural products and drug molecules remains a cornerstone of modern chemistry. The central importance of organolithium reagents drives the discovery of new methodologies and reagents. This thesis focuses on the development of new methodologies using the common reagents *s*-BuLi and *n*-BuLi in their familiar role as strong bases.

1.1.1 Structure and Reactivity of Common Organolithium Reagents

While it is tempting to think of alkyllithium reagents in purely ionic terms, a closer inspection reveals that the C–Li bond which, while ionic in nature, exhibits significant covalent character. This makes organolithium reagents very reactive nucleophiles and bases, with pK_as >35. Although the presence of a highly ionic bond would suggest otherwise, organolithium reagents are surprisingly soluble in a range of organic solvents. The most common reagents, the BuLi's, are commercially available in a variety of hydrocarbon solvents (commonly cyclohexane/mixed hexanes) and at a range of concentrations. Such solutions can be kept for many months in the absence of water and air at low (~5 °C) temperatures.[2] Two other common organolithium reagents, MeLi and PhLi, are less soluble in purely hydrocarbon solutions, and are solubilised by the addition of ethereal cosolvents.[2] *s*-BuLi (which contains a stereogenic centre) is widely used in place of the stereochemically simpler *i*-PrLi since *i*-PrLi is pyrophoric.

A single alkyl group does not provide adequate stabilisation to the electron deficient Li atom of organolithium compounds. Thus, while alkyllithiums are commonly thought of as monomers in terms of synthetic design, in reality they exist in hydrocarbon solution as

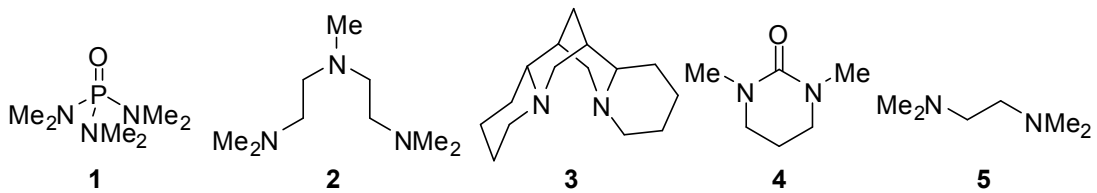
one of a range of aggregates. Primary alkyllithiums such as EtLi and *n*-BuLi exist in solution as hexamers, with an octahedral arrangement of Li atoms bridged by the alkyl groups.[2] The more sterically demanding alkyllithiums *i*-PrLi, *s*-BuLi and *t*-BuLi are tetramers, with a tetrahedron of Li atoms bridged by the alkyl groups. Dimeric aggregates occur with the very sterically hindered alkyl groups benzyllithium and menthyllithium.[2] The propensity of alkyllithium reagents to form aggregates in solution allows chemists to carefully modulate their reactivity by addition of cosolvents. By providing an alternative source of electron density for the Li atom, we can favour the formation of lower aggregates. While it is commonly thought that forming lower aggregates increases the reactivity of the alkyllithium, in reality the nature of the ligand plays an equally important role in modulating organolithium reactivity.

1.1.2 Ligands for Organolithium Reagents: Modifying Reactivity

Frequently, organolithium reagents are used in conjunction with a ligand additive to modulate their reactivity. Most commonly, reactions are carried out in diethyl ether or THF. Donation of electron density from oxygen favours the formation of smaller aggregates than those which occur in hydrocarbon solvents. Thus, in diethyl ether and THF, MeLi, EtLi and *n*-BuLi form tetramers, whereas *i*-PrLi, *s*-BuLi, *t*-BuLi and PhLi form dimers.[2, 3] Monomers are formed for benzyllithium, *t*-BuLi and PhLi in THF at temperatures below –100 °C.

Deaggregation of alkyllithium reagents can also be achieved by the addition of diamine or polyamine ligands. These are typically used in proportion to the organolithium reagent rather than as solvents. The most important examples are HMPA **1**, PMDTA **2**, (–)-sparteine **3**, DMPU **4** and TMEDA **5** (figure 1.1).[2]

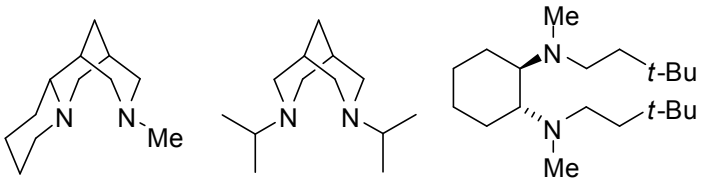
Figure 1.1



1 **2** **3** **4** **5**

Other important diamine ligands used in the research described in this thesis include the (+)-sparteine surrogate **6**[4] developed in our group, di-*i*-Pr bispidine **7**,[5] and the cyclohexane diamine (*R*,*R*)-**8**[6] first developed by Alexakis (figure 1.2).

Figure 1.2



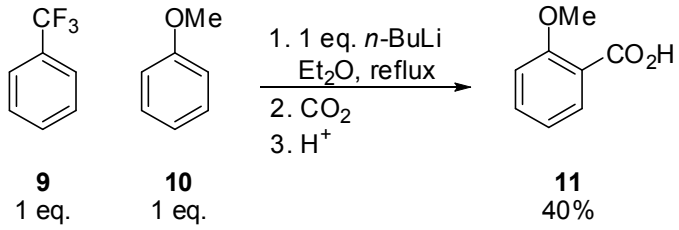
6 **7** (*R*,*R*)-**8**

It is important to note that although the reactivity of an organolithium reagent generally increases with the deaggregating power of the ligand present, this does not completely explain the differences between different organolithium-ligand complexes in solution. Care must be taken to avoid confusion between the deaggregating power of the ligand and the ability of the organolithium-ligand complex to effect the desired reaction.

1.2 Directed Lithiation of Substrates Using Organolithium Reagents

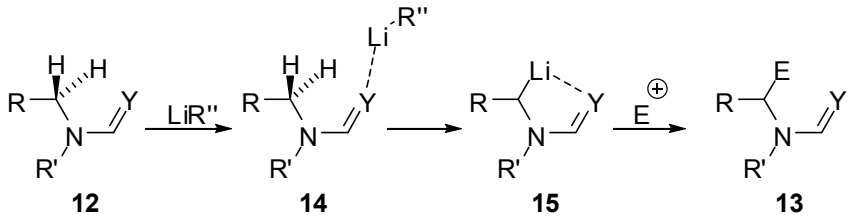
Substrate-directed deprotonation reactions provide a method for selective lithiation of starting materials. The first example of such a method was reported in 1946 by Roberts.[7] It was shown that lithiation of trifluoromethylbenzene **9** with *n*-BuLi gave solely *ortho*- and *meta*-lithiation. Furthermore, a competition experiment treating 1 equivalent of each of **9** and anisole **10** with 1 equivalent of *n*-BuLi followed by trapping with CO_2 gave only *ortho*-anisic acid **11** (scheme 1.1). It was concluded that regioselectivity was achieved through precomplexation of the alkyllithium to either CF_3 or OMe and that OMe was a better coordinating group than CF_3. Competition experiments allowed the determination of the relative coordinating abilities of a small range of aromatic substituents.[7]

Scheme 1.1



Directed lithiation has been co-opted for the installation of electrophile-derived substituents in synthesis. Typically, such a strategy involves installation of a directing group C=Y onto an unprotected heteroatom (*e.g.* nitrogen) to give **12** which enables lithiation at the position α to the heteroatom substituent. Electrophilic trapping then gives **13** (scheme 1.2). Subsequent removal of the directing group would release the newly modified substrate.

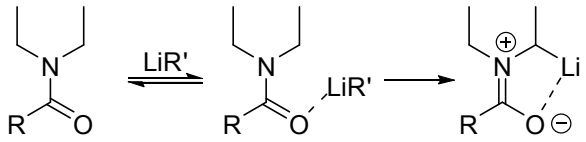
Scheme 1.2



This mechanism, wherein the Lewis basic directing group C=Y of substrate **12** facilitates formation of complex **14** prior to lithiation was termed the "complex induced proximity effect" (CIPE) by Beak and Meyers in 1986.[8] In 1984,[9] Beak reviewed

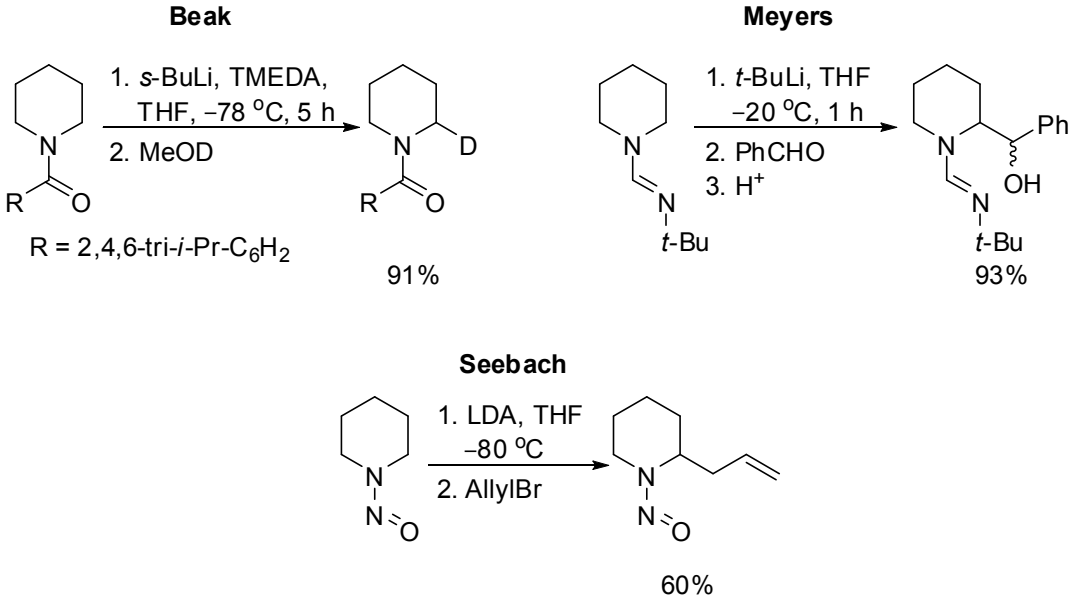
directed lithiations of amines, and further progress *via* the CIPE facilitated lithiations on a range of substrates was reviewed in 1996[10] and 2004.[11] Complex **14** was termed the "prelithiation complex." Reactivity towards deprotonation is increased by the prelithiation complex holding the alkyllithium reagent in close proximity to the reactive α-proton. Additionally, lithiated intermediate **15** is stabilised by an adjacent positive charge on the heteroatom – a so-called dipole stabilised carbanion. Examples of the prelithiation complex and the dipole stabilised carbanion for an amide directing group are shown in scheme 1.3.[12]

Scheme 1.3



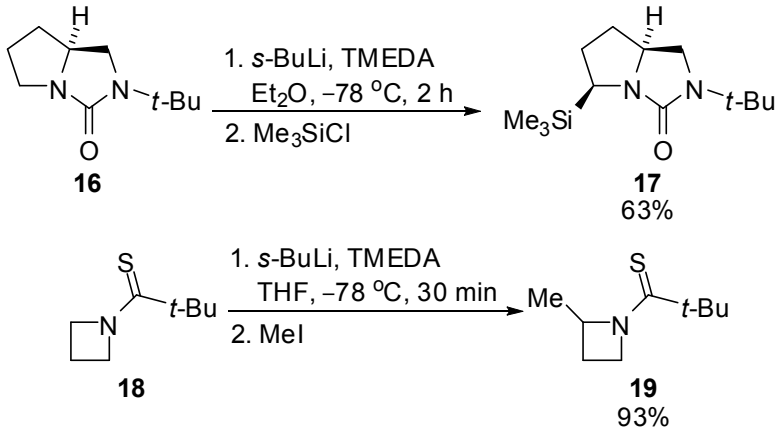
The groups of Beak, Seebach and Meyers were instrumental in the development of CIPE lithiation methodologies, reporting a number of different directing groups. Extensively investigated examples include amides used by Beak,[9, 13-20] formamidines used by Meyers,[9, 21-24] and the more exotic nitroso group used by Seebach (scheme 1.4).[25, 26]

Scheme 1.4



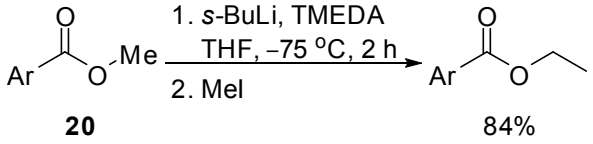
Amides, formamidines and the nitroso group are not the only directing groups that have been used. The requirements for CIPE directing groups are Lewis basicity to allow complexation of the organometallic reagent and a low reactivity towards nucleophilic attack to allow deprotonation to occur. Typically, α-deprotonation is favoured by installation of a sterically hindered directing group. A recent example of lithiation mediated by a different directing group is the lithiation of urea **16**, reported by Metallinos. In this case, lithiation *cis* to the directing group occurred to give **17** in 63% yield (scheme 1.5).[27] Another recent example is Hodgson's thioamide-mediated lithiation of azetidine **18** to give methylated azetidine **19** in 93% yield (scheme 1.5).[28] This thesis will focus on lithiation of *N*-Boc secondary amines, first reported by Beak, and use of the *N*-Boc group is covered in detail in section 1.3.[29]

Scheme 1.5

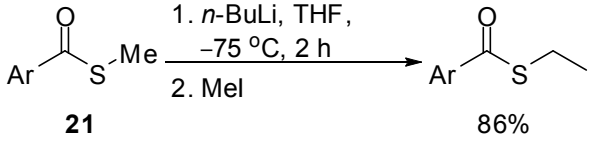


Given the requirement for a directing group to be resistant to nucleophilic attack by the base used for deprotonation, it is perhaps surprising that esters can be used to effect directed lithiation. Beak used a very hindered ester **20** to achieve substitution of methanol (scheme 1.6).[30] Beak also reported using a similarly hindered system to carry out lithiation-trapping of thioester **21** (scheme 1.6).[13]

Scheme 1.6



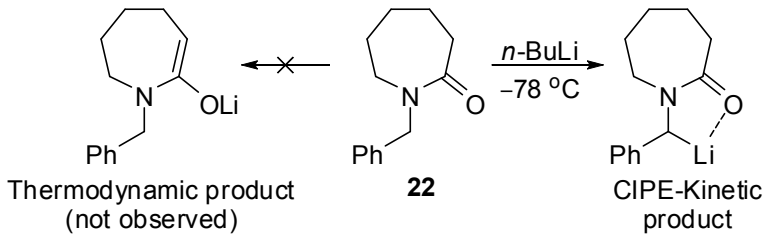
Ar = 2,4,6-tri-*i*-Pr-C_6H_2



Ar = 2,4,6-tri-Et-C_6H_2

As well as facilitating lithiation α to heteroatoms, the CIPE also affects the regiochemistry of lithiation to favor kinetic products. For example, lithiation of *N*-benzylamide **22** gave exclusively benzylic lithiation as opposed to the thermodynamically favoured enolate lithiation product (scheme 1.7).[8, 31]

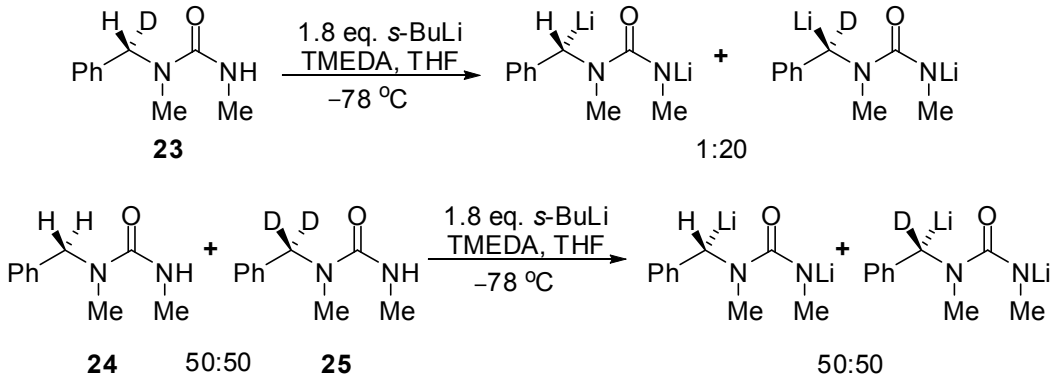
Scheme 1.7



While the CIPE can explain observed products from lithiation reactions, some debate in the literature has taken place over the precise mechanistic details. For example, it was initially unclear whether the prelithiation complex existed in solution as a discrete species (the CIPE model), or whether deprotonation takes place as soon as the alkyllithium reagent becomes associated with the directing group (the "kinetically enhanced metallation" model).[32] Beak attempted to probe the formation of the prelithiation complex using deuterated ureas. Lithiation of α-monodeuterated urea **23** with *s*-BuLi/TMEDA resulted in a 20:1 preference for the removal of the proton over deuterium. This was expected based on the kinetic isotope effect. However, lithiation using *s*-BuLi/TMEDA of a 50:50 mixture of undeuterated urea **24** and α,α-dideuterated urea **25** resulted in a 50:50 mixture of lithiated products. No preference for the removal of a

proton over deuterium was observed. This suggested that the first step in the lithiation is the *irreversible* formation of a prelithiation complex (scheme 1.8).[33] In contrast, it can be imagined that if lithiation proceeded *via* the kinetically enhanced metallation model, a 20:1 kinetic isotope effect would be observed. *In situ* infra-red spectroscopic studies have also been used to verify the CIPE model and these will be presented in chapter 2.

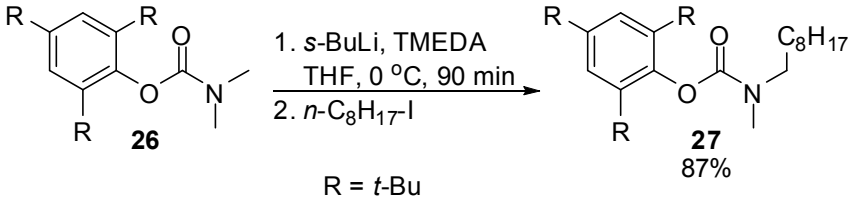
Scheme 1.8



1.3 Lithiation-Trapping of Carbamates

Seebach reported the first use of carbamates as a directing group for lithiation.[34] Using sterically bulky carbamate **26**, *s*-BuLi/TMEDA-mediated lithiation was carried out to give substituted dimethylamines such as **27** (scheme 1.9).

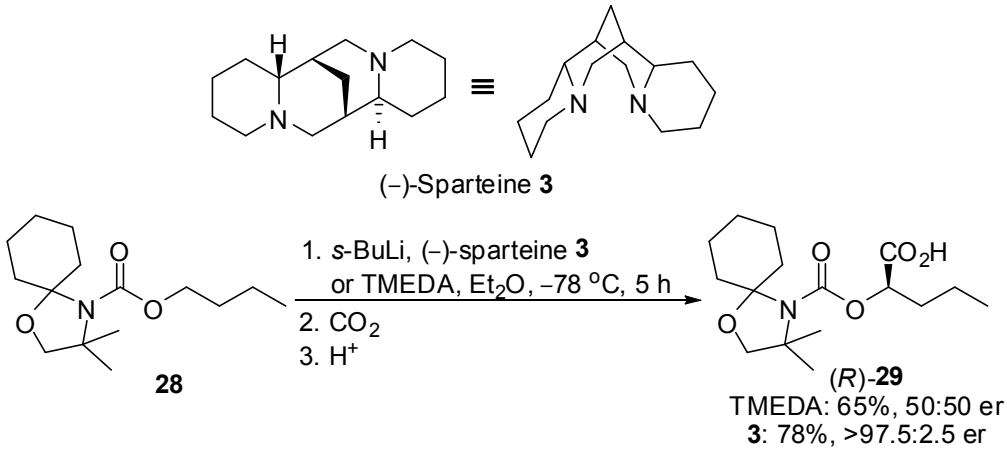
Scheme 1.9



1.3.1 Lithiation α to Oxygen in *O*-Alkyl Carbamates

Complexes of alkyllithiums and chiral diamine ligands can be used to effect enantioselective lithiation of carbamate substrates. The most commonly used chiral diamine ligand is (–)-sparteine **3**. Early work on *s*-BuLi/(–)-sparteine **3**-mediated lithiations of carbamates was carried out by Hoppe. Lithiation α to oxygen in *O*-alkyl carbamates using *s*-BuLi/TMEDA was investigated in the 1980s.[35-37] For example, lithiation of *O*-alkyl carbamate **28** with *s*-BuLi/TMEDA and then trapping with carbon dioxide gave a 65% yield of acid *rac*-**29** (scheme 1.10) Subsequently, Hoppe reported enantioselective lithiation of *O*-alkyl carbamates using the *s*-BuLi/(–)-sparteine **3** complex. Thus, treatment of carbamate **28** with *s*-BuLi/(–)-sparteine **3** and then trapping with carbon dioxide gave acid (*R*)-**29** in 78% yield and >97.5:2.5 er (scheme 1.10).[38, 39]

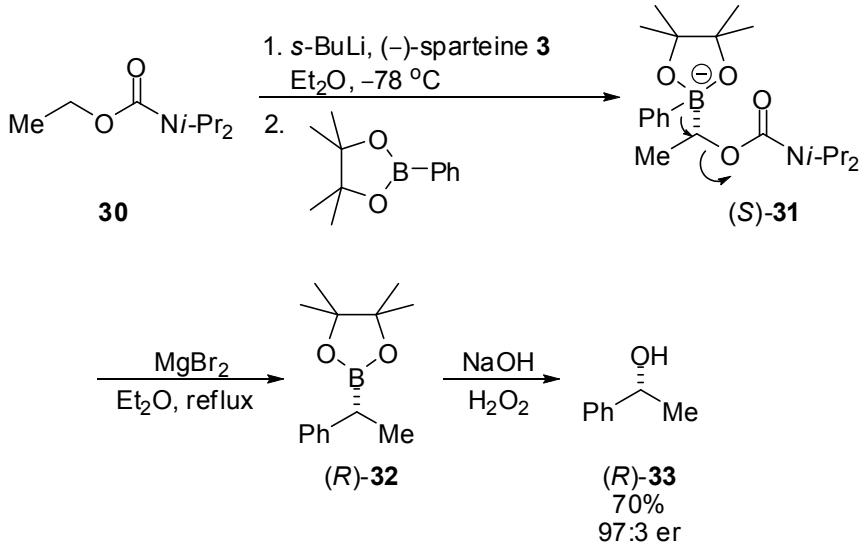
Scheme 1.10



Enantioselective lithiation of *O*-alkyl carbamates was extensively studied by the Hoppe group throughout the 1990s and 2000s. In 2005, Würthwein and Hoppe published DFT calculation evidence which confirmed the experimental observations of the preferential removal of the *pro*-*S* proton by the *s*-BuLi/(–)-sparteine **3** complex.[40] Hoppe's methodology has found some synthetic use as a convenient synthesis of enantioenriched 2-substituted alcohols. Examples of its use in total syntheses include Hoppe's syntheses of (*R*)-pantolactone[41] and (*S*)-1-methyldodecylacetate,[42] a fruit fly pheromone, Taylor's synthesis of (*R*)-japonilure[43] and Brückner's synthesis of an algae nonaether.[44]

A further development of Hoppe's methodology involves trapping a lithiated carbamate with an organoboron electrophile and subsequent rearrangement of the trapped product. Kocienski and Hoppe both showed that such a trapped product underwent a 1,2-rearrangement to give a new organoboronate product with loss of the carbamoyl motif.[45-47] The full utility of this methodology was ultimately revealed by Aggarwal and co-workers, who further optimised the method and applied it to new substrates.[48] Thus, *O*-alkyl carbamate **30** was lithiated and trapped with a boronate ester to give boronate (*S*)-**31**, which underwent rearrangement in the presence of magnesium bromide to give a new boronate ester (*R*)-**32**. Cleavage of the C–B bond with H_2O_2 then reinstalled a hydroxyl group. In effect, carbamate **30** has been substituted and deprotected to reveal the parent alcohol (*R*)-**33** in one pot (scheme 1.11).

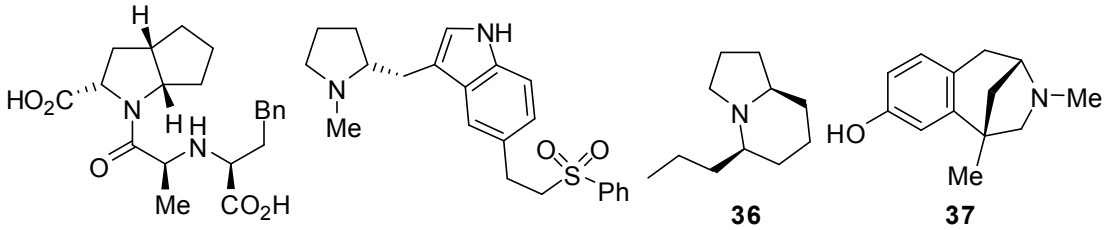
Scheme 1.11



1.3.2 Lithiation-Trapping of *N*-Boc Pyrrolidine

Carbamate-directed lithiations provide a convenient route for the installation of a substituent in the 2-position of pyrrolidines. 2-Substituted pyrrolidines are a common motif in natural products and biologically active molecules. Examples include the drug molecules Altace **34** (King Pharmaceuticals, heart disease) and Relpax **35** (Pfizer, migrane) and the natural products (–)-indolizidine 167B **36** and (–)-aphanorphine **37** (figure 1.3).[49, 50]

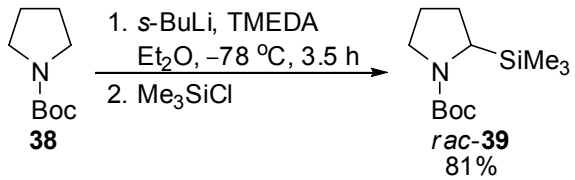
Figure 1.3



34 **35** **36** **37**

Beak reported in 1989 that treatment of *N*-Boc pyrrolidine **38** with *s*-BuLi/TMEDA followed by electrophilic trapping provided high yields of racemic 2-substituted pyrrolidines. It was found that the *N*-Boc carbamate group both facilitated α-lithiation and was sufficiently sterically hindered to prevent nucleophilic attack by the *s*-BuLi at the carbamate carbonyl group.[29] For example, lithiation of *N*-Boc pyrrolidine **38** with *s*-BuLi/TMEDA and then trapping with trimethylsilyl chloride provided racemic silyl pyrrolidine *rac*-**39** in 81% yield (scheme 1.12). The well-known chemistry of the *N*-Boc protecting group, with ease of installation and removal, was an additional advantage.

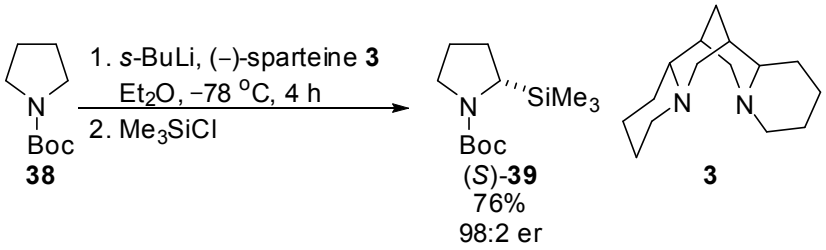
Scheme 1.12



In 1991, Beak expanded this methodology to show that lithiation mediated by *s*-BuLi/(–)-sparteine **3** and then trapping provided high yields of 2-substituted pyrrolidines with

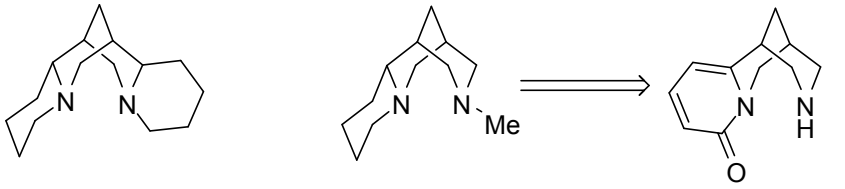
high enantioselectivity. For example, upon trapping with trimethylsilyl chloride (*S*)-**39** was formed in 76% yield and 98:2 er (scheme 1.13).[51, 52]

Scheme 1.13



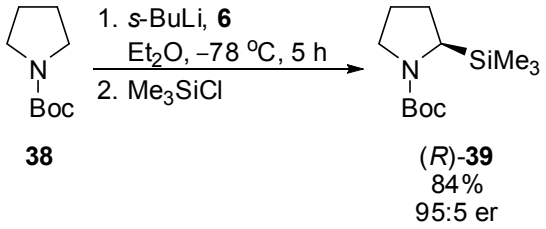
A limitation of this methodology is that sparteine **3** has, up until recently, only been commercially available as the (–)-enantiomer. Currently, even (–)-sparteine **3** is not commercially available. Our group has attempted to address the lack of availability of (+)-sparteine by the development of (+)-sparteine surrogate **6**.[4, 53-56] It is worth noting that the synthesis of (+)-sparteine surrogate **6** starts from the natural product (–)-cytisine **40** which is also only available in one enantiomeric form (scheme 1.14).

Scheme 1.14



It was shown that (+)-sparteine surrogate **6** displays similar yields and enantiocomplementarity to (–)-sparteine **3** in the lithiation-trapping of *N*-Boc pyrrolidine **38**. For example, lithiation of *N*-Boc pyrrolidine **38** with *s*-BuLi/(+)-sparteine surrogate **6** gave (*R*)-**39** in 84% yield and 95:5 er after trapping with trimethylsilyl chloride (scheme 1.15).[4, 57] It was also shown to be successful in lithiations of *O*-alkyl carbamates, providing trapped products in high yield and er.[58]

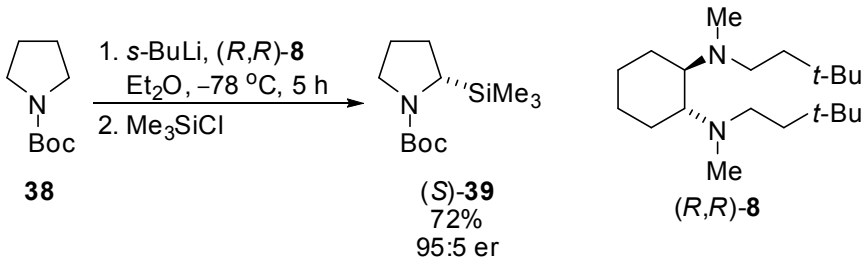
Scheme 1.15



38 (*R*)-**39** 84% 95:5 er

Another alternative chiral diamine ligand for use in the enantioselective lithiation of *N*-Boc pyrrolidine **38** is the cyclohexane diamine-derived ligand (*R*,*R*)-**8**.[59] Lithiation of **38** by *s*-BuLi/(*R*,*R*)-**8** provided substituted pyrrolidines in similar yields and enantioselectivity to (–)-sparteine **3** and (+)-sparteine surrogate **6** (scheme 1.16). Thus, lithiation-trapping of *N*-Boc pyrrolidine **38** with *s*-BuLi/(*R*,*R*)-**8** gave (*S*)-**39** in 72% yield and 95:5 er. Conveniently, the synthesis of **8** began with a resolution of the racemic parent cyclohexane-1,2-diamine. Thus, either enantiomer of **8** could be prepared.[59] Ligand **8** has recently become commercially available (€164.30/1 g for each enantiomer, TCI 2011).

Scheme 1.16

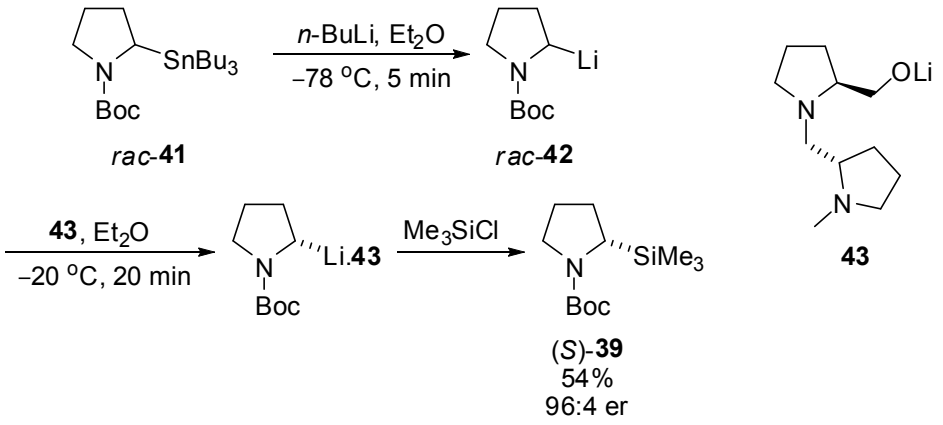


38 (*S*)-**39** 72% 95:5 er (*R*,*R*)-**8**

Mechanistically, Beak showed that the enantioenrichment arises in the deprotonation step – the chiral diamine/alkyllithium complex removes one prochiral proton faster than the other, *i.e.* enantioselectivity is controlled by the kinetics of deprotonation.[52] Another method of obtaining enantioenriched products from lithiation-trapping experiments is the dynamic-thermodynamic resolution (DTR) lithiation protocol developed by Beak.[10] In this case, enantioenrichment arises from equilibration of the diastereomeric complex of lithiated pyrrolidine and chiral ligand to the most thermodynamically favourable diastereomer. Alternatively, one diastereomer can react with the electrophile faster to promote dynamic kinetic resolution (DKR). For example, tin-lithium exchange of racemic stannane *rac*-**41** with *n*-BuLi generated racemic lithiopyrrolidine **42**. Trapping

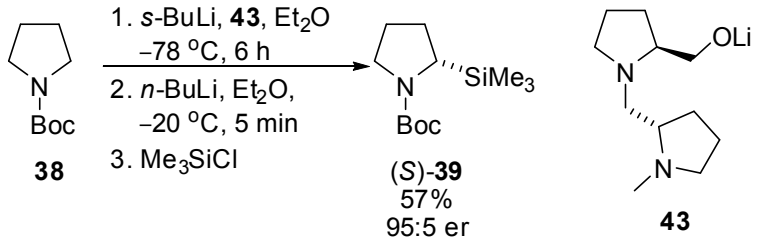
with trimethylsilyl chloride allowed DKR to give substituted pyrrolidines in good yield and high er.Silyl pyrrolidine (*S*)-**39** was obtained in 54% and 96:4 er (scheme 1.17).[60]

Scheme 1.17



DKR *via* deprotonation of *N*-Boc pyrrolidine **38** in the presence of *s*-BuLi/**43** was also reported, with silyl pyrrolidine (*S*)-**39** isolated in 57% yield and 95:5 er (scheme 1.18).[60] DTR of *N*-alkyl 2-lithiated pyrrolidines has also been reported.[61-63]

Scheme 1.18

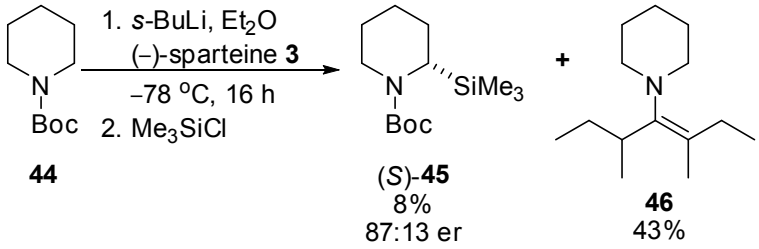


1.3.3 Lithiation-Trapping of *N*-Boc Piperidine

Given the ease of lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi/(–)-sparteine **3**, it is perhaps surprising that the analogous *N*-Boc piperidine **44** is far more difficult to lithiate. The very reactive *s*-BuLi/TMEDA complex can effect lithiation of *N*-Boc piperidine **44**, but less favourable results were obtained with (–)-sparteine **3**.[29, 64] Beak reported the results of a computational study which indicated that the α-protons of *N*-Boc piperidine **44** are less acidic than those of *N*-Boc pyrrolidine **38**.[64] It was also shown that for *N*-Boc piperidine **44**, there was less energetic difference between removal of a *pro-R* and a *pro-S* proton by *s*-BuLi/(–)-sparteine **3** than for *N*-Boc pyrrolidine **38**. Experimentally, lithiation of **38** with *s*-BuLi/(–)-sparteine **3** and then trapping provided a 71% yield of adduct (*S*)-

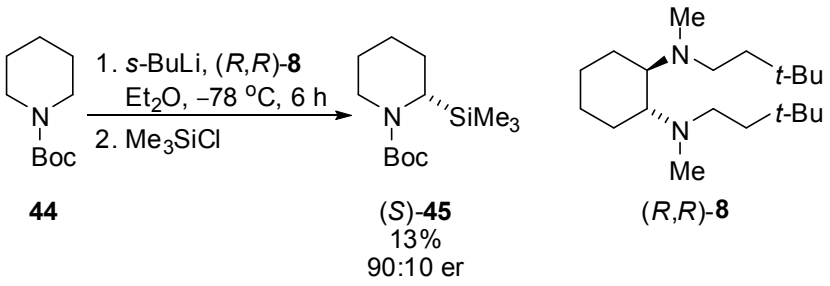
39 after 4-6 h (scheme 1.13), but only 8% of *N*-Boc piperidine product (*S*)-**45**. Additionally, a 43% yield of enamine **46** was obtained, indicating that attack of *s*-BuLi at the Boc group was competitive with deprotonation (scheme 1.19).[64, 65]

Scheme 1.19



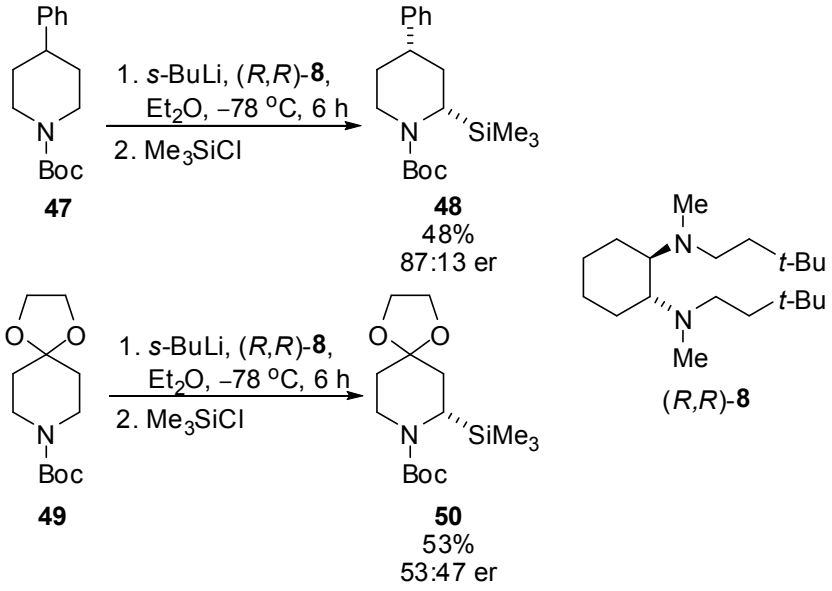
The next development in *N*-Boc piperidine **44** lithiation methodology came in 2007 when it was shown that lithiation of *N*-Boc piperidine **44** with *s*-BuLi/cyclohexane diamine (*R*,*R*)-**8** gave a slightly improved result compared to (–)-sparteine **3**: 13%, 90:10 er of product (*S*)-**45** after 6 h *vs.* 8%, 87:13 er after 16 h (scheme 1.20).[65] Other diamines were also investigated, but gave far lower enantioselectivities.

Scheme 1.20



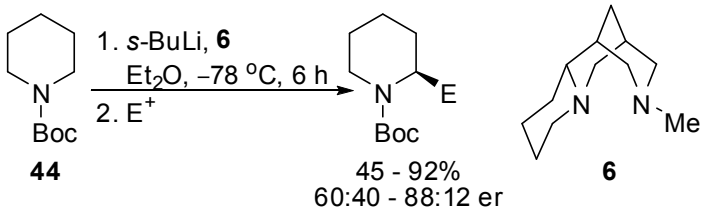
It has also been shown that piperidines with 4-substituents are easier to lithiate than the parent *N*-Boc piperidine **44**. For example, lithiation of 4-phenyl piperidine **47** with *s*-BuLi/(*R*,*R*)-**8** and then trapping with trimethylsilyl chloride gave adduct **48** in 48% yield and 87:13 er. Acetal piperidine **49** was also found to be easier to lithiate than *N*-Boc piperidine **44**. Thus, lithiation with *s*-BuLi/(*R*,*R*)-**8** and then electrophilic trapping gave a 53% yield of silyl piperidine (*S*)-**50** in 53:47 er (scheme 1.21).[65]

Scheme 1.21



Using competition experiments, it was shown that *s*-BuLi/(+)-sparteine surrogate **6** is a faster lithiator than *s*-BuLi/(–)-sparteine **3**.[66] Thus, our group hypothesised that it would be of use in lithiating *N*-Boc piperidine **44**. Indeed, lithiation of *N*-Boc piperidine **44** with *s*-BuLi/**6** gave high yields and ers of substituted piperidines (scheme 1.22).[67] Simultaneously, the configurational stability of the lithiated piperidine was probed. Much like *N*-Boc pyrrolidine **38**, configurational instability of lithiated *N*-Boc piperidine **44** becomes a significant factor at temperatures above –40 °C.[67]

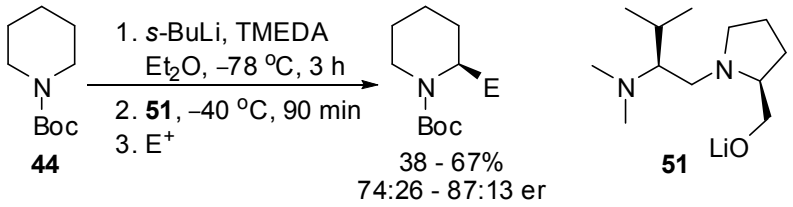
Scheme 1.22



Given that lithiation of *N*-Boc piperidine **44** can easily be effected with *s*-BuLi/TMEDA, DTR lithiation is also an attractive way of generating lithiated piperidines. Coldham showed that, using ligand **51**, trapped piperidines could be obtained in acceptable yields and enantioselectivities. Thus, lithiation of *N*-Boc piperidine **44** using *s*-BuLi/TMEDA, addition of ligand **51** and warming to –40 °C before electrophilic

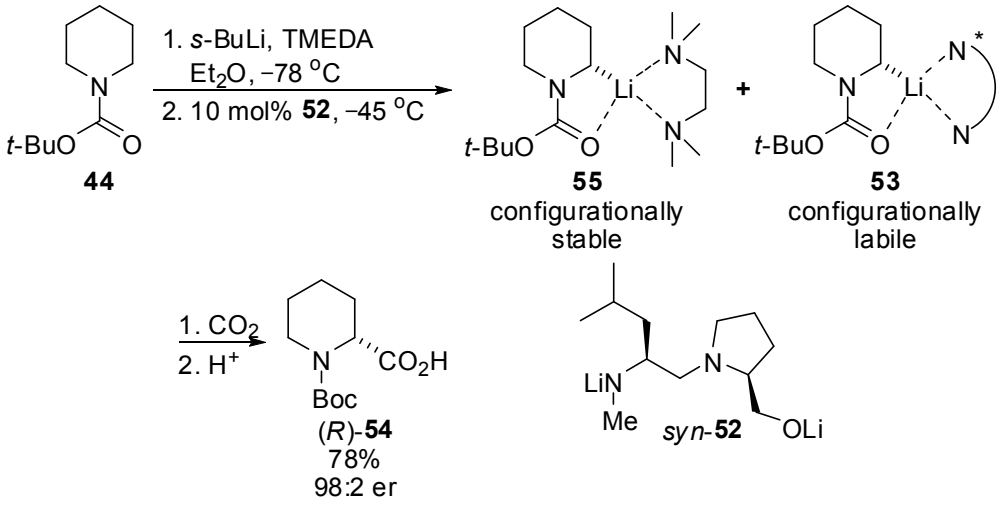
trapping gave 2-substituted piperidines in 38-67% yield and enantioselectivites between 74:26 and 87:13 er (scheme 1.23).[68]

Scheme 1.23



A recent development of this DTR route to substituted piperidines is the catalytic dynamic resolution (CDR) lithiation protocol developed by Gawley. Lithiation of *N*-Boc piperidine **44** was carried out using *s*-BuLi and a stoichiometric amount of TMEDA. Addition of a substoichiometric amount of chiral ligand *syn*-**52**, with warming to –45 °C then followed by electrophilic trapping gives access to substituted piperidines in high yields and enantioselectivity. For example, trapping with CO_2 gives acid (*R*)-**54** in 78% yield and 98:2 er. A satisfactory explaination for the enantioselectivity of this protocol has yet to be proposed. Nevertheless, products were obtained in 98:2 er – a higher enantioselectivity than was obtained using DTR, or enantioselective lithiation.

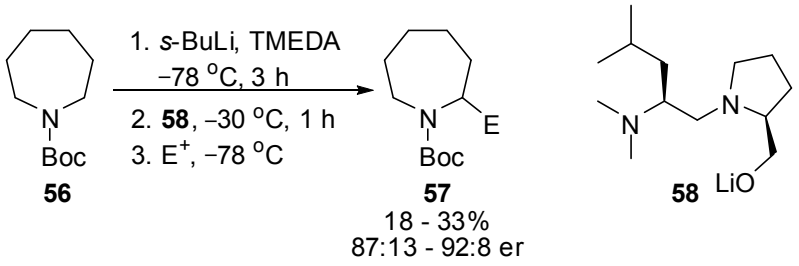
Scheme 1.24



1.3.4 Lithiation-Trapping of Other *N*-Boc Amines

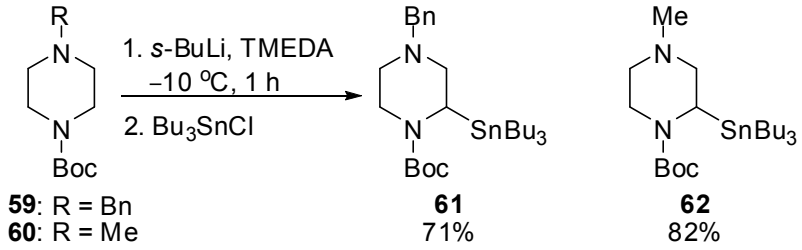
In comparison to pyrrolidine and piperidine, the 7-membered analogue *N*-Boc homopiperidine **56** has received relatively little attention. Beak reported racemic lithiation-trapping using *s*-BuLi/TMEDA and Dieter and co-workers carried out another isolated example.[29, 69] Coldham reported the only example of a lithiation-trapping route to enantioenriched 2-substituted homopiperidines. Using a DTR lithiation strategy, trapped products **57** were obtained in modest yields (18-33%), and enantioselectivity comparable to those obtained in other DTR lithiations (87:13-92:8 er) (scheme 1.25).[68]

Scheme 1.25



The lithiation-trapping of *N*-Boc piperazines **59** and **60** has also been investigated. In 2005, Van Maarseveen reported the *s*-BuLi/TMEDA-mediated racemic lithiation of *N*-Boc-*N*′-benzyl piperazine **59** and *N*-Boc-*N*′-methyl piperazine **60**, obtaining good yields (scheme 1.26).[70] Martin subsequently used this protocol in a synthesis of the natural product (–)-alstonerine.[71]

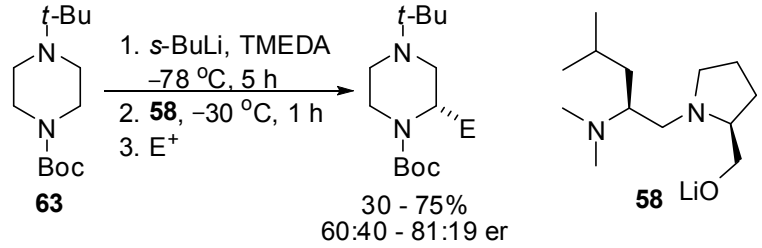
Scheme 1.26



The first example of an enantioselective lithiation of *N*-Boc piperazine was reported by McDermott in 2008. In this case, *N*-Boc-*N*′-*t*-butylpiperazine was lithiated with *s*-BuLi/(–)-sparteine **3**. However, only one electrophile (CO_2) was reported, and the conditions were not optimised.[72] In contrast, Coldham applied DTR lithiation conditions to *N*-Boc-*N*′-*t*-butylpiperazine **63**, trapping with a range of electrophiles in modest yields and ers

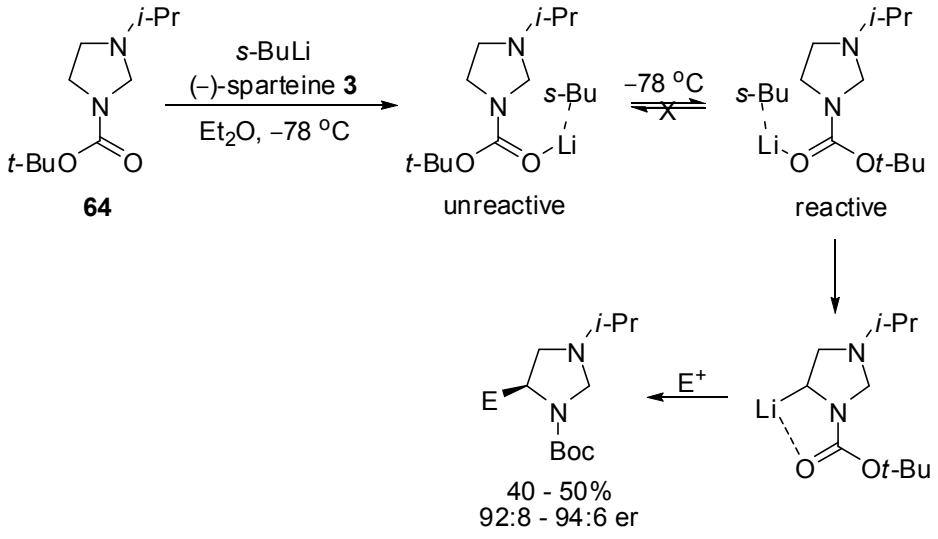
(scheme 1.27). Selected examples of *N*-Boc-*N*′-methyl and *N*-Boc-*N*′-benzyl piperazines **60** and **59** were also reported.[73]

Scheme 1.27



In 2001, the enantioselective lithiation of *N*-Boc imidazolidines was reported by Coldham. For example, treatment of *N*-Boc-*N*′-isopropylimidazolidine **64** with *s*-BuLi/(–)-sparteine and then electrophilic trapping gave products in high er, but with ≤50% yield.[74, 75] It was hypothesised that at –78 °C, the *N*-Boc rotamers do not interconvert. As lithiation depends on the Boc directing group orientating the alkyllithium reagent towards the acidic proton, the maximum theoretical yield was defined by the ratio of the Boc rotamers in solution (scheme 1.28).[74]

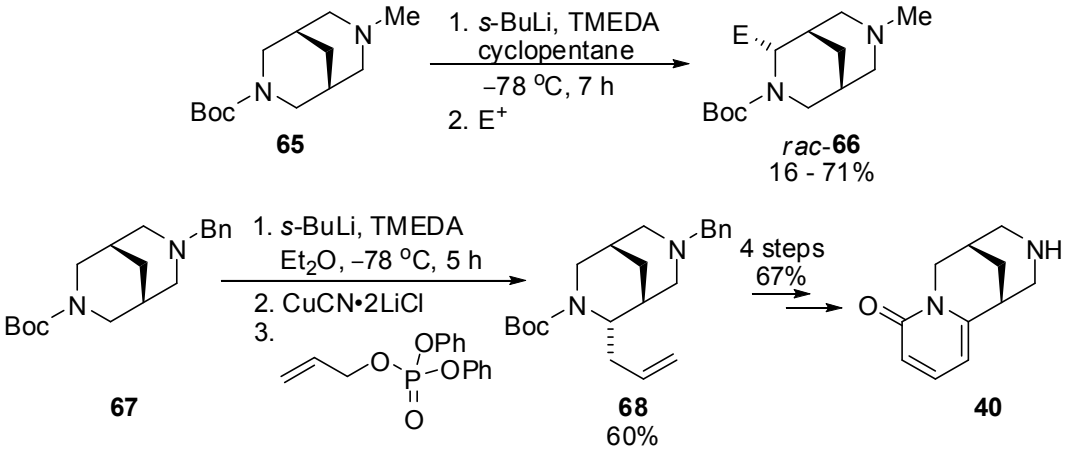
Scheme 1.28



Lithiation of fused ring systems has also been investigated. Our group reported the racemic lithiation of *N*-Boc-*N*′-methylbispidine **65** using *s*-BuLi/TMEDA and trapped products were obtained in modest yields (scheme 1.29).[76] Lithiation-trapping of the

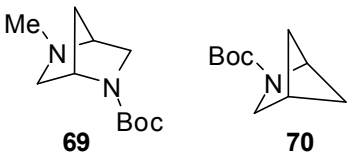
analogous *N*-Boc-*N*′-benzylbispidine **67** was later used to complete a total synthesis of the natural product (±)-cytisine **40** (scheme 1.29).[77]

Scheme 1.29



Other examples of racemic lithiations of fused ring amines include the *s*-BuLi/TMEDA-mediated deprotonation of **69**, reported by Jordis *et al.*,[78] and of **70**, reported by Krow *et al.* (figure 1.4).[79]

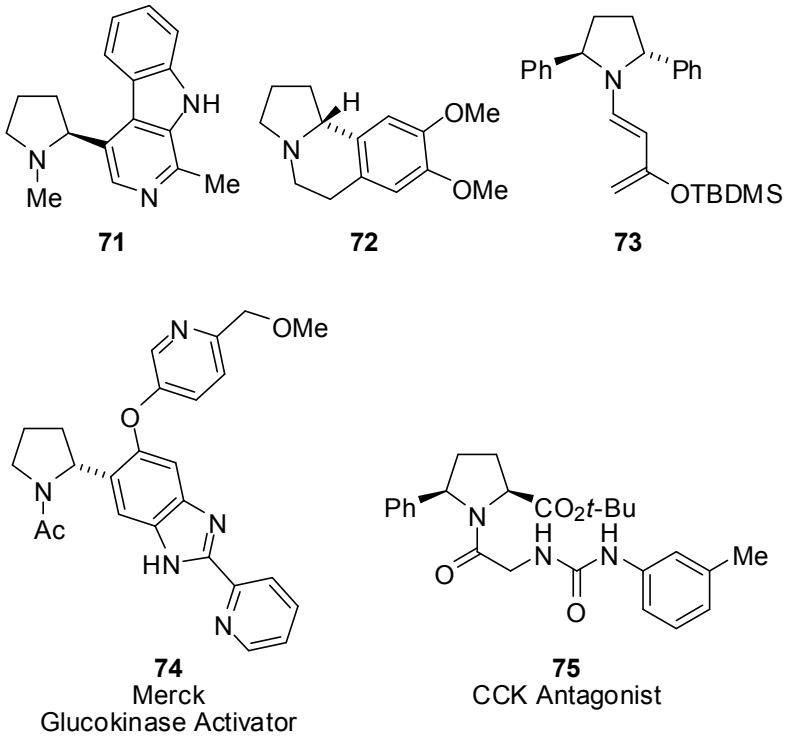
Figure 1.4



1.4 Beyond Simple Electrophiles: Lithiation-Arylations

Although lithiation-trapping gives access to a range of 2-substituted pyrrolidines in potentially high yield and enantioselectivity, 2-aryl and 2-vinyl pyrrolidines are not obtainable using this method. A convenient route to such systems is potentially useful as a wide range of synthetic targets bear this motif, for example the natural products brevicoline **71**[80] and crispine A **72**[81], the C_2-symmetric chiral auxiliary **73**[82] developed by Rawal, and the drug molecules **74**[83] and **75**[84] (figure 1.5).

Figure 1.5



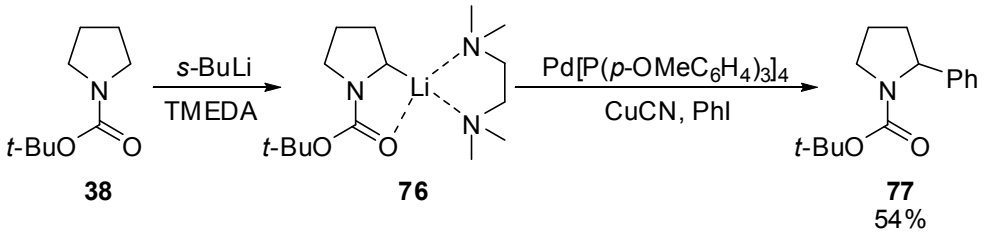
A number of different synthetic routes to the 2-aryl pyrrolidine motif have been explored. Ring closing to form the pyrrolidine with an aryl group in place has been investigated by a number of different groups, as has transition metal-catalysed installation of an aryl group onto a pre-existing ring. Several different lithiation-arylation and lithiation-vinylation protocols have also been reported.

1.4.1 Previous Lithiation-Arylation and Lithiation-Vinylation of *N*-Boc Pyrrolidine 38

Arylation and vinylation of pyrrolidine have been reported by Dieter. In 1995, it was shown that lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi/TMEDA to form lithiopyrrolidine **76** followed by coupling of electron rich aryl iodides in the presence of 5

mol% Pd and 10 mol% copper(I) cyanide provided 2-aryl pyrrolidines in modest yields. In this case, *rac*-**77** was obtained in 54% yield (scheme 1.30).[85] It was found that coupling did not proceed with electron-poor aryl iodides. Arylation of piperidines was also successful.[85]

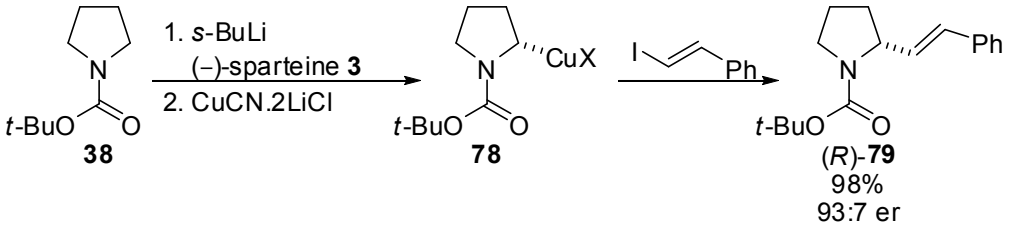
Scheme 1.30



Dieter subsequently found that higher yields could be obtained with softer palladium ligands such as $AsPh_3$ and $PbPh_3$. Vinylations *via* coupling of vinyl iodides were also carried out. However, only racemic lithiation-couplings were reported, and the group were still unable to effect coupling with electro-poor aryl iodides.[86]

Enantioselective lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi/(–)-sparteine **3** followed by transmetallation with copper(I) cyanide to organocuprate **78** and then trapping with vinyl iodides gave 2-alkenyl pyrrolidines in high yields. For example, vinyl pyrrolidine (*R*)-**79** was obtained in 98% yield and 93:7 er (scheme 1.31). It was found that enantioselectivities varied greatly depending on the electrophile used.[87, 88] Arylations were not, however, reported.[87, 88]

Scheme 1.31

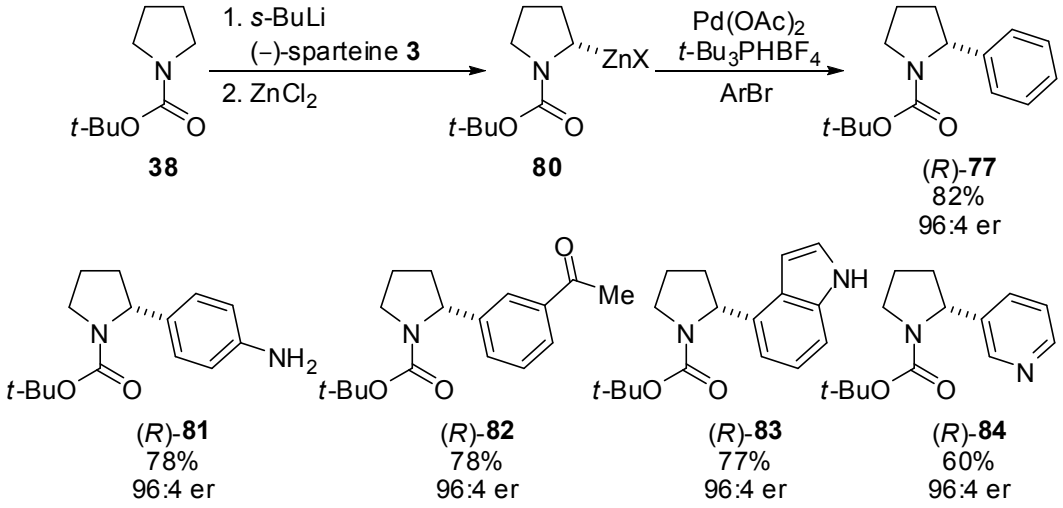


1.4.2 Lithiation-Negishi coupling of *N*-Boc Pyrrolidine

In 2006, Campos presented a new paradigm in pyrrolidine lithiation chemistry.[89] Lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi/(–)-sparteine **3** and then transmetallation with zinc chloride gave organozinc species **80**. A palladium-catalysed Negishi coupling

was then used to install aryl substituents in high yields and ers (scheme 1.32).[89] For example, reaction with bromobenzene gave (*R*)-**77** in 82% yield and 96:4 er.

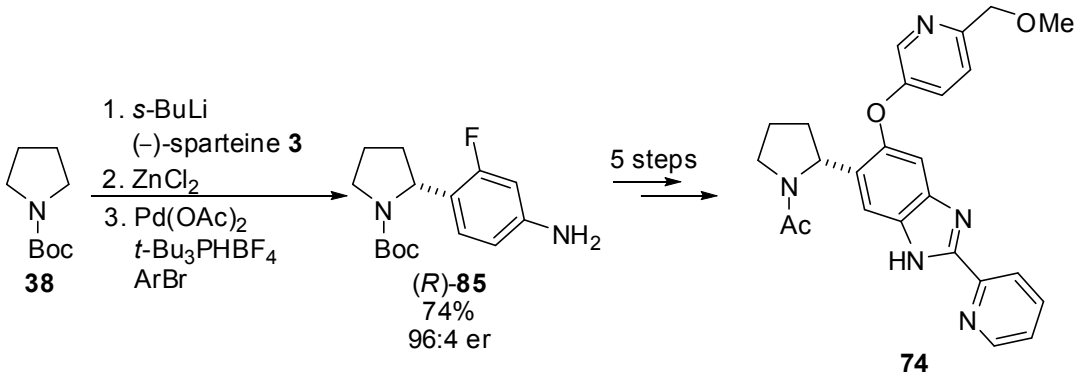
Scheme 1.32



During optimisation of the arylation protocol, it was shown that the highest yields were achieved with palladium(II) acetate and *t*-Bu_3PHBF_4, developed by Fu.[89, 90] Interestingly, it was shown that $PdCl_2$(dppf), regarded as the optimal catalyst for effecting Negishi couplings gave <5% yield.[89, 91] Aryl bromides were the coupling agents of choice – reduced yields were obtained when using chlorobenzene or pseudohalides. A wide range of aryl bromides were successfully used including unprotected amines to give (*R*)-**81** (78%) and (*R*)-**82** (77%). Couplings were performed at rt, with the exception of 3-bromopyridine, which required coupling to be performed at 60 °C and gave (*R*)-**84** in 60% yield. Two recent reviews have summarised lithiation-arylations of carbamates and synthetic methods for the installation of substituents including aryl groups in the α-position of *N*-heterocycles, including Campos' new protocol.[47, 92]

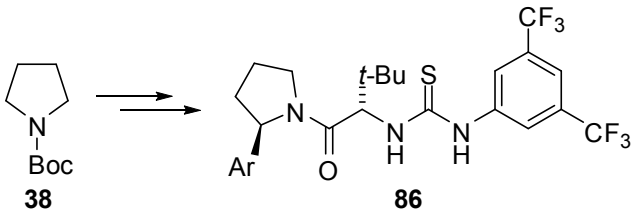
With the new methodology in hand, Campos was then able to carry out the synthesis of glucokinase activator **74** on a large scale, *via* coupling to give (*R*)-**85**.[83] As a measure of the utility of the Negishi coupling strategy, the new protocol was used to provide (*R*)-**85** of 96:4 er in 2.13 kg from two lithiation-arylation batches, each on a 6.0 mol scale (scheme 1.33).[83]

Scheme 1.33



Other groups have made use of this convenient route to 2-aryl pyrrolidines. In the first reported example, Jacobsen used Campos' methodology as a route to a range of thiourea organocatalysts of the general structure **86** (scheme 1.34).[93] The products were investigated as catalysts for the addition of 1-chloroisochromans to ketene acetals.[93] Jacobsen also used this method for the synthesis of 2-aryl pyrrolidine thiourea organocatalysts for addition of indoles to *N*-acyliminiums and catalytic polycyclisations.[94, 95]

Scheme 1.34

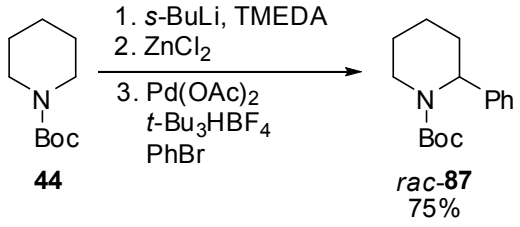


A feature of the lithiation-transmetallation-coupling sequence is that while lithiated pyrrolidine **42** is subject to epimerisation at high temperatures (≥–40 °C in diethyl ether), organozinc **80** remains chemically and configurationally stable up to 60 °C.[52, 96, 97] Sutton and co-workers took advantage of this fact during a parallel synthesis of a range of Hsp90 inhibitors. A large batch of organozinc **80** was synthesised and then aliquots were separated out for coupling with different aryl bromides.[98] Campos had also taken advantage of this feature when optimising the reaction conditions.[89]

1.4.3 Lithiation-Negishi Coupling of Other *N*-Boc Heterocycles

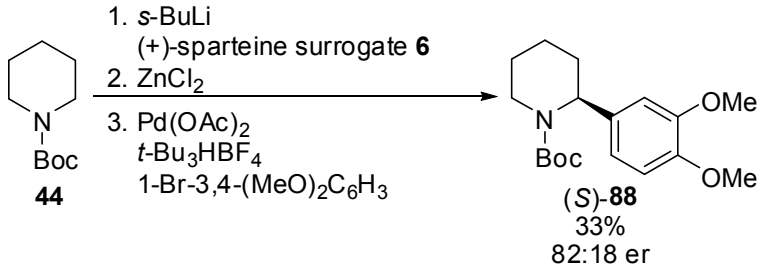
The lithiation-Negishi coupling methodology has been applied to the arylation of *N*-Boc piperidine **44**. Coldham reported a racemic arylation procedure *via s*-BuLi/TMEDA mediated lithiation in 2008.[99] Coupling of a range of aryl bromides was reported and, as a representative example, phenyl piperidine *rac*-**87** was obtained in 75% yield (scheme 1.35).[99]

Scheme 1.35



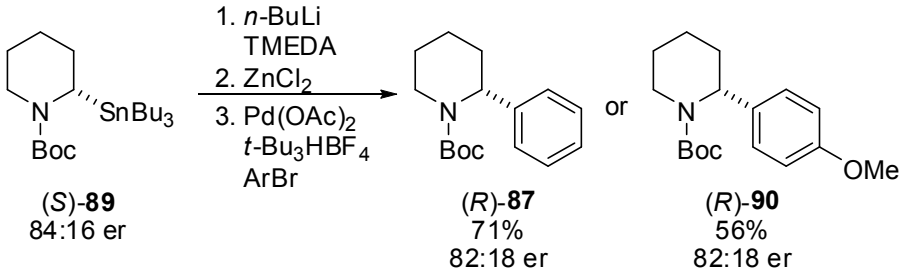
Our group recently reported an isolated example of enantioselective synthesis of an aryl piperidine *via* lithiation of *N*-Boc piperidine **44** with *s*-BuLi/(+)-sparteine surrogate **6**.[67] Yield and enantioselectivity were modest: aryl piperidine (*S*)-**88** of 82:18 er was obtained in 33% yield (scheme 1.36).[67]

Scheme 1.36



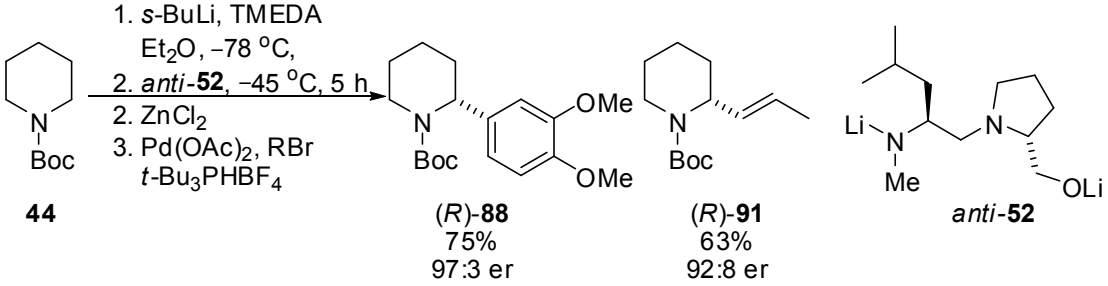
Coldham attempted to apply the DTR lithiation procedure to form 2-arylpiperidines, but was unable to effect coupling.[68] It was shown that transmetallation to the organozinc proceeded, and it was thus hypothesised that residual DTR ligand prevented palladium-catalysed coupling. Instead, tin-lithium exchange of enantioenriched piperidinyl stannane (*S*)-**89** was used to access lithiated piperidine, and coupling was achieved in high yields, although modest ers. Phenyl piperidine (*R*)-**87** was obtained in 71% yield and 82:18 er, while (*R*)-**90** was obtained in 56% yield and the same er (scheme 1.37).[68]

Scheme 1.37



As an alternative, Gawley has recently shown that lithiation of *N*-Boc piperidine **44** by *catalytic* dynamic resolution allows coupling to give 2-aryl piperidines in high yields and enantioselectivities. Vinylations were also reported (scheme 1.38).[100] Presumably, either the CDR ligand does not interfere with coupling in the same manner as Coldham's DTR ligand, or the lower amount of lithium ligand present allows coupling of uncomplexed/TMEDA complexed organozinc species. Thus, for example, aryl piperidine (*R*)-**88** was obtained in 75% yield and 97:3 er and vinyl piperidine (*R*)-**91** of 92:8 er was formed in 63% yield.

Scheme 1.38



Racemic arylation of *N*-Boc piperidine **44** can be accomplished using a *s*-BuLi/TMEDA-mediated lithiation as reported by Coldham. Access to enantioenriched 2-aryl piperidines, which has proved problematic using kinetically-controlled lithiation or DTR lithiation conditions, can now be effected using the CTR lithiation-arylation procedure demonstrated by Gawley.

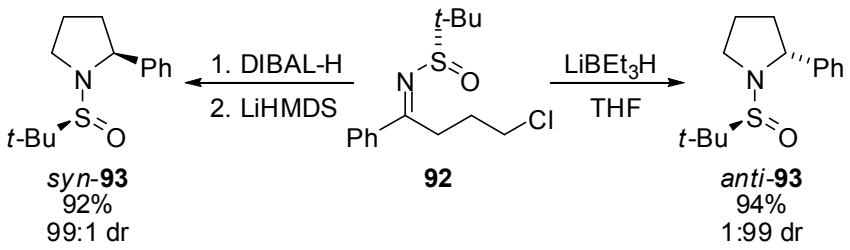
Recently, Knochel reported the use of lithiation-arylations on substituted *N*-Boc piperidines. Thus, disubstituted piperidines were formed in high yields and enantioselectivities.[101]

1.5 Alternative Routes to 2-Aryl Pyrrolidines

Several different routes have been investigated as alternatives to lithiation-arylation of *N*-Boc pyrrolidine **38** for the synthesis of 2-aryl pyrrolidines. In 1992, Meyers reported a ring closing protocol for the formation of 2-substituted pyrrolidines, including 2-phenylpyrrolidine.[102] Savoia presented an alternative route to (*S*)-2-phenylpyrrolidine beginning from (*S*)-valine two years later.[103] Higashiyama[104] and Ellman[105] have also reported ring closing syntheses of 2-aryl pyrrolidines. Cyclisation of sulfinyl imines has perhaps shown the most promise as a protocol for the formation of aryl pyrrolidines. Beak presented a lithiation protocol on an acyclic *N*-Boc amine, using an internal electrophile to effect cyclisation to a pyrrolidine ring.[106] Transition metal-catalysed processes have been presented as an alternative to cyclisation routes to 2-aryl pyrrolidines. Buchwald reported a titanium-catalysed reduction of 2-phenyl-1-pyrroline.[107] Sames used a ruthenium catalyst to effect arylation of pyrrolidine *via* C–H activation to give 2,5-diaryl pyrrolidines.[108] The same catalyst was used in a decarboxylative coupling of a methyl proline ester, affording racemic 2-aryl pyrrolidines in moderate yields.[109]

Of these approaches, two are discussed in detail. De Kimpe reported the reductive ring closing of γ-chloro-*N*-sulfinyl ketimine **92** using $LiBEt_3H$.[110] Simultaneously, however, Reddy reported the reduction of **92** with $LiBEt_3H$ with greater yield (94%) and improved diastereoselectivity (99:1 dr). Furthermore, it was found that reductive cyclisation using DIBAL-H then LiHMDS gave comparable (92%) yield of the opposite diastereomer with the same degree of selectivity (scheme 1.39).[111] Reddy also demonstrated the methodology with a wide range of different aryl groups, as well as an extended sulfinyl ketimine to access 2-phenylpiperidine.[111]

Scheme 1.39



syn-**93**
92%
99:1 dr

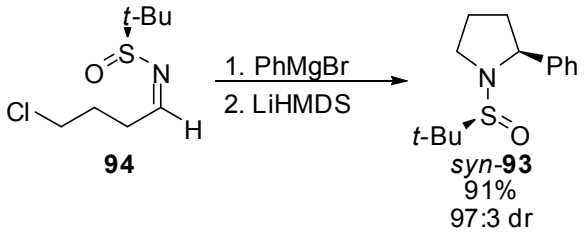
92

anti-**93**
94%
1:99 dr

The methodology reported by Reddy and De Kimpe requires the synthesis of sulfinylketimine **92** with the required aryl group already in place. As an alternative,

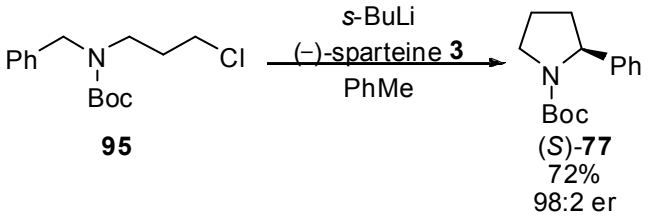
Reddy developed a slightly different protocol, wherein a stock starting material **94** was treated with any one of a range of organomagnesium chlorides to effect installation of the required group and cyclisation to a pyrrolidine ring in one pot (scheme 1.40).[112] A variety of aryl, vinyl and alkyl organometallic reagents were investigated, giving high yields and drs (91%, 97:3 dr for phenyl). While this method is more convenient for the synthesis of a series of 2-arylpyrrolidine, both stereochemical series of product are not accessible from the same enantiomer of starting material.

Scheme 1.40



A final ring closing strategy to 2-arylpyrrolidines relies on *s*-BuLi/(–)-sparteine **3**-mediated lithiation of an *N*-Boc amine **95** followed by intramolecular trapping with an alkyl halide. A range of different aryl groups were used to access a range of 2-aryl pyrrolidines in modest yields (21 – 75%) but acceptable enantioselectivities (92:8 – 98:2 er).[106] It is notable that this lithiation-trapping route results in a product of the opposite enantiomeric series to that obtained from (–)-sparteine/*s*-BuLi mediated lithiation-arylation of *N*-Boc pyrrolidine (scheme 1.41).[106]

Scheme 1.41

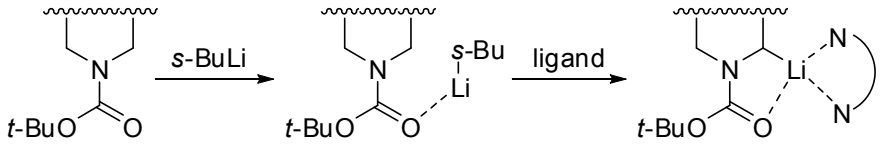


Beak's work was carried out before our group reported the use of (+)-sparteine surrogate **6** in lithiations. Thus, it was only possible to access the (*S*)-enantiomeric series of 2-aryl pyrrolidines. This route also constitutes an example of lithiation-trapping using an internal electrophile. Lithiation of the benzylic position takes place preferentially to nucleophilic attack of *s*-BuLi at the alkyl halide.

1.6 Project Outline

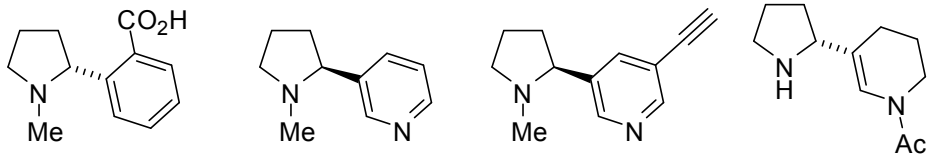
This thesis will focus on a number of different areas of research concerning the lithiation-trapping of *N*-Boc heterocycles. Using a newly acquired ReactIR system, we hoped to use *in situ* infra-red spectroscopy to observe formation of prelithiation complexes, and also to follow the progress of α-lithiation by observing changes in the carbamate $\nu_{C=O}$ stretch (scheme 1.42). The intention was to directly compare different carbamate substrates and diamine ligands in lithiation reactions (chapter 2).

Scheme 1.42



Our group has previously reported a two-ligand catalytic lithiation of *N*-Boc pyrrolidine **38**, allowing the use of substoichiometric amounts of chiral diamines to obtain high yields of trapped products in high enantioselectivities. We wished to further investigate this protocol, assaying a number of new "secondary" ligands, and also applying this methodology to two-ligand catalytic lithiation-arylations (chapter 3). It was also hoped to use Campos' lithiation-arylation methodology in the total syntheses of the natural products (*R*)-dihydroshihunine (*R*)-**96** and (*S*)-nicotine (*S*)-**97** and the drug molecule SIB1508Y (*S*)-**98**. Additionally, we hoped to modify Campos' procedure to allow for lithiation-vinylations, and complete a total synthesis of the natural product (*R*)-maackiamine (*R*)-**99** (figure 1.6). The results are presented in chapter 4.

Figure 1.6

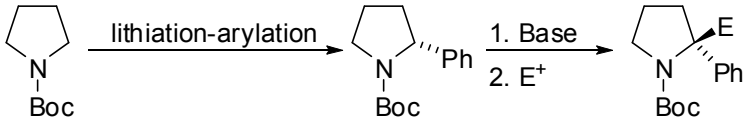


(*R*)-**96** (*S*)-**97** (*S*)-**98** (*R*)-**99**

As detailed in chapter 5, we then decided to investigate a new *racemic* lithiation protocol. We hoped that this methodology, carried out at high (–30 °C) temperature and without the use of a diamine, would prove useful to chemists operating on a large-scale. Finally, we wished to take the products of a lithiation-arylation reaction and resubject

them to lithiation-trapping, forming a new quaternary stereocentre α to nitrogen (scheme 4.3) (chapter 6).

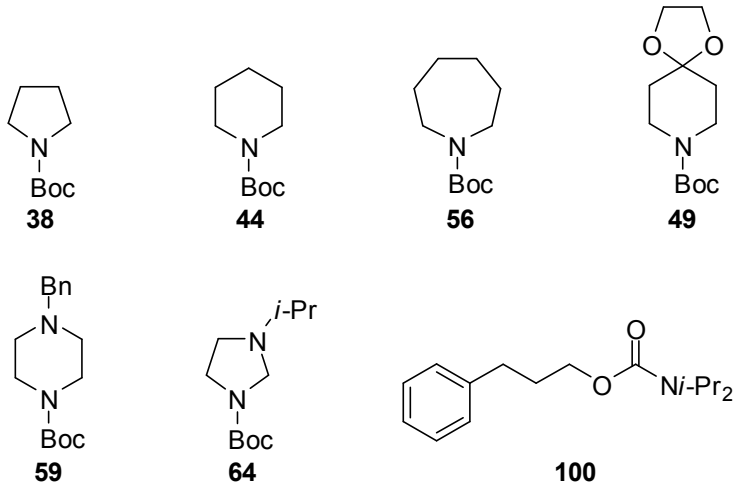
Scheme 4.3



Chapter 2: *In Situ* ReactIR Spectroscopic Monitoring of Carbamate Lithiations

This chapter is concerned with following *s*-BuLi/diamine-mediated lithiations in diethyl ether using *in situ* infra-red spectroscopy *via* a ReactIR system. The seven carbamates shown in figure 2.1 were selected for our studies. To directly compare different ring sizes of nitrogen heterocycles, lithiations of *N*-Boc pyrrolidine **38**, *N*-Boc piperidine **44** and *N*-Boc homopiperidine **56** were investigated. Lithiations of *N*-Boc acetal piperidine **49** and *N*-Boc piperazine **59** were also studied, in order to compare their rate of lithiation with that of *N*-Boc piperidine **44**. *N*-Boc imidazolidine **64** was chosen as we were interested in exploring the issue of regiochemistry and the affect of *N*-Boc group rotamers on the lithiation. Finally, lithiation α to oxygen of *O*-alkyl carbamate **100** would provide a comparison to the *N*-Boc nitrogen heterocycles.

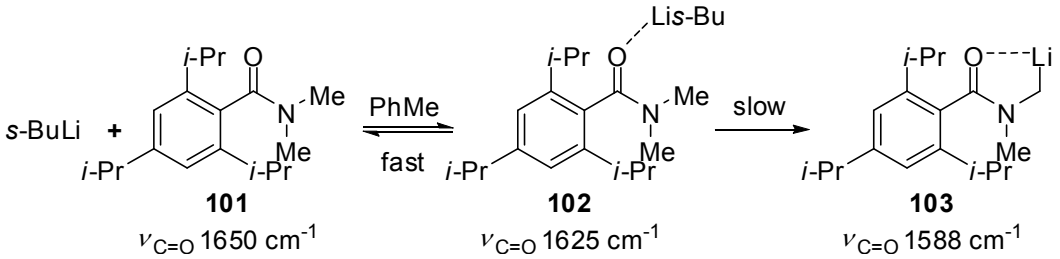
Figure 2.1



2.1 Previous *In Situ* Infra-Red Spectroscopic Monitoring of Lithiations

Substrate-directed lithiations at sp^3 carbon centres have previously been followed by *in situ* infra-red spectroscopy. An early example was reported by Beak in 1983.[16, 18] Using a stopped-flow infra-red apparatus, direct observation of a prelithiation complex was achieved.[16] Studying the reaction of aryl amide **101** ($\nu_{C=O}$ 1650 cm^{-1}) with *s*-BuLi in toluene, rapid formation of prelithiation complex **102** ($\nu_{C=O}$ 1625 cm^{-1}) was observed followed by the slower conversion of **102** to lithiated intermediate **103** ($\nu_{C=O}$ 1588 cm^{-1}) (scheme 2.1).[16]

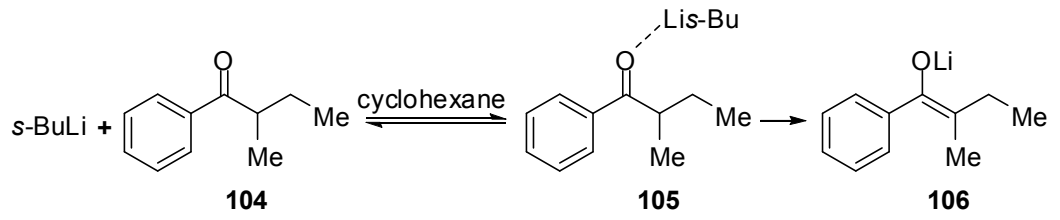
Scheme 2.1



Beak then expanded this work with an investigation into the kinetics of lithiation of aryl amide **101** by *s*-BuLi in toluene, both by free alkyllithium and in the presence of TMEDA.[18] Interestingly, it was concluded that prelithiation complex **102** was formed between aryl amide **101** and alkyllithium aggregates, rather than monomeric *s*-BuLi.[18]

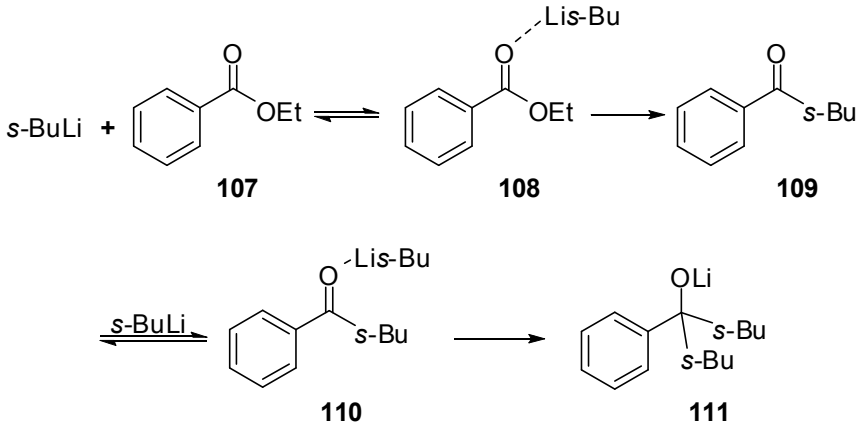
In 1984, Smith reported following the reaction of *s*-BuLi or *n*-BuLi with ketone **104** *via* prelithiation complex **105** to give lithium enolate **106** in cyclohexane (scheme 2.2).[113] As with Beak's work, it was found that in cyclohexane, both formation of prelithiation complex **105** and lithiation to give **106** involved the action of complex alkyllithium aggregates.[113] In this study, $\nu_{C=O}$ stretches were broad and exact wavenumbers were not reported.

Scheme 2.2



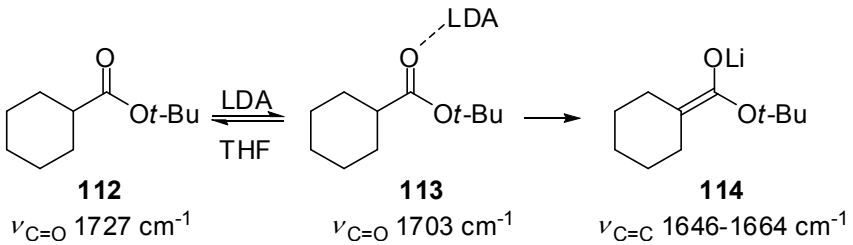
Next, Smith investigated the reaction of alkyllithiums with esters.[114] Working in cyclohexane, it was shown that substrates formed complexes with alkyllithium aggregates. Upon treating aryl ester **107** with *s*-BuLi, it proved possible to observe both ester-*s*-BuLi complex **108** *and* intermediate ketone-*s*-BuLi complex **110** (scheme 2.3). The kinetics of the reaction of *s*-BuLi with ester **107** and a range of aryl-substituted analogues were also reported.[114]

Scheme 2.3



In comparison to Beak and Smith's work, Collum reported a study of the LDA-mediated enolisation of esters.[115] The reactive LDA-THF complex was determined to be a dimeric complex LDA_2THF_2. When ester **112** ($\nu_{C=O}$ 1727 cm^{-1}) was treated with LDA in Et_2O, prelithiation complex **113** ($\nu_{C=O}$ 1703 cm^{-1}) was observed before deprotonation to give enolate **114** ($\nu_{C=C}$ 1646-1664 cm^{-1}) (scheme 2.4).[115] Subsequently, Collum studied a range of lithiation conditions/solvents and used kinetic data to place different LDA-solvent complexes in order of lithiation activity.[116]

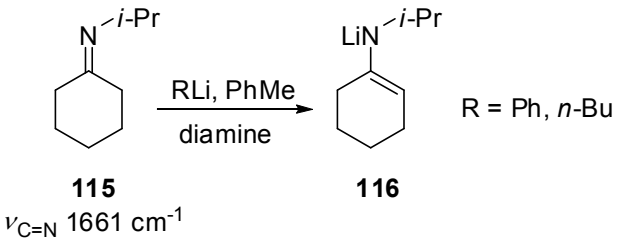
Scheme 2.4



Although the carbonyl group presents itself as an ideal spectroscopic "handle" for following reactions by infra-red spectroscopy due to a clear $\nu_{C=O}$ remote from other

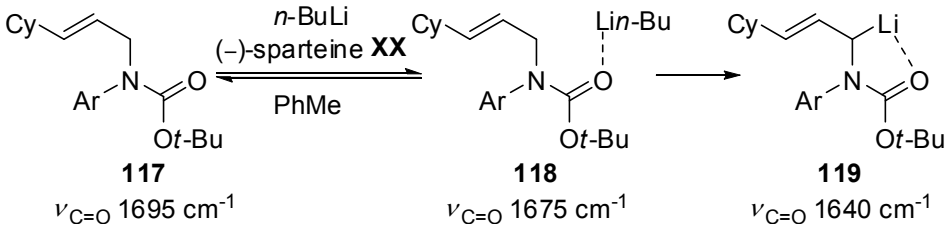
absorbances, the imine $\nu_{C=N}$ has also been used. For example, Collum followed the lithiation of imine **115** ($\nu_{C=N}$ 1661 cm^{-1}) to give enamide **116** with *n*-BuLi and PhLi (scheme 2.5).[117] By following the disappearance of $\nu_{C=N}$, the kinetics of lithiation with different organolithium/diamine complexes was studied. The nucleophilic addition of PhLi and *n*-BuLi to a different imine has also been investigated.[117]

Scheme 2.5



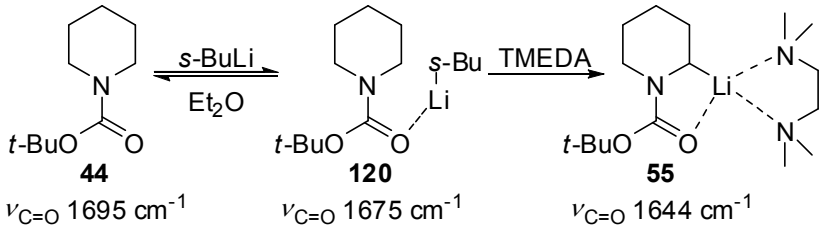
Two previous examples of the use of *in situ* ReactIR spectroscopy to monitor the lithiation of *N*-Boc activated substrates have been reported. In 2001, Beak used ReactIR to determine the kinetics of lithiation of allylamine **117** ($\nu_{C=O}$ 1695 cm^{-1}) to lithiated product **119** ($\nu_{C=O}$ 1640 cm^{-1}) *via* prelithiation complex **118** ($\nu_{C=O}$ 1675 cm^{-1}) (scheme 2.6).[118]

Scheme 2.6



Most recently, in collaboration with Campos at Merck, our group has reported the ReactIR spectroscopic monitoring of the lithiation of *N*-Boc piperidine **44** ($\nu_{C=O}$ 1695 cm^{-1}) by *s*-BuLi/TMEDA, *s*-BuLi/(–)-sparteine **3** or *s*-BuLi/(+)-sparteine surrogate **6**.[67] For example, treatment of *N*-Boc piperidine **44** with *s*-BuLi in diethyl ether led to the formation of prelithiation complex **120** ($\nu_{C=O}$ 1675 cm^{-1}). Then, addition of TMEDA promoted reaction to give lithiated intermediate **55** ($\nu_{C=O}$ 1644 cm^{-1}) (scheme 2.7). It was shown that lithiation with *s*-BuLi/(+)-sparteine surrogate **6** led to rapid formation of **55** whereas use of *s*-BuLi/(–)-sparteine **3** gave only a small amount of **55** after 6 h.[67]

Scheme 2.7



2.2 ReactIR Spectroscopic Monitoring of Carbamate Lithiations

Several limitations were imposed by the equipment that was available for our use. The apparatus was equipped with a silicon-tipped (SiComp) ReactIR probe tip. As we were worried about potential degradation of the silicon window, lithiations were run at the maximum dilution which still allowed clear observation of the relevant $\nu_{C=O}$ peak. Typically, reactions were carried out with 1.0 mmol of substrate in 14 mL of solvent. This is more dilute than standard synthetic experimental conditions which are usually 2.0 mmol of substrate in 7 mL of solvent.

Additionally, the reaction flask was not completely air-tight as the ReactIR probe tip was inserted into the flask though a pierced Suba-Seal®. Trial and error testing suggested that at reaction times of longer than 90 min, an unacceptable quenching of alkyllithium reagent or lithiated substrate took place. We therefore limited the gathering of data to within this time period.

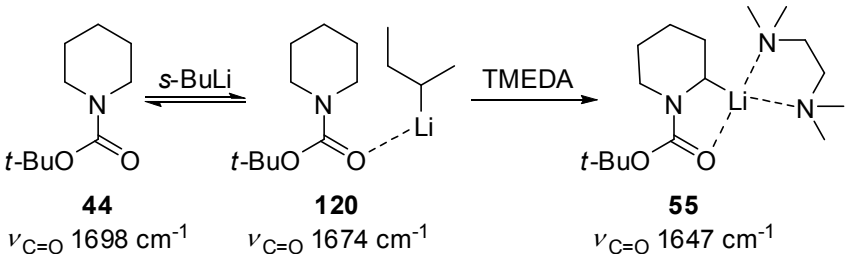
The ReactIR reactions were run under two different protocols. In one method, we hoped to form a prelithiation complex by reacting the substrate with *s*-BuLi alone. Then, some time later, diamine would be added to effect lithiation. In the second method, we wished to investigate conditions used in synthetic experiments. In this case, substrate and diamine would be premixed, and then *s*-BuLi added to effect the lithiation depending on the substrate and diamine.

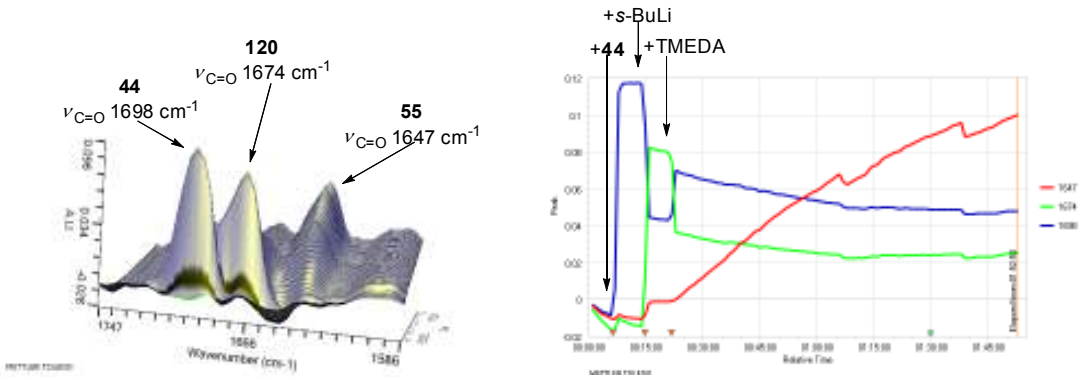
2.2.1 *N*-Boc Piperidine

To begin our investigations, we verified the previously reported observations for the lithiation of *N*-Boc piperidine **44** carried out by Campos.[67] The intention was to form a prelithiation complex between *N*-Boc piperidine **44** and *s*-BuLi in diethyl ether at –78 °C and then TMEDA would be added to initiate the lithiation. The ReactIR results are presented in two forms in scheme 2.8. The three-dimensional plot (A) allows the appearance and disappearance of new signals to be clearly seen as a reaction progresses. Alternatively, the absorbance of a specific wavelength can be plotted as a function of time (B). In graph B, units of time are expressed as days:hours:minutes.

In this case, when *s*-BuLi was added, a decrease in absorbance of the 1698 cm^{-1} peak ($\nu_{C=O}$ of *N*-Boc piperidine **44**) was observed, with an increase in the 1674 cm^{-1} peak ($\nu_{C=O}$ of prelithiation complex **120**). After addition of TMEDA, an immediate increase in the 1698 cm^{-1} peak and a corresponding decrease in the 1674 cm^{-1} peak was noted. Then, a slow increase in absorbance at 1647 cm^{-1} ($\nu_{C=O}$ of lithiated intermediate **55**) was observed. Lithiation was found to be complete after 90 min.

Scheme 2.8





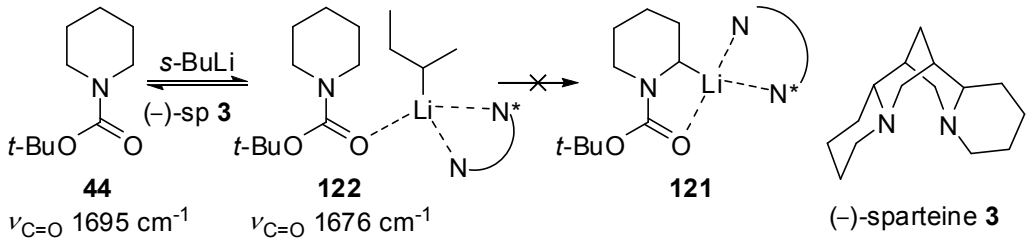
A **B**

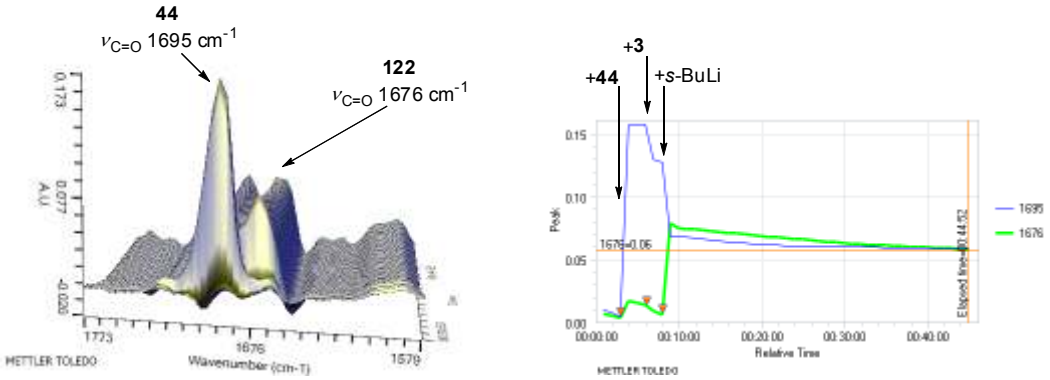
Since the lithiation of *N*-Boc piperidine **44** by *s*-BuLi/TMEDA is complete in 90 min the 3.5 h lithiation time used by Beak in typical synthetic experiments is clearly unnecessary.[29] Interestingly, after TMEDA addition, some of prelithiation complex **120** ($\nu_{C=O}$ 1674 cm^{-1}) reverted back to uncomplexed *N*-Boc piperidine **44** ($\nu_{C=O}$ 1698 cm^{-1}). This observation indicates that the position of the substrate-prelithiation complex equilibrium is affected by the presence of diamine ligands.

Next, the reaction of *N*-Boc piperidine **44** with *s*-BuLi and (–)-sparteine **3** under experimental conditions was investigated. It was likely that we would not observe lithiated piperidine **121**, as Beak had previously shown only 8% lithiation after 16 h under these conditions.[64] Thus, *N*-Boc piperidine **44** ($\nu_{C=O}$ 1695 cm^{-1}) and (–)-sparteine **3** were premixed in diethyl ether at –78 °C. Then, *s*-BuLi was added. A new peak emerged at 1676 cm^{-1}, which was assigned to $\nu_{C=O}$ in prelithiation complex **122** (scheme 2.9).

In the time period (40 min), no peak corresponding to $\nu_{C=O}$ in lithiated piperidine **121** (expected in the range 1640-1650 cm^{-1}) was observed. After addition of *s*-BuLi, only partial formation of prelithiation complex **122** observed. This confirms the observation (scheme 2.8) that the presence of a diamine ligand affects the position of the substrate-prelithiation complex equilibrium.

Scheme 2.9

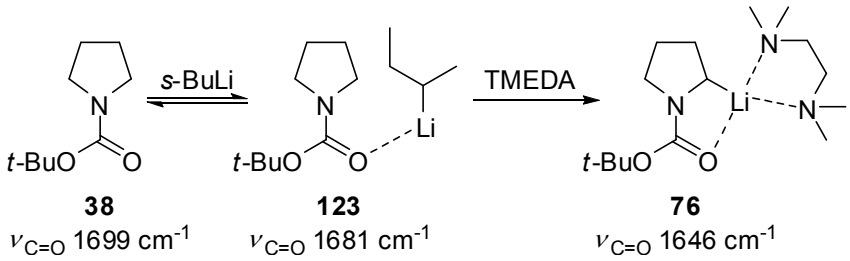


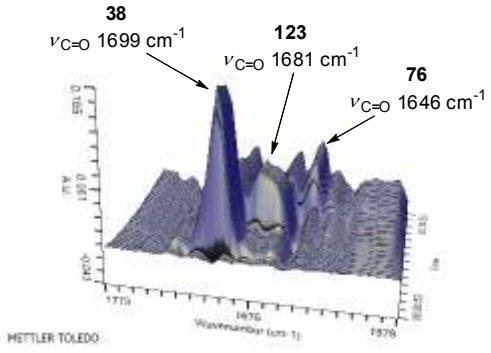


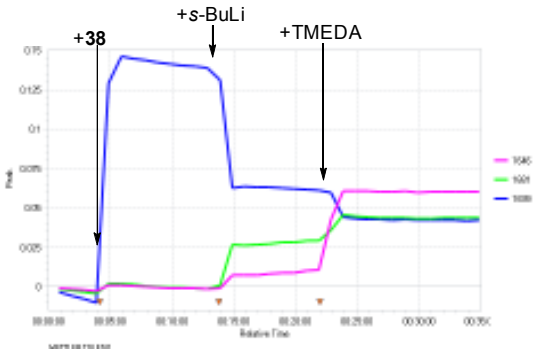
2.2.2 *N*-Boc Pyrrolidine

For comparison, the lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi/TMEDA was then investigated.[29] We planned to form the prelithiation complex between *s*-BuLi and *N*-Boc pyrrolidine **38** and then effect lithiation by addition of TMEDA. Thus, *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1699 cm^{-1}) was stirred in diethyl ether at –78 °C and *s*-BuLi was added. A new peak appeared, which was assigned to prelithiation complex **123** ($\nu_{C=O}$ 1681 cm^{-1}). Finally, TMEDA was added, and another peak appeared, assigned to lithiated pyrrolidine **76** ($\nu_{C=O}$ 1646 cm^{-1}) (scheme 2.10).

Scheme 2.10



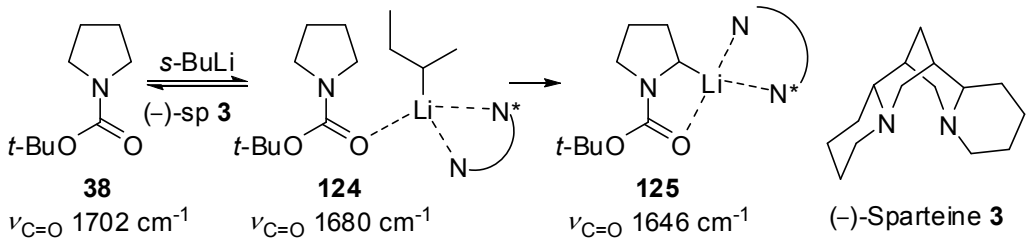


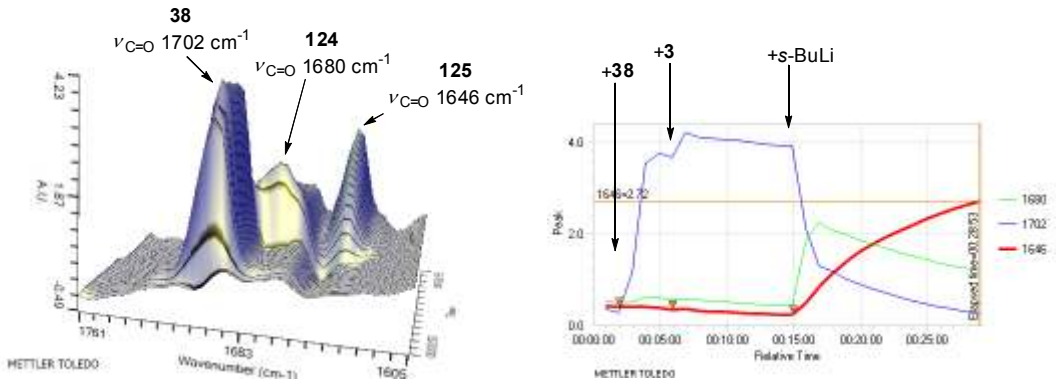


Unlike *N*-Boc piperidine **44**, after the addition of TMEDA no dissociation of *s*-BuLi from complex **123** was observed. Lithiation was very fast and complete formation of lithiated pyrrolidine **76** was observed within 3 min of addition of TMEDA. The 3.5 h lithiation time reported by Beak is unnecessary.[29] It is also worth noting that in the absence of diamine, no lithiation was observed. We conclude that diethyl ether is not a sufficiently activating ligand to effect this lithiation at –78 °C.

Then, the lithiation of *N*-Boc pyrrolidine **38** under typical experimental conditions using *s*-BuLi and (–)-sparteine **3** was investigated.[52] Thus, *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1702 cm^{-1}) and (–)-sparteine **3** were premixed at –78 °C in diethyl ether. Then, *s*-BuLi was added, and a new peak emerged ($\nu_{C=O}$ 1680 cm^{-1}) which was assigned to prelithiation complex **124**. The formation of lithiated pyrrolidine **125** ($\nu_{C=O}$ 1646 cm^{-1}) also began with the addition of *s*-BuLi (scheme 2.11).

Scheme 2.11



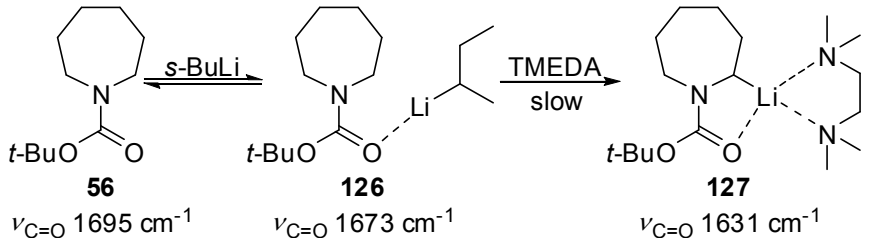


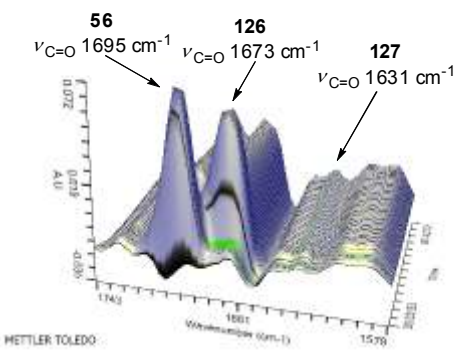
Formation of prelithiation complex **124** was very fast, happening within 2 min. Lithiation to give **125** was also fast and was complete within 15 min. As with the TMEDA example, this lithiation proceeds more quickly than suggested by previous literature: Beak reported lithiating *N*-Boc pyrrolidine **38** with *s*-BuLi/(–)-sparteine for 4 h.[51]

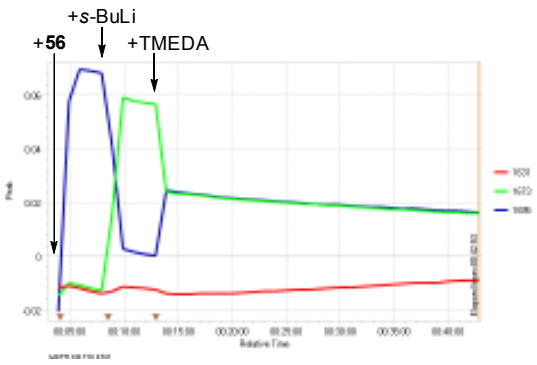
2.2.3 *N*-Boc Homopiperidine

Following *in situ* infra-red spectroscopic monitoring of the lithiation of *N*-Boc pyrrolidine **38** and *N*-Boc piperidine **44**, the investigation of different ring sizes of *N*-Boc nitrogen heterocycles was completed by monitoring the lithiation of *N*-Boc homopiperidine **56**. Beak has previously reported the *s*-BuLi/TMEDA-mediated lithiation-trapping of *N*-Boc homopiperidine **56**: after trapping, an adduct was obtained in 72% yield.[119] The slower rate of lithiation of *N*-Boc homopiperidine **56** compared to *N*-Boc pyrrolidine **38** has been noted.[68] First, formation of the prelithiation complex was studied. Thus, *N*-Boc homopiperidine **56** ($\nu_{C=O}$ 1695 cm^{-1}) was stirred in diethyl ether at –78 °C and *s*-BuLi was added. A new peak appeared, which was assigned to prelithiation complex **126** ($\nu_{C=O}$ 1673 cm^{-1}). Then, TMEDA was added and the slow evolution of a new peak at 1631 cm^{-1} was observed. This peak was assigned to $\nu_{C=O}$ in the lithiated product **127** (scheme 2.12).

Scheme 2.12



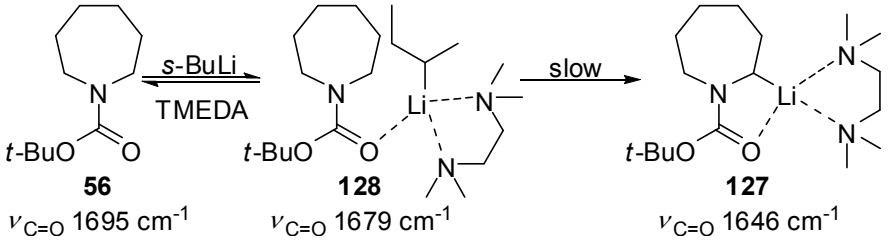


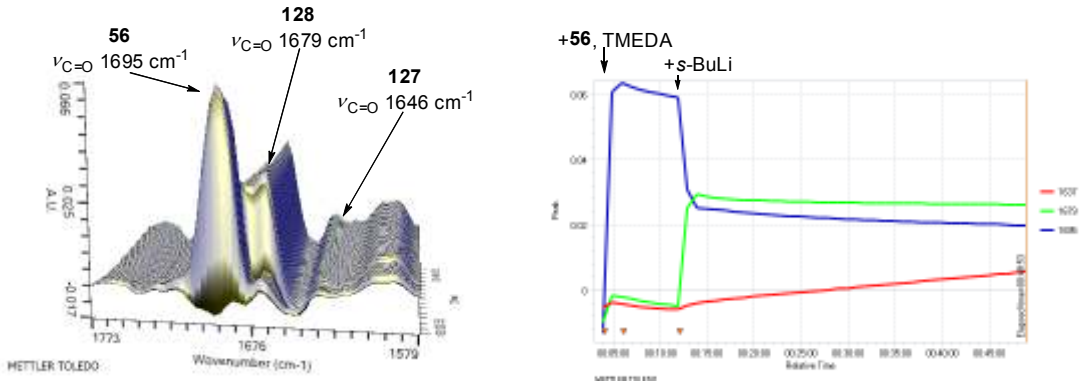


After addition of TMEDA, some of prelithiation complex **126** reverted to uncomplexed *N*-Boc homopiperidine **56** and *s*-BuLi – a 50:50 mixture of **56** and **126** was observed. Then, lithiation took place slowly and only a small amount of lithiated product **127** was observed after a reaction time of 40 min.

Next, the lithiation of *N*-Boc homopiperidine **56** by *s*-BuLi/TMEDA under typical experimental conditions was investigated. *N*-Boc homopiperidine **56** ($\nu_{C=O}$ 1695 cm^{-1}) and TMEDA were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. A peak at 1679 cm^{-1} appeared ($\nu_{C=O}$ in prelithiation complex **128**), followed by the slow emergence of a peak at 1646 cm^{-1} ($\nu_{C=O}$ in lithiated homopiperidine **127**) (scheme 2.13).

Scheme 2.13

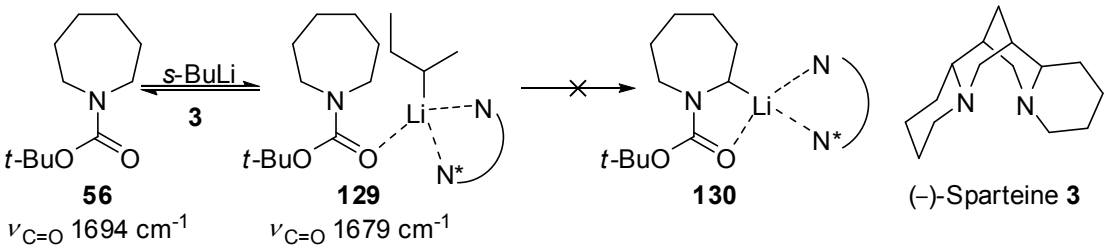


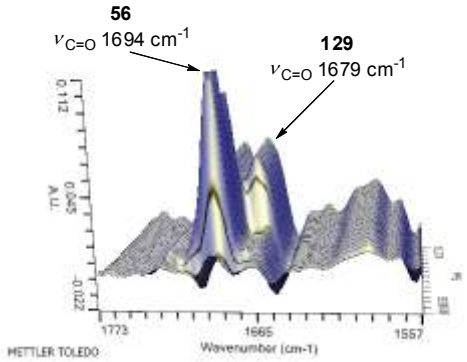


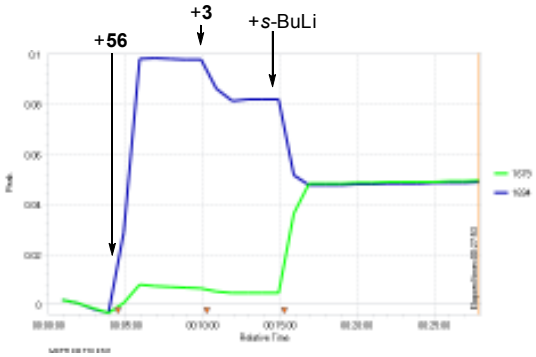
Incomplete formation of prelithiation complex **128** was observed after addition of *s*-BuLi. Then, lithiation to give lithiated substrate **127** was slow. Only partial lithiation was observed after 40 min reaction time. We note that in this experiment, lithiated product **127** shows an absorbace at $\nu_{C=O}$ 1646 cm^{-1}, compared with $\nu_{C=O}$ 1631 cm^{-1} from the previous experiment (scheme 2.12). As the two solutions contained the same species at identical concentrations and temperature, this discrepancy is presumably due to software issues.

Since only slow lithiation of *N*-Boc homopiperidine **56** had been observed using *s*-BuLi and TMEDA, we expected that lithiation using *s*-BuLi/(–)-sparteine **3** would not proceed. To verify this, *N*-Boc homopiperidine **56** ($\nu_{C=O}$ 1694 cm^{-1}) and (–)-sparteine **3** were mixed in diethyl ether at –78 °C and then *s*-BuLi was added. The appearance of a new peak at 1679 cm^{-1} was observed and assigned to $\nu_{C=O}$ in the prelithiation complex **129** (scheme 2.14).

Scheme 2.14



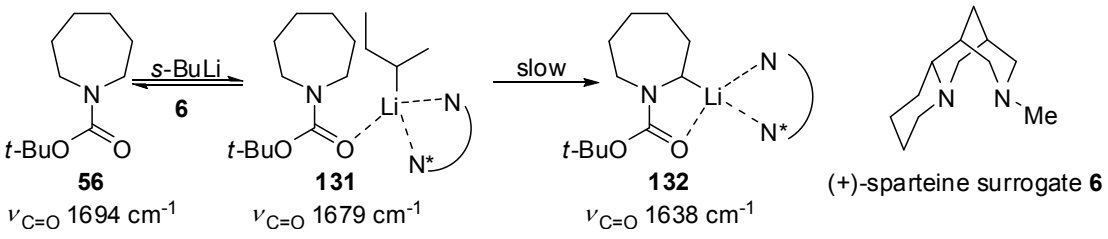


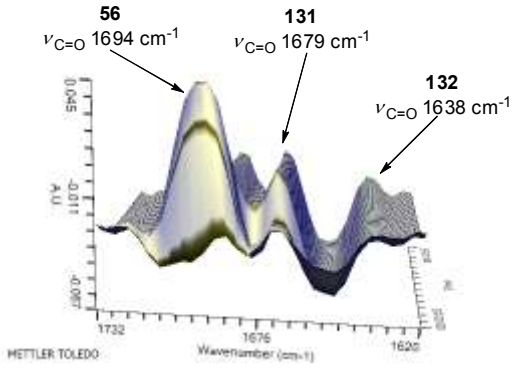


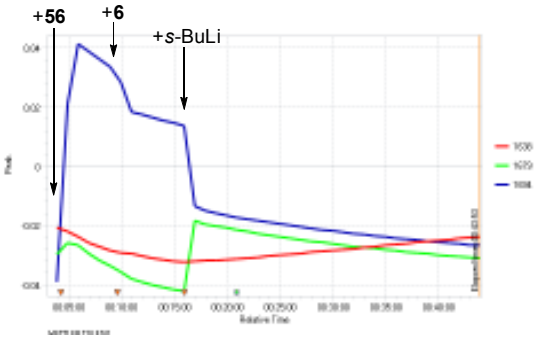
In common with the lithiation of *N*-Boc homopiperidine **56** using *s*-BuLi/TMEDA, only partial formation of prelithiation complex **129** was observed. In this case, no peak corresponding to lithiated product **130** was seen.

The complex of *s*-BuLi/(+)-sparteine surrogate **6** has been shown to be a more effective lithiator than *s*-BuLi/(–)-sparteine **3**.[66] We therefore decided to investigate the use of (+)-sparteine surrogate **6** in the lithiation of *N*-Boc homopiperidine **56**. Thus, *N*-Boc homopiperidine **56** ($\nu_{C=O}$ 1694 cm^{-1}) and (+)-sparteine surrogate **6** were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. After addition of *s*-BuLi, a new peak corresponding to prelithiation complex **131** ($\nu_{C=O}$ 1679 cm^{-1}) appeared. Then, another peak corresponding to lithiated product **132** ($\nu_{C=O}$ 1638 cm^{-1}) slowly emerged (scheme 2.15).

Scheme 2.15





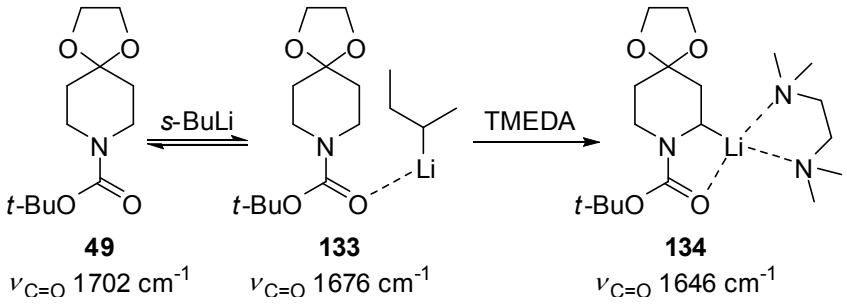


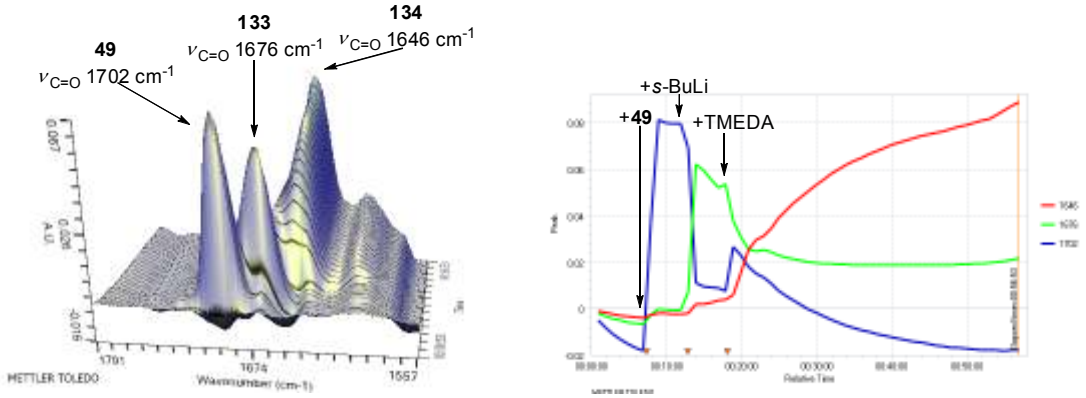
After addition of *s*-BuLi, only partial formation of prelithiation complex **131** was observed, as observed with treatment of **56** with *s*-BuLi/TMEDA and *s*-BuLi/(+)-sparteine surrogate **6**. Partial lithiation of *N*-Boc homopiperidine **56** by *s*-BuLi/(+)-sparteine surrogate **6** was noted after 30 min reaction time. Possible future work may involve synthetic experiments utilising *s*-BuLi/(+)-sparteine surrogate **6**-mediated asymmetric lithiation of **56**, although a long lithiation time of 3-6 h is likely to be needed.

2.2.4 *N*-Boc Acetal Piperidine

Beak reported the *s*-BuLi/TMEDA-mediated lithiation-trapping of *N*-Boc acetal piperidine **49** in 1989.[29] It was shown in 2007 that the α-*N* position of *N*-Boc acetal piperidine **49** was easier to lithiate than that of parent *N*-Boc piperidine **44**. For example, lithiation mediated by *s*-BuLi/cyclohexane diamine (*R*,*R*)-**8** and trapping with trimethylsilyl chloride gave a 53% yield of silyl adduct, compared with 13% yield from lithiation-trapping of *N*-Boc piperidine **44** under the same conditions.[65] We therefore decided to investigate the lithiation of **49** using *in situ* infra-red spectroscopy. First, the lithiation of **49** *via* formation of prelithiation complex **133** was studied. *N*-Boc acetal piperidine **49** ($\nu_{C=O}$ 1702 cm^{-1}) was stirred in diethyl ether at –78 °C and *s*-BuLi was added. A new peak corresponding to prelithiation complex **133** ($\nu_{C=O}$ 1676 cm^{-1}) appeared. Then, TMEDA was added and a new peak at $\nu_{C=O}$ 1646 cm^{-1} was observed and assigned to $\nu_{C=O}$ in the lithiated product **134** (scheme 2.16).

Scheme 2.16

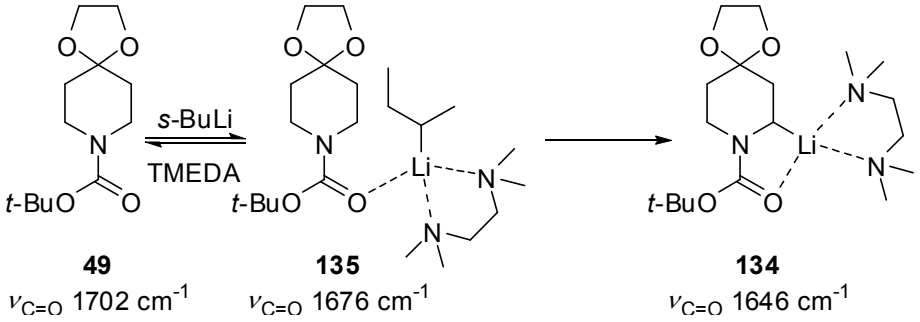


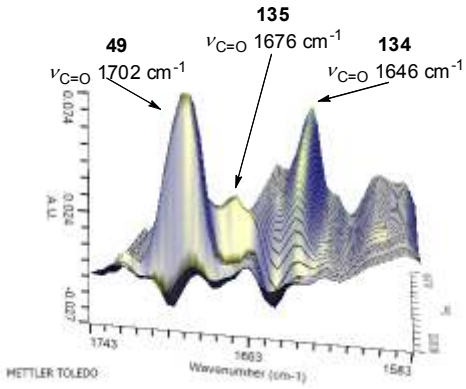


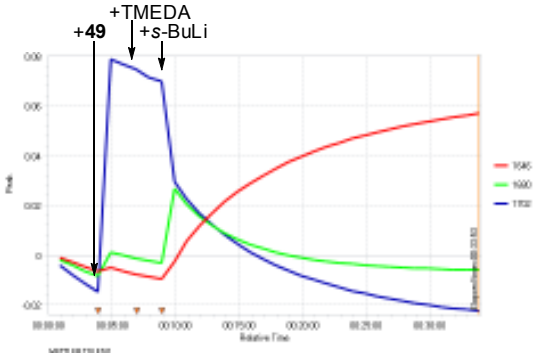
After TMEDA addition, a small amount of prelithiation complex **133** dissociated to free *N*-Boc acetal piperidine **49** and *s*-BuLi. Then, lithiation took place. Complete lithiation was observed after 40 min reaction time.

Lithiation of *N*-Boc acetal piperidine **49** by *s*-BuLi/TMEDA was then repeated under typical experimental condtions. Thus, **49** ($\nu_{C=O}$ 1702 cm^{-1}) and TMEDA were mixed in diethyl ether at –78 °C and then *s*-BuLi was added. A new peak appeared at 1680 cm^{-1}, assigned to $\nu_{C=O}$ in the prelithiation complex **135**. Then, lithiation to give organolithium species **134** ($\nu_{C=O}$ 1646 cm^{-1}) took place (scheme 2.17).

Scheme 2.17



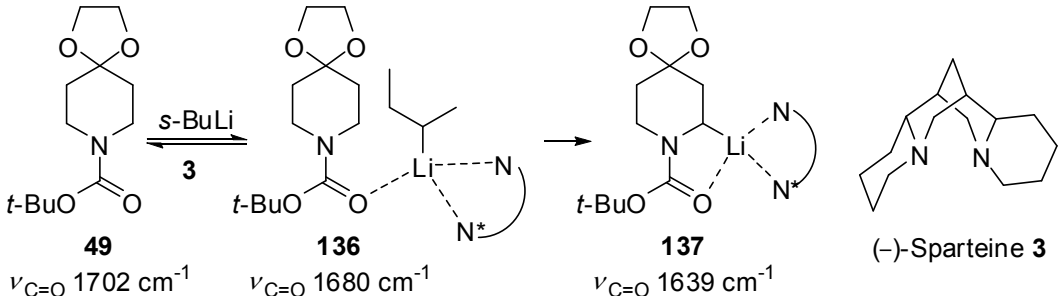


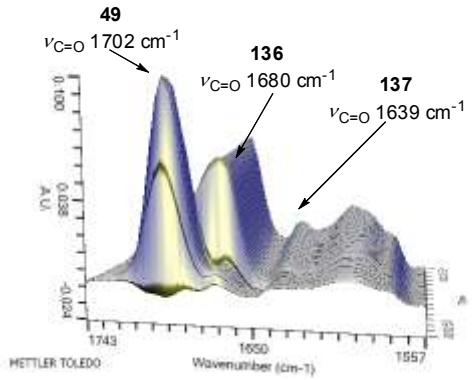


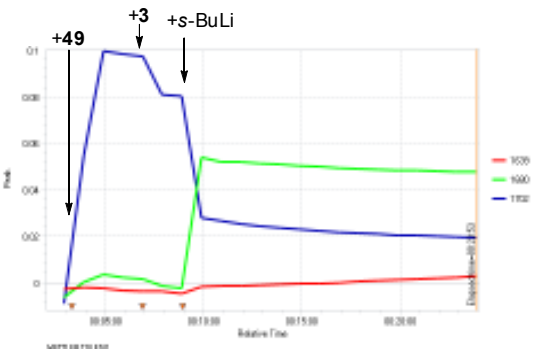
After addition of *s*-BuLi, lithiation of *N*-Boc acetal piperidine **49** to give **135** was relatively fast – complete lithiation was observed within 25 min, indicating that extended lithiation times are unnecessary.[29] This is a shorter lithiation time than the 90 min reaction time required for complete lithiation of *N*-Boc piperidine **44** (see scheme 2.8).

Next, lithiation of **49** using *s*-BuLi/(–)-sparteine **3** was studied. *N*-Boc acetal piperidine **49** ($\nu_{C=O}$ 1702 cm^{-1}) and (–)-sparteine **3** were stirred in diethyl ether at –78 °C and *s*-BuLi was added. Formation of prelithiation complex **136** ($\nu_{C=O}$ 1680 cm^{-1}) and then slow lithiation to give product **137** ($\nu_{C=O}$ 1639 cm^{-1}) was observed (scheme 2.18).

Scheme 2.18



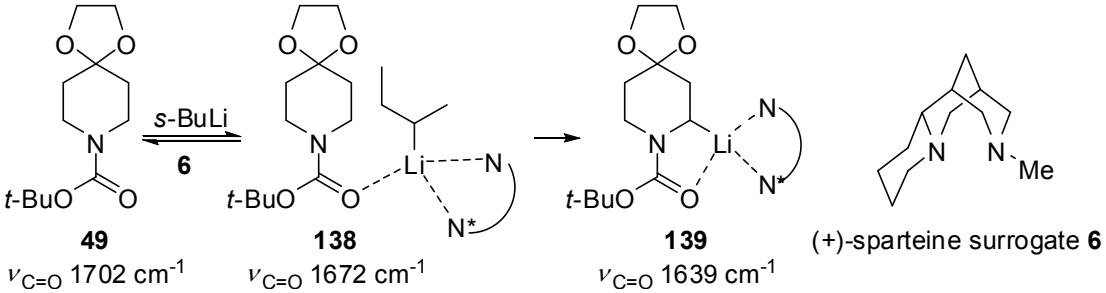


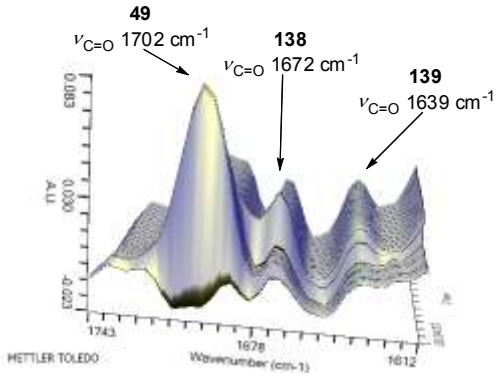


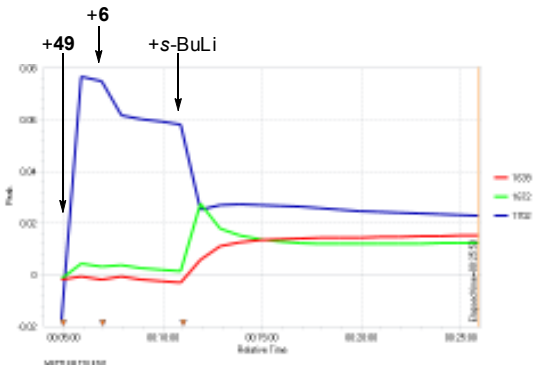
Although it has previously been reported that attempted lithiation-trapping of *N*-Boc acetal piperidine **49** mediated by *s*-BuLi and (–)-sparteine **3** gave no products,[65] we were able to observe a small amount of lithiation after a reaction time of 15 min. It is possible that repeated synthetic experiments under these conditions allowing longer lithiation times may be successful in producing 2-substituted analogues of **49**.

Finally, the *s*-BuLi/(+)-sparteine surrogate **6**-mediated lithiation of *N*-Boc acetal piperidine **49** was investigated. Thus, **49** and (+)-sparteine surrogate **6** ($\nu_{C=O}$ 1702 cm^{-1}) were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. Peaks corresponding to prelithiation complex **138** ($\nu_{C=O}$ 1672 cm^{-1}) and lithiated product **139** ($\nu_{C=O}$ 1639 cm^{-1}) were observed (scheme 2.19).

Scheme 2.19





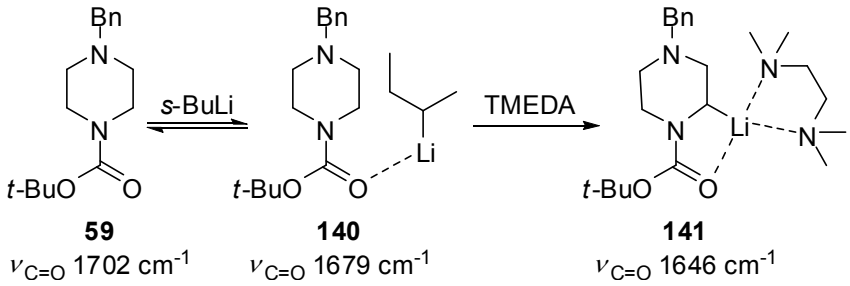


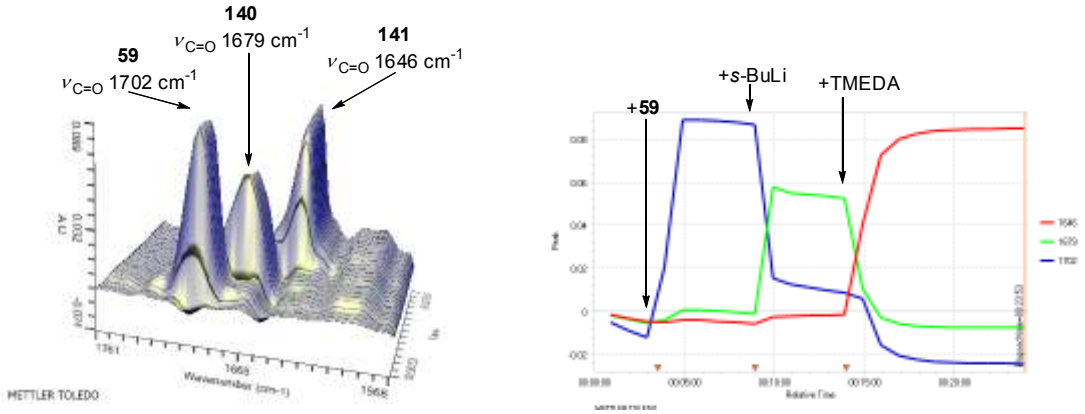
After *s*-BuLi addition, fast but incomplete lithiation to give **139** was observed. Previous lithiations of *N*-Boc acetal piperidine **49** (using other diamines) have used a 6 h lithiation time.[65] When using (+)-sparteine surrogate **6**, it appears that such a long reaction time would not be needed. The reason for incomplete lithiation in this case is not known.

2.2.5 *N*-Boc-*N*′-Benzylpiperazine

The next substrate selected for monitoring by *in situ* infra-red spectroscopy was *N*-Boc-*N*′-benzylpiperazine **59**. First, lithiation *via* formation of prelithiation complex **140** was investigated. Thus, piperazine **59** ($\nu_{C=O}$ 1702 cm^{-1}) was stirred in diethyl ether at –78 °C and *s*-BuLi was added. A new peak at 1679 cm^{-1} emerged and was assigned to $\nu_{C=O}$ in prelithiation complex **140**. Then, TMEDA was added to effect lithiation, and a peak at 1646 cm^{-1} was observed (scheme 2.20).

Scheme 2.20

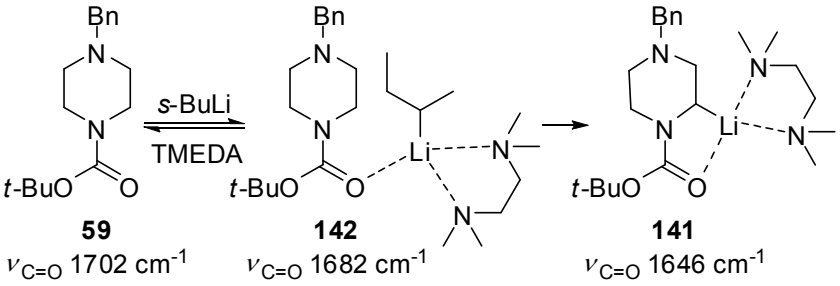


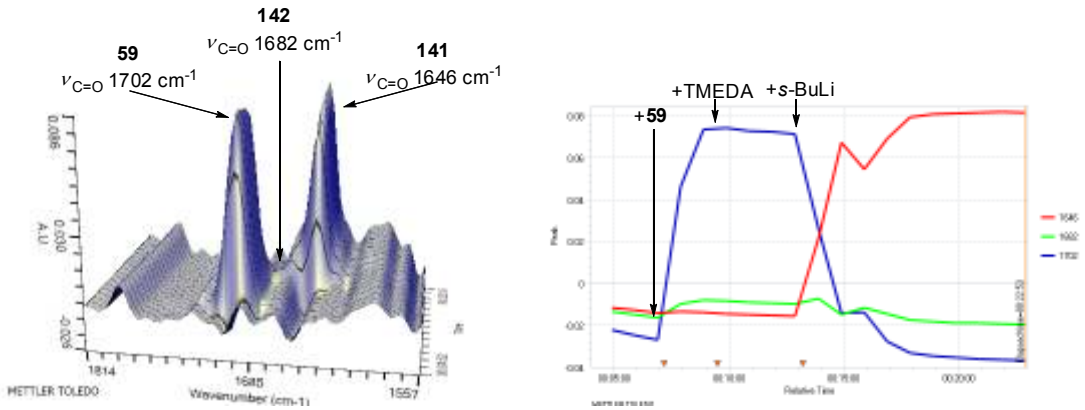


After addition of *s*-BuLi, complete formation of prelithiation complex **140** was observed. Then, after TMEDA addition, lithiation to give lithiated product **141** ($\nu_{C=O}$ 1646 cm^{-1}) was fast. Lithiation was complete within 5 min. No dissociation of prelithiation complex **140** to free piperazine **59** and *s*-BuLi was observed after addition of TMEDA.

Next, the lithiation of *N*-Boc-*N*′-benzyl piperazine **59** under experimental conditions was investigated. Piperazine **59** ($\nu_{C=O}$ 1702 cm^{-1}) and TMEDA were stirred in diethyl ether at –78 °C and *s*-BuLi was added. A small peak corresponding to prelithiation complex **142** ($\nu_{C=O}$ 1682 cm^{-1}) appeared, as did a peak at 1646 cm^{-1}, assigned to $\nu_{C=O}$ in lithiated product **141** (scheme 2.21).

Scheme 2.21

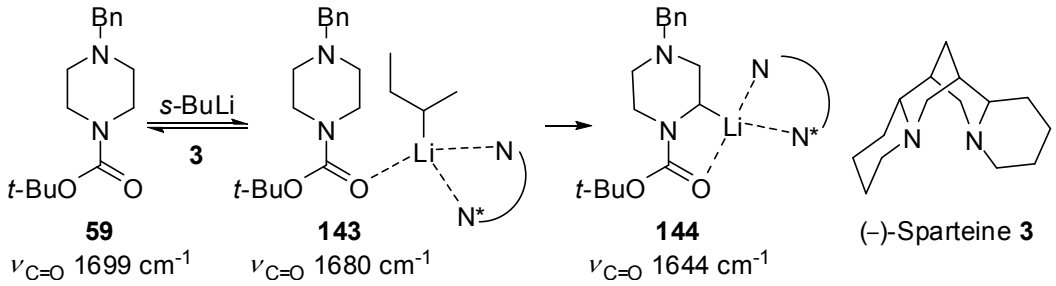


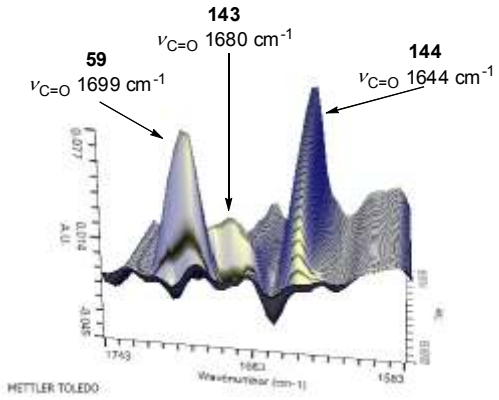


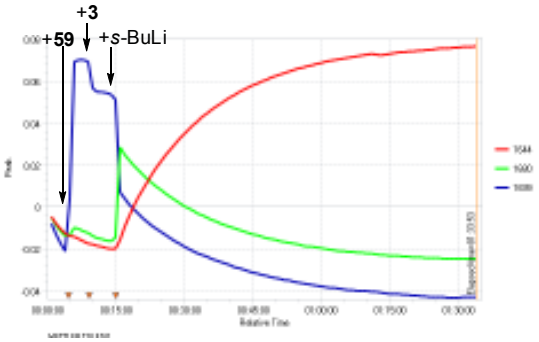
After addition of *s*-BuLi, lithiation to give lithiated product **141** was very fast. Complete formation of **141** was observed within 5 min. Consequently, it was hard to observe prelithiation complex **142**, which appeared only as a small peak presumably due to its transience.

Then, lithiation of piperazine **59** using *s*-BuLi/(–)-sparteine **3** was investigated. Thus, **59** ($\nu_{C=O}$ 1699 cm^{-1}) and (–)-sparteine **3** were premixed in diethyl ether at –78 °C and then *s*-BuLi was added. After addition of *s*-BuLi, formation of prelithiation complex **143** ($\nu_{C=O}$ 1680 cm^{-1}) took place, followed by lithiation to give lithiated piperazine **144** ($\nu_{C=O}$ 1644 cm^{-1}) (scheme 2.22). Upon addition of *s*-BuLi, formation of prelithiation complex **143** was instant, and then lithiation to give lithiated product **144** was found to be complete after 75 min.

Scheme 2.22

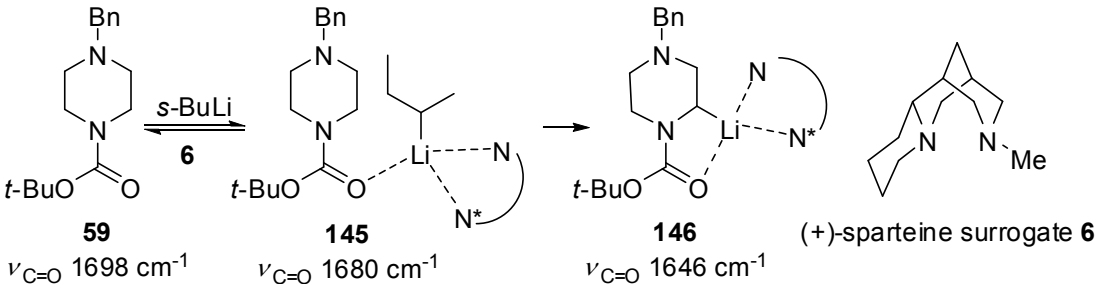


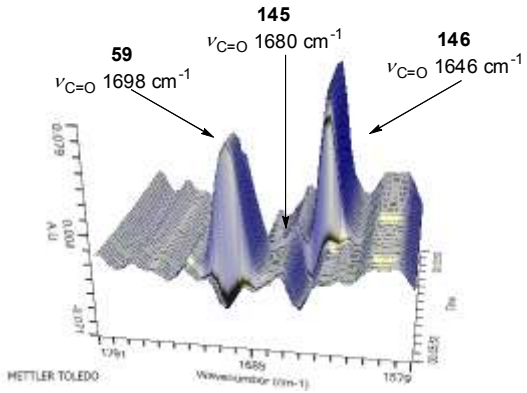


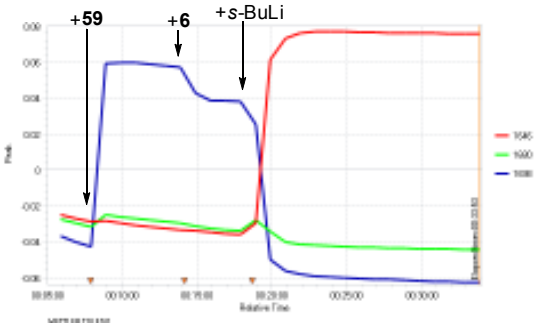


For comparison to the use of (–)-sparteine **3**, we next investigated the lithiation of *N*-Boc-*N*′-benzyl piperazine **59** by *s*-BuLi/(+)-sparteine surrogate **6**. Thus, **59** ($\nu_{C=O}$ 1698 cm^{-1}) and **6** were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. After addition of *s*-BuLi, peaks corresponding to prelithiation complex **145** ($\nu_{C=O}$ 1680 cm^{-1}) and lithiated piperazine **146** ($\nu_{C=O}$ 1646 cm^{-1}) were observed (scheme 2.23).

Scheme 2.23





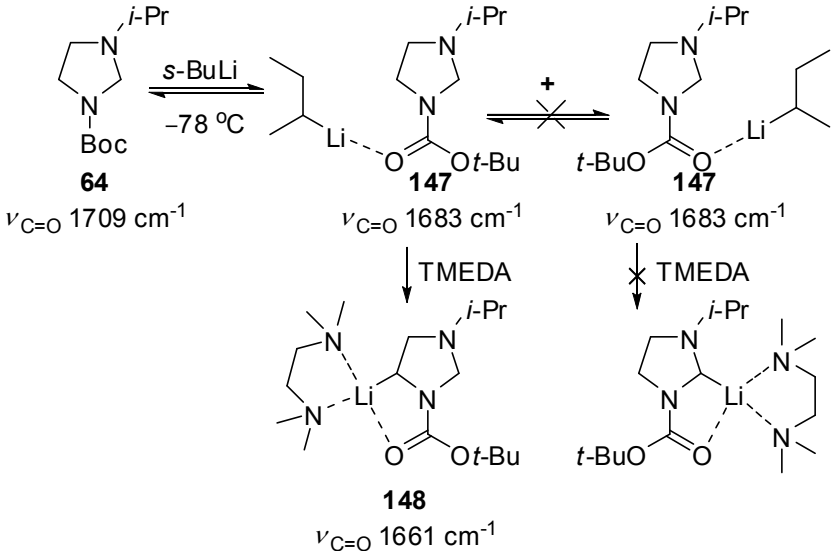


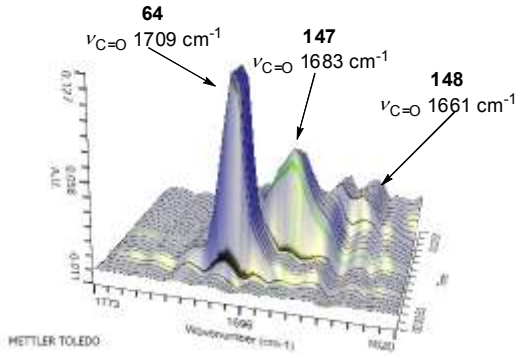
After addition of *s*-BuLi, lithiation of *N*-Boc-*N*′-benzyl piperazine **59** to give **146** was complete within 5 min. This lithiation time is the same as that observed using TMEDA. Due to the fast lithiation, prelithiation complex only appeared briefly as a small peak.We note that *N*-Boc-*N*′-benzyl piperazine **59** and *N*-Boc pyrrolidine **38** are similarly easy to lithiate, although the results of lithiation using *s*-BuLi/(–)-sparteine **3** indicate that *N*-Boc pyrrolidine **3** is easier to lithiate (see schemes 2.11 and 2.22).

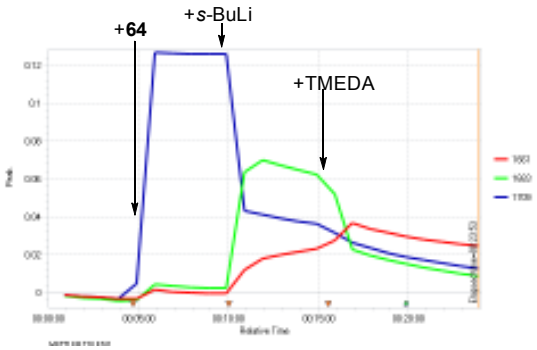
2.2.6 *N*-Boc-*N*′-isopropylimidazolidine

Coldham has previously reported both the racemic and enantioselective lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** at –78 °C, obtaining maximum yields of 50%.[74, 75] It was proposed that modest yields were obtained due to a lack of *N*-Boc rotamer interconversion at –78 °C (see scheme 1.28). We wished to study this phenomenon using *in situ* infra-red spectroscopic monitoring. Thus, *N*-Boc imidazolidine **64** ($\nu_{C=O}$ 1709 cm^{-1}) was stirred in diethyl ether at –78 °C and then *s*-BuLi was added. A new peak was observed at 1683 cm^{-1} and assigned to $\nu_{C=O}$ in prelithiation complex **147**. Then, TMEDA was added and a peak corresponding to lithiated product **148** $\nu_{C=O}$ 1661 cm^{-1} emerged (scheme 2.24).

Scheme 2.24



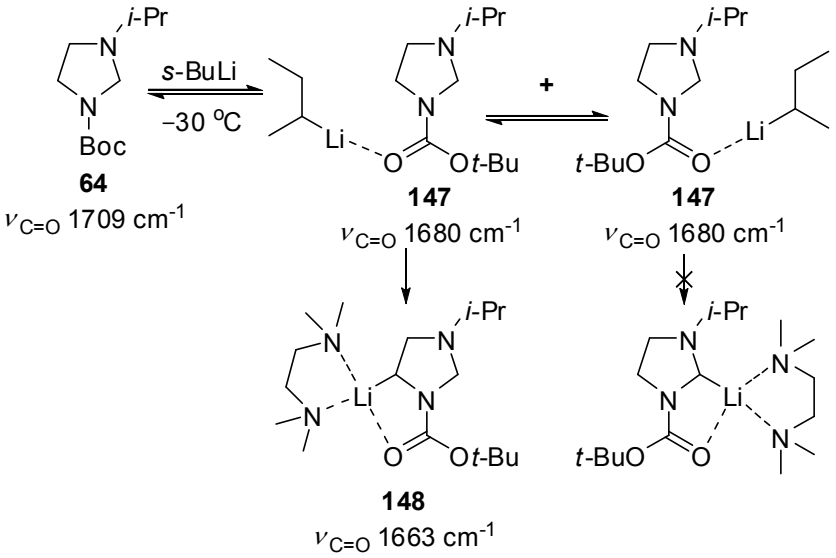


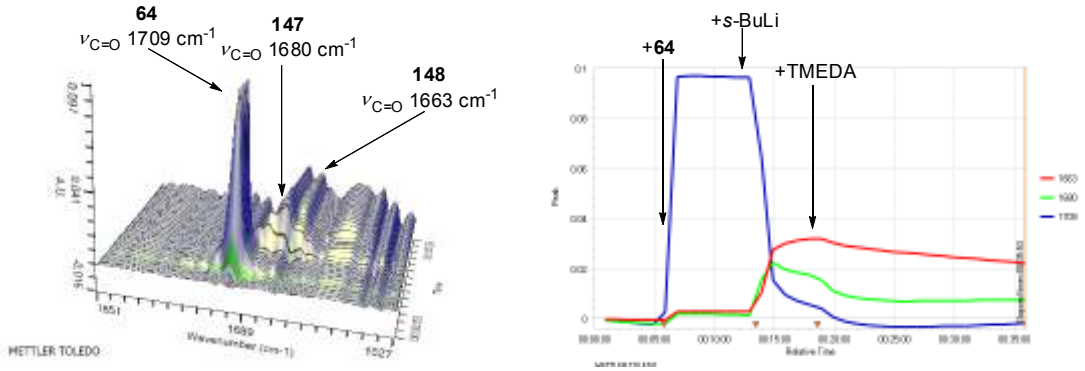


After addition of *s*-BuLi, formation of prelithiation complex **147** by the majority of imidazolidine **64** present was observed, as well as partial lithiation. After addition of TMEDA, the rate of lithiation increased.

For comparison to the lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** at –78 °C, we decided to investigate lithiation at a higher temperature where the *N*-Boc rotamers could interconvert. Thus, imidazolidine **64** ($\nu_{C=O}$ 1709 cm^{-1}) was stirred in diethyl ether at –30 °C and then *s*-BuLi was added. New peaks were observed at 1680 cm^{-1} ($\nu_{C=O}$ in prelithiation complex **147**) and 1663 cm^{-1} ($\nu_{C=O}$ in lithiated product **148**). Then, TMEDA was added (scheme 2.25).

Scheme 2.25



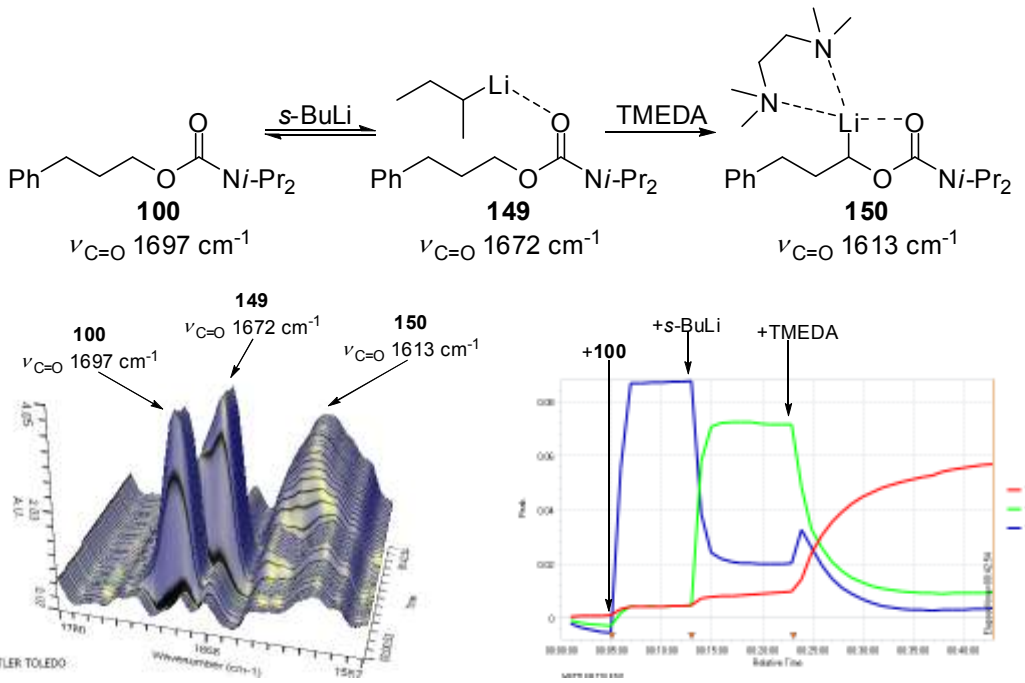


We note that upon addition of *s*-BuLi, formation of both prelithiation complex **147** and lithiated product **148** took place. Lithiation of imidazolidine **64** took place in diethyl ether at –30 °C in the absence of diamine. Lithiation mediated by *s*-BuLi only also took place at –78 °C, to a lesser degree (scheme 2.24). After 10 min of reaction time, both *N*-Boc-*N*′-*i*-Pr imidazolidine **64** and prelithiation complex **147** had been consumed, indicating that at –30 °C the *N*-Boc rotamers interconvert and complete lithiation of **64** may be carried out.

2.2.7 *O*-Alkyl Carbamate

Thus far, only lithiations of *N*-Boc heterocycles had been studied using *in situ* infra-red spectroscopy. Wishing to expand the range of our study, we turned our attention to the lithiation of *O*-alkyl carbamate **100**. The first reaction conditions to be studied were formation of the prelithiation complex then addition of TMEDA. Thus, *O*-alkyl carbamate **100** ($\nu_{C=O}$ 1697 cm^{-1}) was stirred in diethyl ether at –78 °C and *s*-BuLi was added. A new peak appeared at 1672 cm^{-1} and was assigned to $\nu_{C=O}$ in prelithiation complex **149**. Then, TMEDA was added and a peak corresponding to lithiated carbamate **150** ($\nu_{C=O}$ 1613 cm^{-1}) emerged (scheme 2.26).

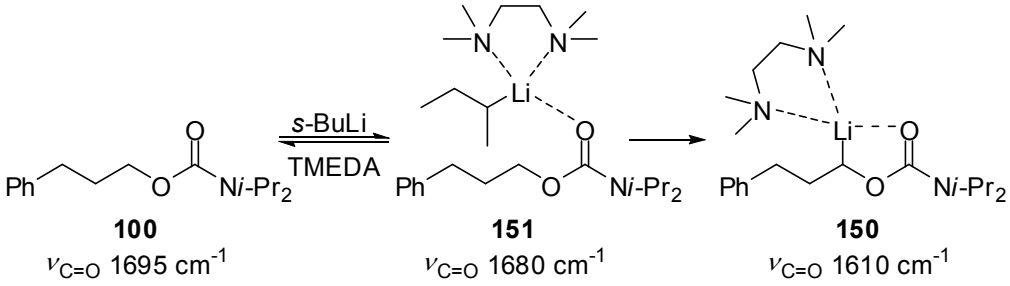
Scheme 2.26

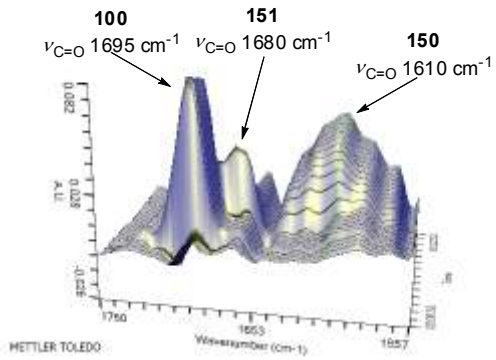


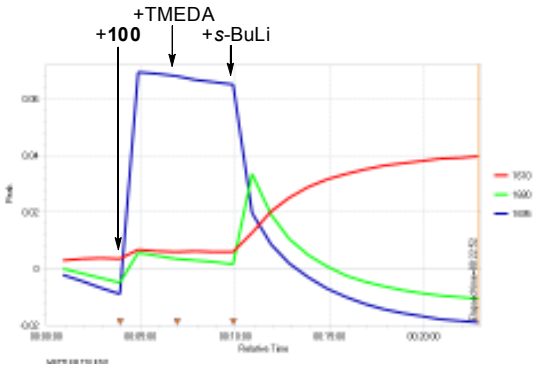
After addition of TMEDA, lithiation proceeded quickly and complete formation of lithiated product **150** was observed after 20 min. The peak corresponding to $\nu_{C=O}$ of lithiated product **150** was broader than those of lithiated *N*-Boc heterocyles **38**, **44**, **49**, **56** **59** and **64**, which may be due to a greater conformational flexibility in this acyclic compound.

Next, *s*-BuLi/TMEDA-mediated lithiation of carbamate **100** was investigated under typical experimental conditions. Thus, *O*-alkyl carbamate **100** ($\nu_{C=O}$ 1695 cm^{-1}) and TMEDA were mixed in diethyl ether at –78 °C and then *s*-BuLi was added. New peaks corresponding to prelithiation complex **151** ($\nu_{C=O}$ 1680 cm^{-1}) and lithiated product **150** ($\nu_{C=O}$ 1610 cm^{-1}) emerged (scheme 2.27).

Scheme 2.27



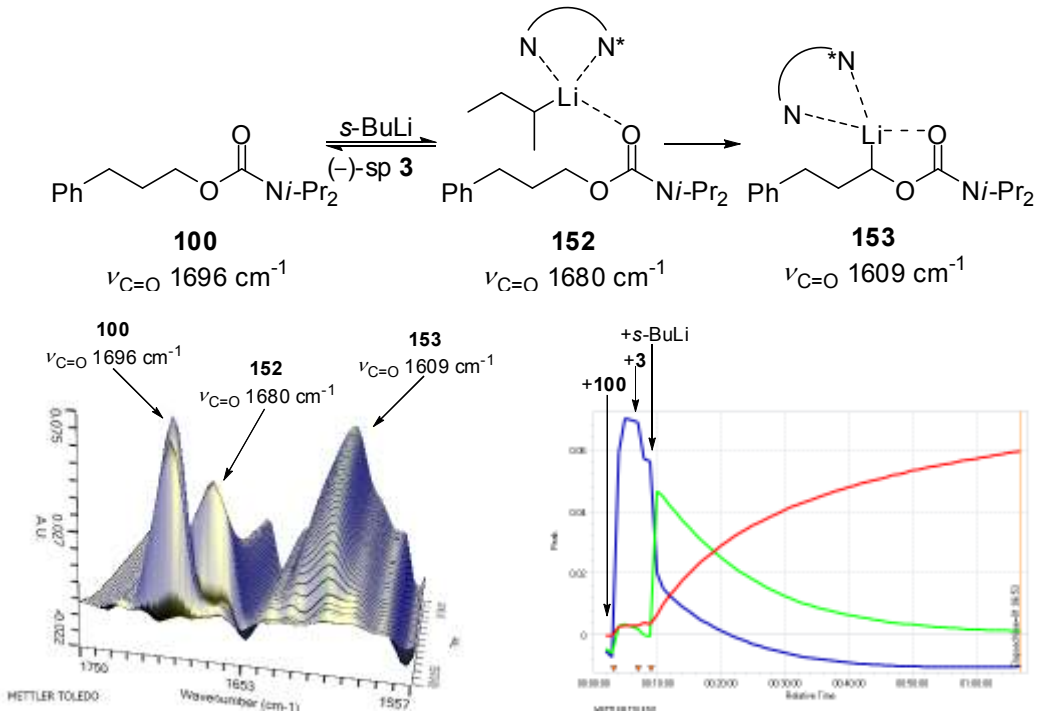




After addition of *s*-BuLi, lithiation proceeded quickly and formation of lithiated product **151** was found to be complete within 15 min. We note, however, that lithiation of *O*-alkyl carbamate **100** by *s*-BuLi/TMEDA is slower than the corresponding lithiation of *N*-Boc pyrrolidine **38** (3 min lithiation time, see scheme 2.10).

Then, the lithiation of **100** using *s*-BuLi/(–)-sparteine **3** was monitored using *in situ* infra-red spectroscopy. Thus, *O*-alkyl carbamate **100** ($\nu_{C=O}$ 1696 cm^{-1}) and (–)-sparteine **3** were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. Peaks assigned to prelithiation complex **152** ($\nu_{C=O}$ 1680 cm^{-1}) and lithiated carbamate **153** ($\nu_{C=O}$ 1609 cm^{-1}) were observed (scheme 2.28).

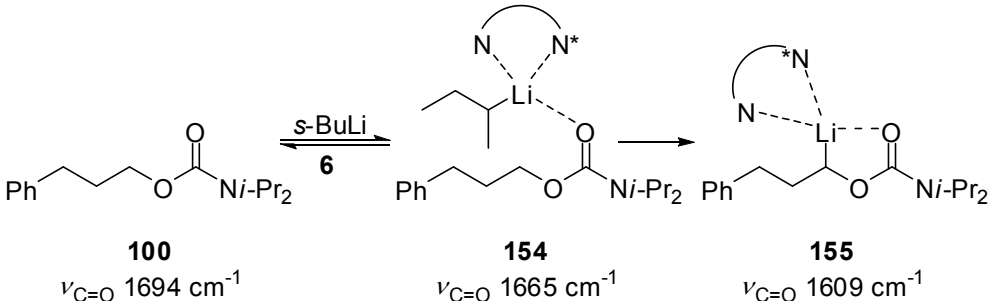
Scheme 2.28

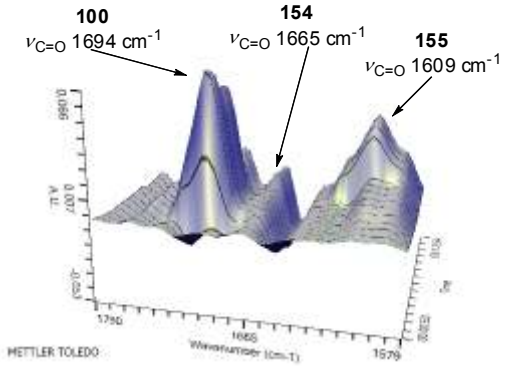


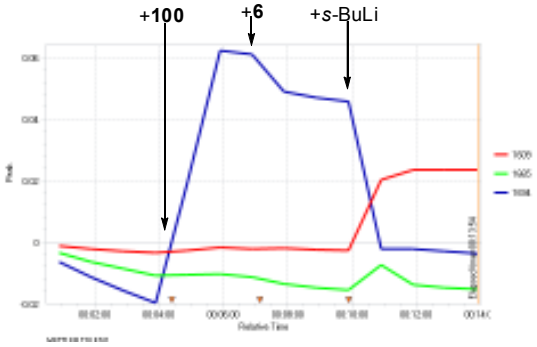
After addition of *s*-BuLi, complete lithiation to give product **153** was observed in 45 min. As with TMEDA, it was found that lithiation of *O*-alkyl carbamate **100** using *s*-BuLi/(–)-sparteine **3** was slower than the corresponding lithiation of *N*-Boc pyrrolidine **38**.

For a final comparison, lithiation of **100** using *s*-BuLi/(+)-sparteine surrogate **6** was investigated. Thus, *O*-alkyl carbamate **100** ($\nu_{C=O}$ 1694 cm^{-1}) and (+)-sparteine surrogate **6** were stirred in diethyl ether at –78 °C and then *s*-BuLi was added. Peaks at 1665 cm^{-1} ($\nu_{C=O}$ in prelithiation complex **154**) and 1609 cm^{-1} ($\nu_{C=O}$ in lithiated carbamate **155**) were observed (scheme 2.29).

Scheme 2.29





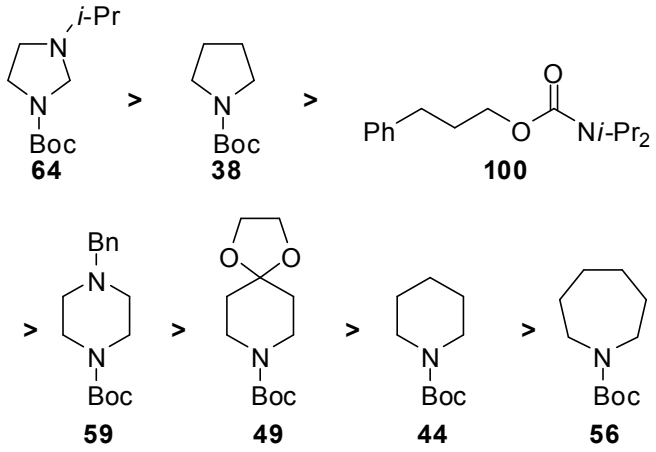


We note that after addition of *s*-BuLi, lithiation to give **155** was faster than the lithiation using *s*-BuLi/TMEDA (scheme 2.27), with complete formation of lithiated product **155** observed in 3 min. Due to the fast reaction, prelithiation complex **154** was only observable as a small peak.

2.3 Conclusions and Future Work

Using *in situ* infra-red spectroscopic monitoring of carbamate lithiations, we are able to place the carbamates examined in order of reactivity to deprotonation using *s*-BuLi/diamines, as shown in figure 2.2.

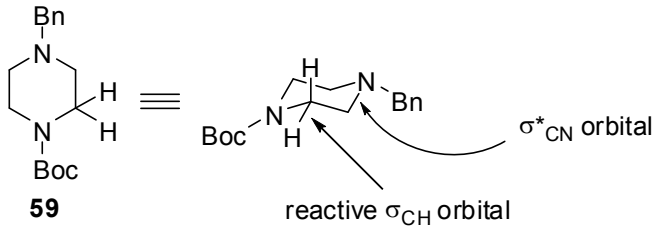
Figure 2.2



As the only substrate to undergo some lithiation in the presence of *s*-BuLi/Et_2O, *N*-Boc-*N*′-isopropylimidazolidine **64** is the most easily deprotonated compound (schemes 2.24 and 2.25). Then, comparing *s*-BuLi/(–)-sparteine **3**-mediated lithiations, lithiation of *N*-Boc pyrrolidine **38** was fastest (20 min, scheme 2.11), followed by *O*-alkyl carbamate **100** (45 min, scheme 2.28) and then *N*-Boc-*N*′-benzyl piperazine **59** (75 min, scheme 2.22). *N*-Boc heterocycles **44**, **49** and **56** did not undergo complete lithiation by *s*-BuLi/(–)-sparteine **3** (schemes 2.9, 2.14 and 2.18). Instead, considering the results from forming a prelithiation complex then adding TMEDA, *N*-Boc acetal piperidine **49** was lithiated in 35 min (scheme 2.16), *N*-Boc piperidine **44** was lithiated in 90 min (scheme 2.8) and *N*-Boc homopiperidine **56** underwent incomplete lithiation in 45 min (scheme 2.12), but was visibly slower than *N*-Boc piperidine **44** under the same conditions.

We have observed that *N*-Boc-*N*′-isopropylimidazolidine **64** and *N*-Boc-*N*′-benzyl piperazine **59** are both easier to lithiate than their respective analogues *N*-Boc pyrrolidine **38** and *N*-Boc piperidine **44**, which lack a second nitrogen. A possible explanation for this is that the reactive C–H bond α to nitrogen is weakened by feeding electron density into the antiperiplanar σ* C-N anti-bonding orbital, as shown in scheme 2.3.

Figure 2.3



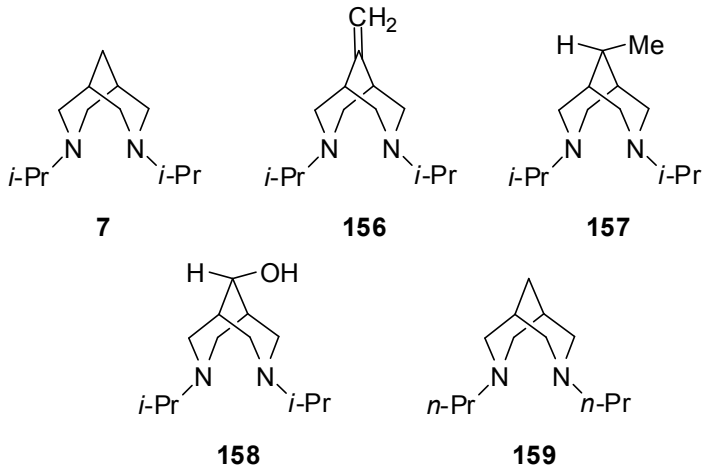
It is clear that ReactIR is a powerful tool for the chemist interested in carbonyl-directed lithiations. Even without gathering kinetic data, it is possible to ascertain the time taken for a particular reaction without the need for multiple synthetic experiments with different reaction times. Information on the mechanism of reaction can be determined by observing the formation of intermediates and products. Finally, in the investigation of the lithiation of a new substrate, the facility of reaction can be determined without worrying about inefficient trapping – formation of the lithated product is observed directly rather than *via* a potentially uncooperative electrophile. Our work represents a preliminary set of results in the ReactIR observation of *N*-Boc heterocycle lithiations. Several further avenues of inquiry are immediately apparent. Imidazolidine **64** displays low yielding lithiation at low temperatures due to a lack of interconversion of an unreactive *N*-Boc rotamer. At higher temperatures, interconversion, and so higher degrees of lithiation take place. It is obvious that a further investigation of this system with chiral ligands, and of other non-symmetric *N*-Boc heterocycles would be of interest.

N-Boc piperidine **44** and *N*-Boc homopiperidine **56** display incomplete formation of prelithiation complexes under experimental conditions. Furthermore, when deliberately forming a prelithiation complex, addition of diamine ligand causes dissociation back to uncomplexed substrate. It may be that investigation of lithiation of these heterocycles with different alkyllithium aggregates of alkyllithium/diamine complexes may give rise to conditions which favour greater formation of prelithiation complex, and thus more facile lithiation.

Chapter 3: Two-Ligand Catalytic Asymmetric Lithiation of *N*-Boc Pyrrolidine

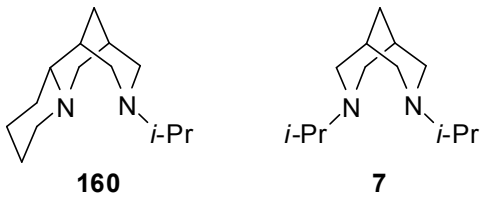
This chapter is concerned with the development of two-ligand catalytic asymmetric lithiation of *N*-Boc pyrrolidine **38** using a substoichiometric amount of a chiral diamine in the presence of a stoichiometric amount of a secondary achiral diamine. For comparison to previously reported achiral diamine **7**, new ligands **156-159** were synthesised and evaluated in catalytic lithiations (figure 3.1).

Figure 3.1



In addition, two-ligand catalytic lithiation-arylation of *N*-Boc pyrrolidine is described. Finally, lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi and diamines **160** and **7** was followed using *in situ* infra-red spectroscopic monitoring in order to gain insight into lithiation mediated by such hindered ligands (figure 3.2).

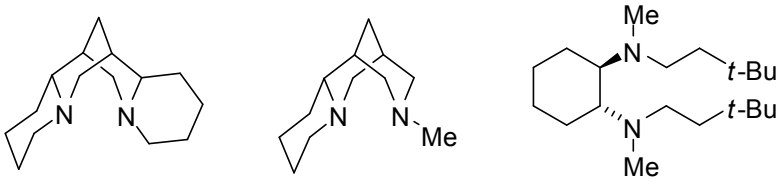
Figure 3.2



3.1 Two-Ligand Catalytic Asymmetric Lithiation of Carbamates

Enantioselective lithiation-trapping is a facile route to α-substituted carbamates in high yields and enantioselectivity. However, this methodology is hindered by the lack of an ideal chiral ligand. (–)-Sparteine **3** can be obtained by extraction from papilionaceous plants such as *C. scoparius*.[120] It is thus suitable for use on a small scale but is rather expensive for industrial use (£181.50/100 g, Aldrich, 2009). Unreliable supply is also a problem, as (–)-sparteine has been commercially unavailable throughout 2010/early 2011. (+)-Sparteine surrogate **6** is accessed through a three-step synthesis, starting from the natural product (–)-cytisine **40** (US$ 920.00/50 g, Chemdel, 2011). (–)-Cytisine **40** may also be extracted in the laboratory from the seeds of *L. anagyroides cytisus*.[121] (+)-Sparteine surrogate **6** has recently become commercially available but is expensive even for use on a small scale in the research laboratory (£140.50/100 mg, Aldrich 2011). In 2008, our group reported the use of *trans*-cyclohexane diamine (*R*,*R*)-**8** in lithiations of *N*-Boc pyrrolidine **38**.[59] Originally introduced by Alexakis, (*R*,*R*)- and (*S*,*S*)-**8** have since become commercially available, but remain expensive (€164.30/1 g for either enantiomer, TCI, 2011).[6]

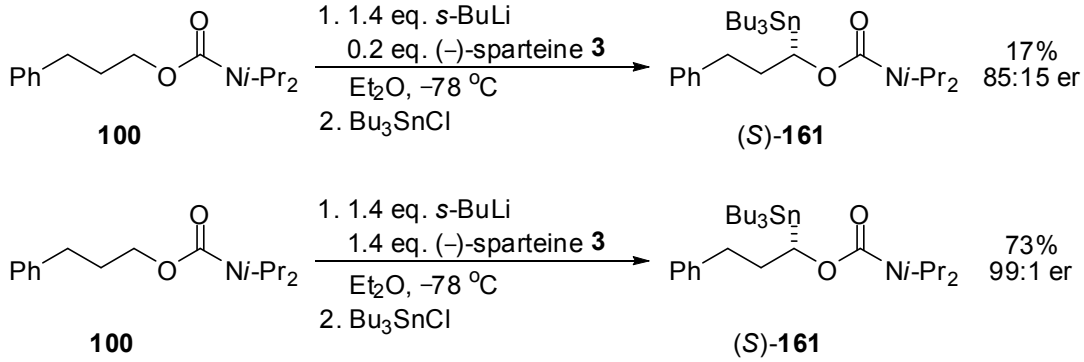
Figure 3.3



3 **6** (*R*,*R*)-**8**

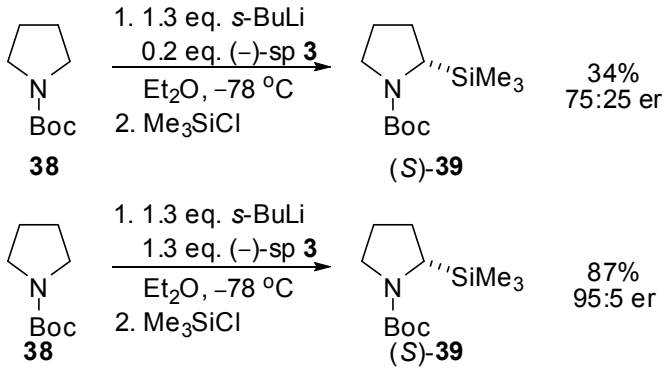
Due to the lack of a readily accessible or cheap chiral diamine, our group decided to investigate lithiation using a substoichiometric amount of chiral diamine. Simply reducing the amount of chiral diamine in the lithiation reaction did not facilitate catalytic turnover. For example, lithiation of *O*-alkyl carbamate **100** with 1.4 equivalents of *s*-BuLi and 0.2 equivalents of (–)-sparteine **3** followed by trapping with *n*-Bu_3SnCl gave stannane (*S*)-**161** in only 17% yield and 85:15 er, compared to the 73% yield and 99:1 er obtained with stoichiometric (–)-sparteine **3** (scheme 3.1).[5]

Scheme 3.1



Similarly, lithiation of *N*-Boc pyrrolidine **38** with 1.3 equivalents of *s*-BuLi and 0.2 equivalents of (–)-sparteine **3** followed by trapping with trimethylsilyl chloride gave silyl pyrrolidine (*S*)-**39** in 34% yield and 75:25 er compared with 87% yield and 95:5 er for lithiation using a stoichiometric amount of chiral diamine (scheme 3.2).[5]

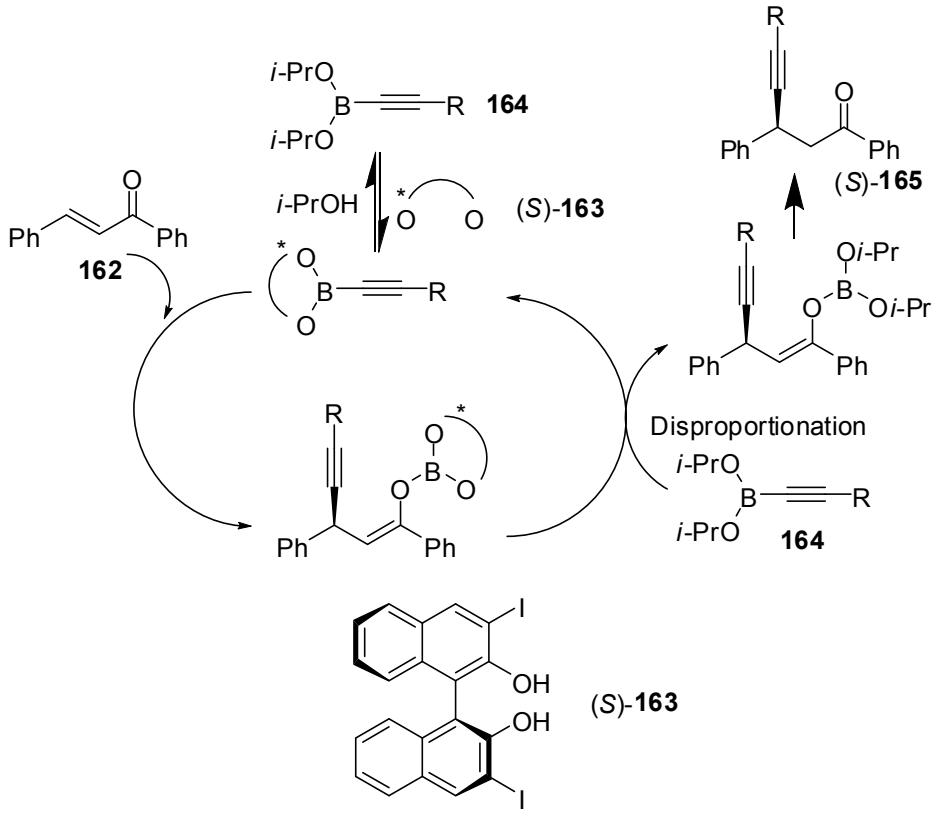
Scheme 3.2



In the case of both *N*-Boc pyrrolidine **38** and *O*-alkyl carbamate **100**, low enantioselectivities are obtained due to competing *racemic* lithiation from a *s*-BuLi/Et_2O complex. Low yields are obtained as the most active lithiating species, the *s*-BuLi/(–)-sparteine complex, is only present in low amounts. After lithiation, the chiral diamine remains coordinated to the lithiated carbamate intermediate until electrophile is added.

In 2005, Chong reported an asymmetric alkynyl boration of enones such as **162**.[122] In this study, boration was achieved using a substoichiometric amount of chiral binaphthol (*S*)-**163**. Following the boration of one molecule of substrate, cheap achiral boronate **164** was used to displace the chiral ligand back into solution, where further enantioselective boration could then take place (scheme 3.3).[122]

Scheme 3.3



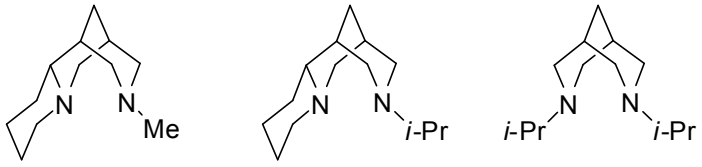
A range of enones were boronated using this methodology, giving >78% yields of products and better than 91:9 er. Chong's work demonstrated a synthetic example wherein a substoichiometric amount of a chiral ligand can be used to effect an enantioselective reaction by releasing the chiral ligand from the reaction intermediate using a second achiral ligand. It was hypothesised in our group that this approach could allow use of a substoichiometric amount of chiral diamine in asymmetric lithiations. Such a protocol is termed "two-ligand catalysis" or "ligand exchange catalysis."

Chong's work suggested a plausible experimental set-up under which catalytic turnover of a chiral ligand in asymmetric lithiations might be achieved. However, a suitable achiral secondary ligand needed to be identified. Our group decided that such a ligand must either be cheap or accessible from cheap starting materials in one or two synthetic steps, must promote catalytic turnover of the chiral ligand, and must not cause competing racemic lithiation *via* its own *s*-BuLi complex.

During research into the development of a (+)-sparteine surrogate **6**, *i*-Pr analogue **160** was synthesised. It was found that *s*-BuLi/**160** did not give rise to lithiation of *N*-Boc pyrrolidine **38**, despite DFT calculations suggesting that if a prelithiation complex formed, lithiation would indeed take place.[123] It was thus suggested that the simpler

diamine di-*i*-Pr bispidine **7** would be a suitable achiral ligand to investigate in ligand exchange catalytic lithiation (figure 3.2).

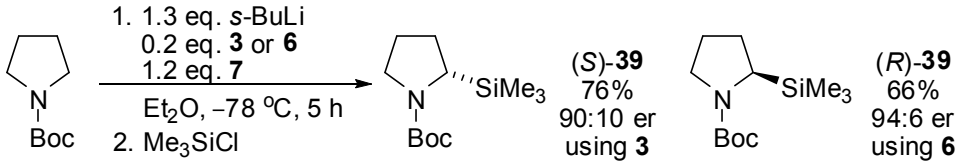
Figure 3.4



6 **160** **7**

Fortunately, di-*i*-Pr bispidine **7** did indeed effect catalytic turnover of both (–)-sparteine **3** and (+)-sparteine surrogate **6**. Thus, lithiation of *N*-Boc pyrrolidine **38** in the presence of 1.3 equivalents of *s*-BuLi, 0.2 equivalents of chiral diamine and 1.2 equivalents of bispidine **7** in Et_2O at –78 °C for 5 h followed by trapping with trimethylsilyl chloride gave silyl pyrrolidine (*S*)-**39** in 76% yield and 90:10 er with (–)-sparteine **3** and (*R*)-**39** in 66% yield and 94:6 er with (+)-sparteine surrogate **6** (scheme 3.4).[5]

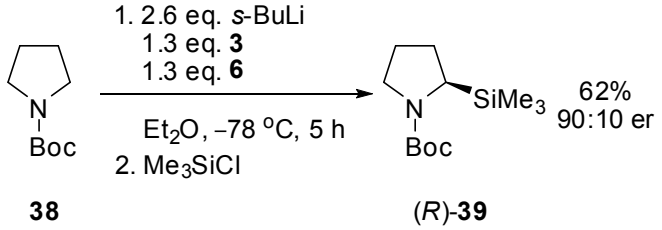
Scheme 3.4



38 (*S*)-**39** (*R*)-**39**

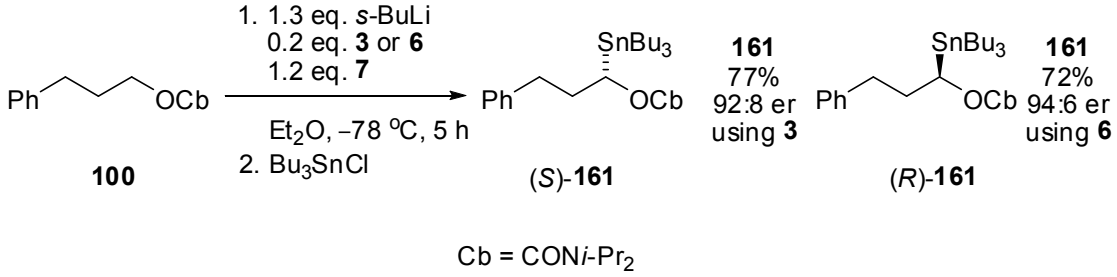
Better enantioselectivity was observed when using (+)-sparteine surrogate **6** compared with (–)-sparteine **3**. This is explained by the observation that the *s*-BuLi complex of **6** is a faster lithiater than *s*-BuLi/(–)-sparteine **3** as shown by a competition experiment. Thus, lithiation of *N*-Boc pyrrolidine **38** with 2.6 equivalents of *s*-BuLi in the presence of 1.3 equivalents each of (–)-sparteine **3** and (+)-sparteine surrogate **6** followed by trapping with trimethylsilyl chloride gave silyl pyrrolidine (*R*)-**39** in 62% yield and 90:10 er (scheme 3.5).

Scheme 3.5



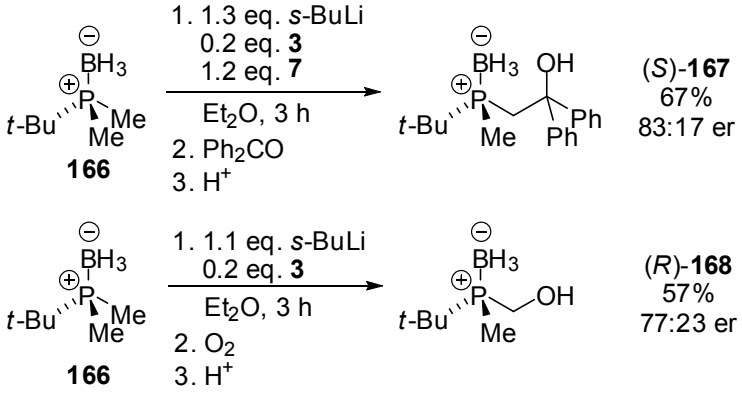
It was shown that two-ligand catalytic lithiations could also be carried out on *O*-alkyl carbamate **100**. Here, lithiation by 1.3 equivalents of *s*-BuLi in the presence of 0.2 equivalents of (–)-sparteine **3** and 1.2 equivalents of di-*i*-Pr bispidine **7** in Et_2O at –78 °C followed by trapping with *n*-Bu_3SnCl gave stannane (*S*)-**161** in 77% yield and 92:8 er. Similarly, lithiation by 1.3 equivalents of *s*-BuLi in the presence of 0.2 equivalents of (+)-sparteine surrogate **6** and 1.2 equivalents of di-*i*-Pr bispidine **7** and trapping gave stannane (*R*)-**161** in 72% yield and 94:6 er (scheme 3.6).[5]

Scheme 3.6



Finally, it was also shown that two-ligand catalytic lithiation could be carried out with phosphine borane **166**. Thus, lithiation of **166** with 1.3 equivalents of *s*-BuLi, 0.2 equivalents of (–)-sparteine **3** and 1.2 equivalents of di-*i*-Pr bispidine **7** followed by trapping with Ph_2CO gave alcohol (*S*)-**167** in 67% yield and 83:17 er.[5] It should be noted, however, that it was later found that unlike the carbamates **38** and **100**, catalytic turnover of chiral diamine was successful with phosphine borane **166** without the need for a secondary ligand. In this case, lithiation of **166** with 1.1 equivalents of *s*-BuLi and 0.2 equivalents of (–)-sparteine **3** followed by trapping with O_2 gave alcohol (*R*)-**168** in 57% yield and 77:23 er (scheme 3.7).[124]

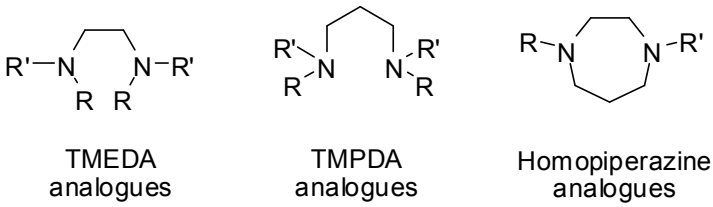
Scheme 3.7



Enantioselective lithiations using a substoichiometric amount of chiral diamine ligand without a secondary achiral ligand have also been reported on a number of other substrates. Examples include cyclooctene-derived epoxides,[125] phosphine sulfides,[126] ferrocene amides[127] and paracyclophanes.[128]

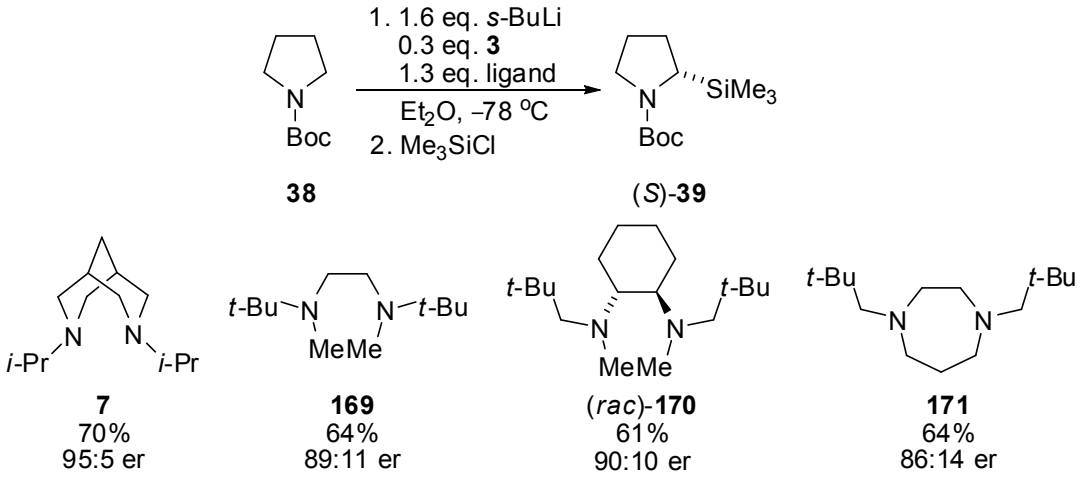
Having demonstrated two-ligand catalytic lithiation using di-*i*-Pr bispidine **7**, our group subsequently investigated other secondary achiral ligands for use with this methodology. A range of different diamines were investigated, roughly divided into three "families": TMEDA analogues, TMPDA analogues, and a hybrid of the two, 1,4-homopiperazine analogues (figure 3.3).

Figure 3.5



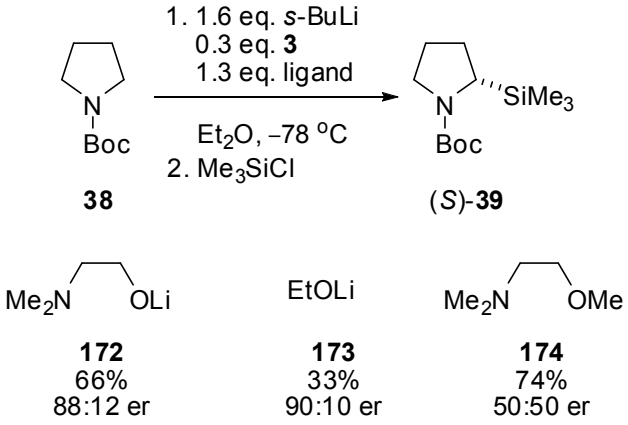
The results of the best ligands are shown in scheme 3.8.[129] Using di-*i*-Pr bispidine **7**, two-ligand catalytic lithiation of *N*-Boc pyrrolidine **38** (using 0.3 equivalents of (–)-sparteine **3**) followed by trapping with trimethylsilyl chloride gave silyl pyrrolidine (*S*)-**39** in 70% yield and 95:5 er. The TMEDA analogue **169** gave (*S*)-**39** in 64% yield and 89:11 er. An alternative TMEDA analogue, *rac*-**170**, gave (*S*)-**39** in 61% yield and 90:10 er. Finally, homopiperazine analogue **171** gave (*S*)-**39** in 64% yield and 86:14 er.[129] Ultimately, it was found that in two-ligand catalytic lithiations the best yields and enantioselectivities were obtained through the use of original bispidine **7**.

Scheme 3.8



A further investigation into other secondary ligands found that high yield and enantioselectivity could be obtained using lithium dimethylamino ethoxide (LiDMAE) **172**: silyl pyrrolidine (*S*)-**39** was obtained in 66% yield and 88:12 er after trapping with trimethylsilyl chloride. Interestingly, it was found that both the dimethylamino motif and the lithium alkoxide motif were necessary for high yield and enantioselectivity. Use of lithium ethoxide gave (*S*)-**39** in low yield (33%) and high er (90:10), while *N*,*N*-dimethyl-2-methoxyethylamine **174** gave *rac*-**39** in 74% yield (scheme 3.9).[130]

Scheme 3.9



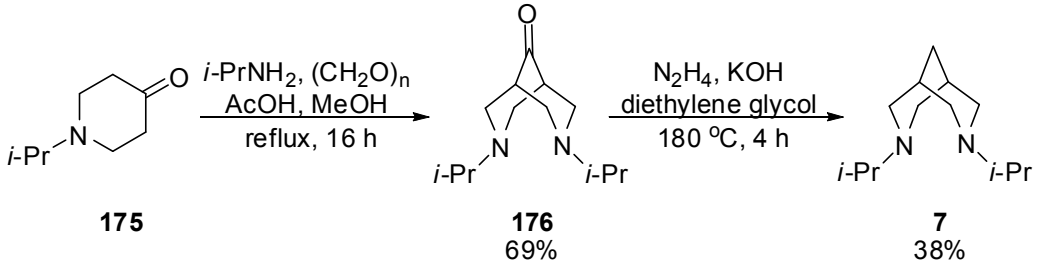
Two-ligand catalytic lithiation-trapping of *N*-Boc pyrrolidine **38** using LiDMAE **172** was then used to complete a formal total synthesis of the neurokinin-1 substance P receptor agonist (+)-L-733,060.[130] The use of LiDMAE **172** differs from diamine secondary ligands as extra equivalent of alkyllithium must be added to the lithiation reaction mixture in order to deprotonate dimethylamino-ethanol. Crucially, however, it was shown that the chiral diamine could be recovered from the reaction mixture after work-up by extraction of *N*,*N*-dimethylamino ethanol into $NaOH_{(aq)}$.[130] Such a separation of chiral diamine from achiral ligands had not previously been demonstrated.

Investigation of the use of a range of secondary achiral ligands in two-ligand catalytic lithiation of *N*-Boc pyrrolidine **38** had failed to discover a ligand superior to di-*i*-Pr bispidine **7**. We therefore wished to investigate the use of a small range of analogous bispidine achiral diamines. As part of this study, we would also attempt to optimise the two-ligand catalytic lithiation conditions. Furthermore, we hoped to use an optimised procedure to effect two-ligand catalytic lithiation-arylations which were previously unreported.

3.2 Synthesis of Achiral Bispidines

Two-ligand catalytic lithiation was shown to give optimal yields and enantioselectivity with di-*i*-Pr bispidine **7**. We were therefore interested in investigating other achiral ligands based on the bispidine motif. A second motivation for pursuing this line of inquiry was the somewhat modest yields obtained in the synthesis of **7** previously reported in our group. A double Mannich reaction of *N*-*i*-Pr-piperid-4-one **175** with paraformaldehyde and *i*-$PrNH_2$ gave bispidone **176** in 69% yield and then a Huang-Minlon modified Wolff-Kishner reduction gave bispidine **7** in 38% yield (scheme 3.10).[131] Both **176** and **7** also required extensive purification by successive distillations.

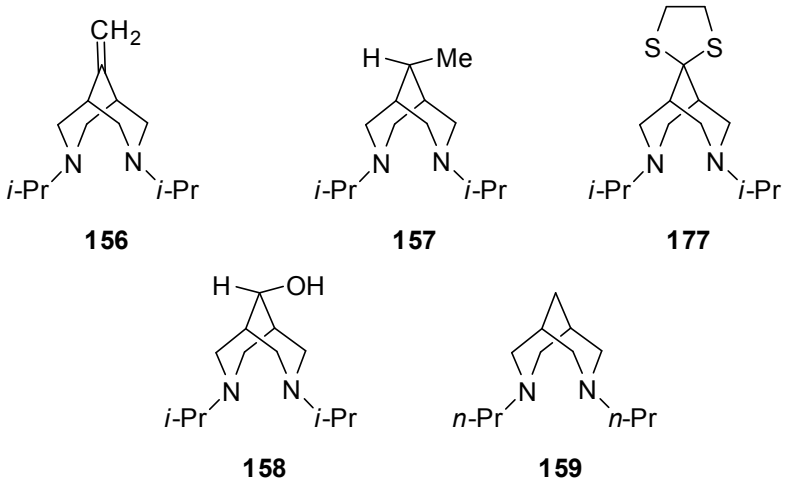
Scheme 3.10



It was hoped that any new bispidine-derived diamine ligands would be accessible in higher yields and more easily than **7**. To start with, we found that bispidone **176** could be accessed cleanly and in acceptable (67%) yields using the same method previously described by employing a careful distillation of starting material, *N*-*i*-Pr piperid-4-one **175**, and then fractional distillation of the crude product. This reaction was reproducible and has been carried out on a 20 g scale.

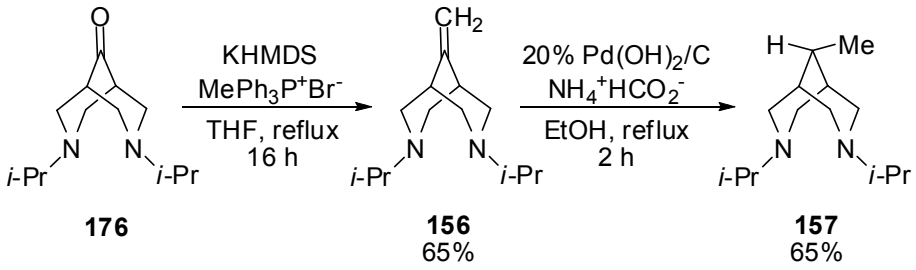
We therefore decided to derive our new ligands from **176**. For example, it was envisioned that the alkyllithium sensitive carbonyl group could be "removed" using a Wittig reaction to give alkene **156**. Further hydrogenation of the alkene would give methyl bispidine **157**. Alternatively, treatment of bispidone **176** with ethane dithiol would give dithiane **177**. Finally, reduction of bispidone **176** would give bispidol **158**. In this case, extra alkyllithium would be added to lithiation mixtures in order to first deprotonate the alcohol, as with dimethylamino ethanol. We also wished to prepare *N*,*N'*-di-*n*-Pr bispidine **159** to investigate whether use of a less hindered bispidine ligand would lead to poor enantioselectivities in two-ligand catalytic lithiations due to increased competing *racemic* lithiation (figure 3.4).

Figure 3.6



To start with, the formation of alkene **156** using a Wittig reaction on bispidone **176** with triphenylmethyl phosphonium bromide was investigated. Use of *n*-BuLi to form the phosphonium ylide did not give rise to alkene **156** at either room temperature or reflux in THF, with reaction times of up to 16 h. It was hypothesised that this was due to coordination of the alkyllithium to bispidone **176**. When KHMDS was used to generate the ylide, alkene **156** was obtained in 65% yield after removal of triphenylphosphine oxide by acid/base washing and purification by Kügelrohr short-path distillation. A reaction time of 16 h at reflux in THF gave the best yield. It was then found that methyl bispidine **157** could be obtained *via* transfer hydrogenation with ammonium formate and Pearlman's catalyst, giving the product in 65% yield (scheme 3.11).

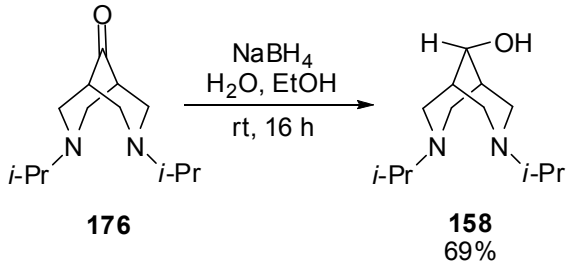
Scheme 3.11



Dithiane bispidine **177** was first described by Garrison and co-workers.[132] Unfortunately, due to difficulty in purification we were unable to prepare dithiane **177** in high enough yields to investigate its use in lithiation reactions. In contrast, reduction of bispidone **176** with sodium borohydride gave bispidol **158** in 69% yield. The crude

product was considered pure enough for use in lithiation reactions without further purification (scheme 3.12).

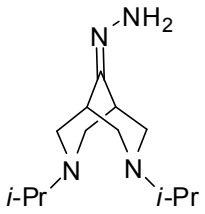
Scheme 3.12



176 **158** 69%

With **156**, **157** and **158** in hand, it was decided to reinvestigate the reduction of bispidone **176** to di-*i*-Pr bispidine **7**. After reaction of bispidone **176** under the original reduction conditions (N_2H_4, KOH, diethylene glycol, 180 °C, 4 h), careful analysis of the ^{1}H NMR spectrum of the crude product revealed a broad singlet at δ 4.91 ppm. We hypothesised that this peak could belong to the NH_2 protons of reaction intermediate **178** (figure 3.5).

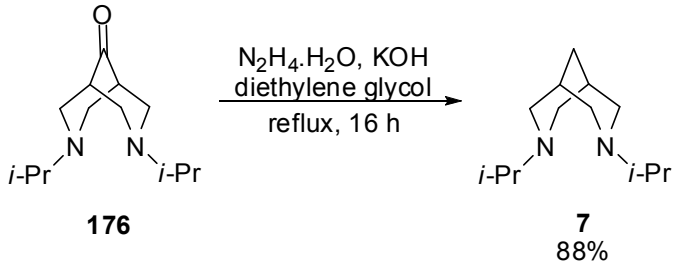
Figure 3.7



178

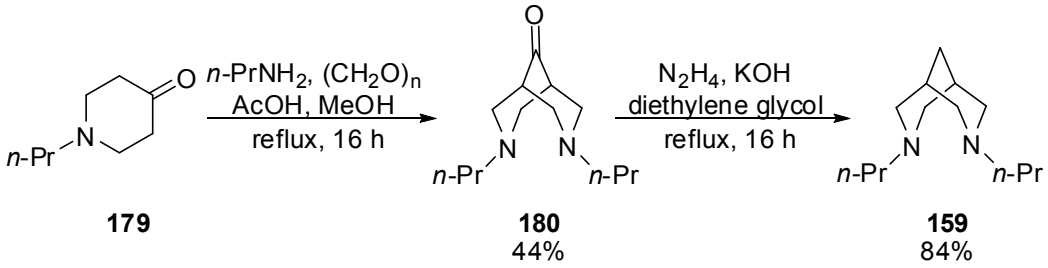
Thus, we proposed that the reason for low yields of di-*i*-Pr bispidine **7** was an incomplete reaction rather than any lack of reactivity or competing side reactions. Gratifyingly, reduction of bispidone **176** with $N_2H_4.H_2O$ and KOH in diethylene glycol at reflux for 16 h gave di-*i*-Pr bispidine **7** in 88% yield (scheme 3.13). Notably, after work-up, di-*i*-Pr bispidine **7** was free of impurities although, as with all diamines, it was distilled over calcium hydride before use in lithiation reactions.

Scheme 3.13



Finally, di-*n*-Pr bispidine **159** was synthesised using the same route as bispidine **7**. Double Mannich reaction of *n*-Pr-piperid-4-one **179** with *n*-$PrNH_2$ and paraformaldehyde gave bispidone **180** in 44% yield. Then, reduction gave di-*n*-Pr bispidine **159** in 84% yield (scheme 3.14). As with **7**, reduction proceeded without the need for further purification. Thus, multi-gram quantities of a range of new bispidines were readily prepared.

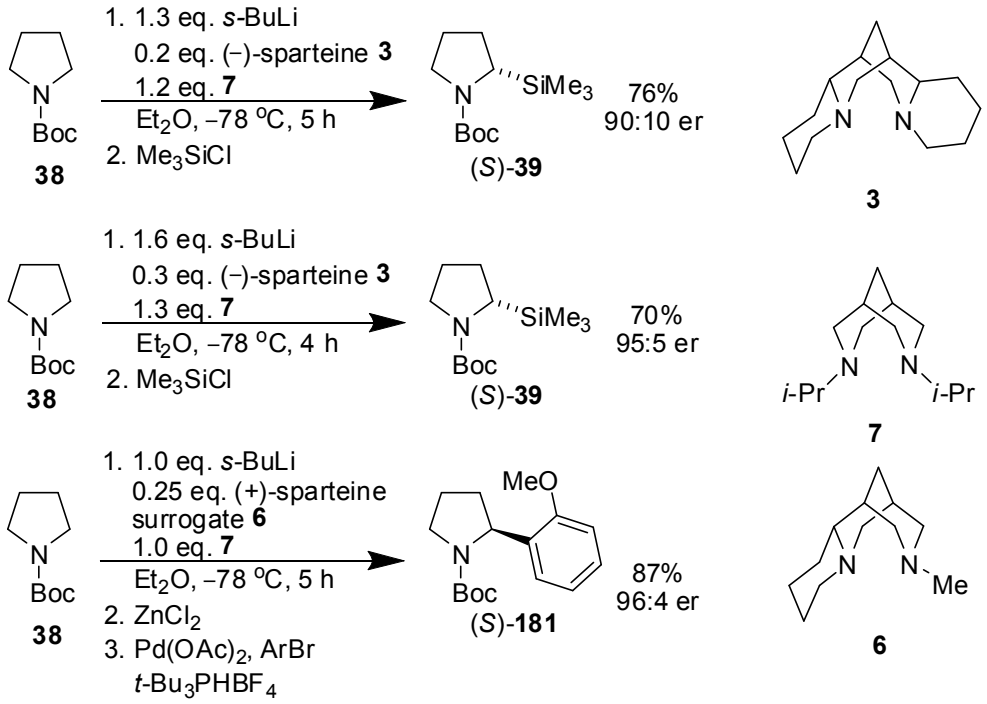
Scheme 3.14



3.3 Two-Ligand Catalytic Lithiation-Trapping of *N*-Boc Pyrrolidine

With our new bispidines in hand, it was decided to first identify the optimal two-ligand catalytic lithiation conditions using the original di-*i*-Pr bispidine **7**. Three different sets of catalytic conditions have previously been used in our group (scheme 3.15). The originally reported two-ligand catalytic lithiation conditions, using 0.2 equivalents of (–)-sparteine **3** in the presence of 1.3 equivalents of *s*-BuLi and 1.2 equivalents of di-*i*-Pr bispidine **7** and trapping with trimethylsilyl chloride gave silyl pyrrolidine (*S*)-**39** in 76% yield and 90:10 er.[5] More recently, work from our group has shown that catalytic lithiation with 0.3 equivalents of (–)-sparteine **3** in the presence of 1.6 equivalents of *s*-BuLi and 1.3 equivalents of di-*i*-Pr bispidine **7** and trapping with trimethylsilyl chloride gave (*S*)-**39** in 70% yield and 95:5 er.[130] A final set of conditions previously used in the group showed that catalytic lithiation with 0.25 equivalents of (+)-sparteine surrogate **6** in the presence of 1.0 equivalent of *s*-BuLi and 1.0 equivalent of di-*i*-Pr bispidine **7** and trapping *via* arylation (Negishi coupling) gave arylated pyrrolidine (*S*)-**181** in 87% yield and 96:4 er (scheme 3.15).[133]

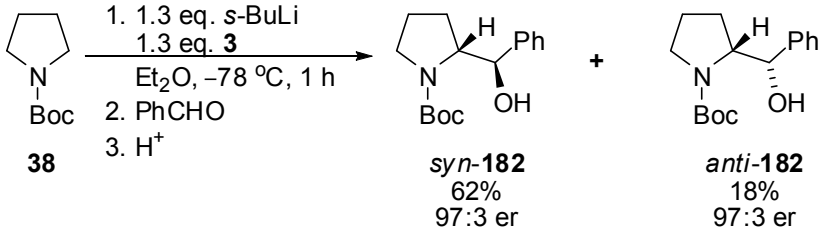
Scheme 3.15



The er of silyl pyrrolidine **39** cannot be determined using the HPLC set-up available in our group. It was therefore decided that our optimisation of two-ligand catalytic

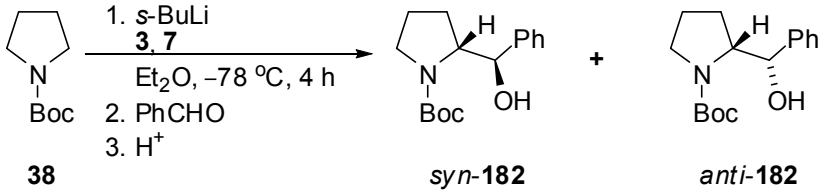
lithiations would be carried out using benzaldehyde as an electrophile. To compare with catalytic lithiations, lithiation of *N*-Boc pyrrolidine **38** with *s*-BuLi and stoichiometric (–)-sparteine **3** was carried out. After trapping with benzaldehyde, alcohol *syn*-**182** was obtained in 62% yield and 97:3 er and alcohol *anti*-**182** was obtained in 18% yield and 97:3 er (scheme 3.16). This is the benchmark for comparing all of our catalytic asymmetric lithiation reactions. The relative stereochemistry of *syn*-**182** and *anti*-**182** was assigened by comparison with a previously reported X-ray crystal structure of *anti*-**182**.[130]

Scheme 3.16



A small range of different catalytic conditions using substoichiometric (–)-sparteine **3** and di-*i*-Pr bispidine **7** was then investigated (Table 3.1). Thus, lithiation with 1.2 equivalents of *s*-BuLi, 0.2 equivalents of (–)-sparteine **3** and 1.0 equivalent of di-*i*-Pr bispidine **7** gave alcohols *syn*-**182** in 55% yield and 85:15 er and *anti*-**182** in 29% yield and 85:15 er (entry 1). Keeping the amounts of *s*-BuLi and **3** the same but increasing the amount of di-*i*-Pr bispidine **7** to 1.2 equivalents made little difference, giving *syn*-**182** in 54% yield and 84:16 er, and *anti*-**182** in 31% yield and 82:18 er (entry 2). The use of 1.3 equivalents of *s*-BuLi with 0.2 equivalents of (–)-sparteine **3** and 1.2 equivalents of di-*i*-Pr bispidine **7** gave *syn*-**182** in 57% yield and 82:18 er and *anti*-**182** in 33% yield and 82:18 er (entry 3). Increasing the loading of (–)-sparteine **3** to 0.25 equivalents, with 1.0 equivalent of *s*-BuLi and 1.0 equivalent of di-*i*-Pr bispidine **7** gave *syn*-**172** in 58% yield and 88:12 er and *anti*-**182** in 29% yield and 88:12 er (entry 4). Finally, a further increase in the (–)-sparteine **3** loading to 0.3 equivalents, along with the use of 1.6 equivalents of *s*-BuLi and 1.3 equivalents of di-*i*-Pr bispidine **7** gave *syn*-**182** in 62% yield and 91:9 er and *anti*-**182** in 33% and 91:9 er (entry 5).

Table 3.1



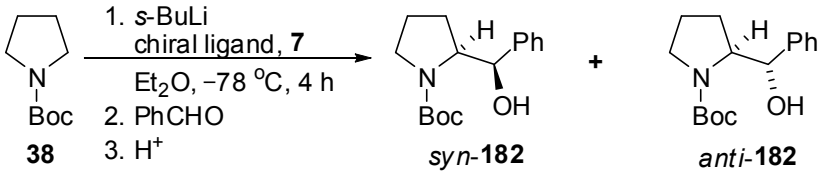
Entry	Eq. *s*-BuLi	Eq. **3**	Eq. **7**	%Yield *syn*-**182** (er)[a]	%Yield *anti*-**182** (er)[a]
1	1.2	0.2	1.0	55 (85:15)	29 (85:15)
2	1.2	0.2	1.2	54 (84:16)	31 (82:18)
3	1.3	0.2	1.2	57 (82:18)	33 (82:18)
4	1.0	0.25	1.0	58 (88:12)	29 (88:12)
5	1.6	0.3	1.3	62 (91:9)	33 (91:9)

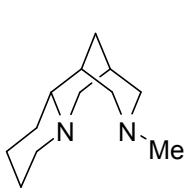
[a] % Yield after chromatography, er determined by CSP-HPLC.

Under all conditions, a high (84-95%) combined yield of diastereomeric products was obtained. The optimum conditions involved the use of 1.6 equivalents of *s*-BuLi with 0.3 equivalents of (–)-sparteine and 1.3 equivalents of di-*i*-Pr bispidine **7**, which gave a combined 95% yield of *syn*-**182** and *anti*-**182** (both in 91:9 er). It was therefore decided that these would be the conditions under which the new bispidine ligands were investigated. First, however, the use of (+)-sparteine surrogate **6** and cyclohexane diamine (*R*,*R*)-**8** under the optimal catalytic conditions was investigated (table 3.2).

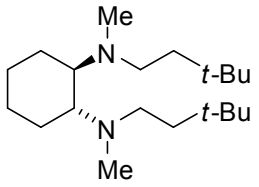
(+)-Sparteine surrogate **6** had previously been used in catalytic lithiation-arylation using the conditions described in entry 1 (see scheme 3.15). When trapping with benzaldehyde, 1.0 equivalent of *s*-BuLi, 0.25 equivalents of **6** and 1.0 equivalent of di-*i*-Pr bispidine **7** gave *syn*-**182** in 56% yield and 93:7 er and *anti*-**182** in 25% yield and 93:7 er. Under our new optimal conditions, 1.6 equivalents of *s*-BuLi with 0.3 equivalents of **6** and 1.3 equivalents of **7** gave slightly improved yield and enantioselectivity, with *syn*-**182** being obtained in 65% yield and 94:6 er and *anti*-**182** in 29% yield and 94:6 er (entry 2). As expected based on previous findings in the literature (see scheme 3.4), (+)-sparteine surrogate **6** gave higher enantioselectivities than (–)-sparteine **3** under the same conditions. Cyclohexane diamine (*R*,*R*)-**8** proved to be less suitable for use in catalytic lithiations, with the optimised conditions giving *syn*-**182** in 63% yield and 84:16 er and *anti*-**182** in 27% yield and 85:15 er (entry 3).

Table 3.2





6



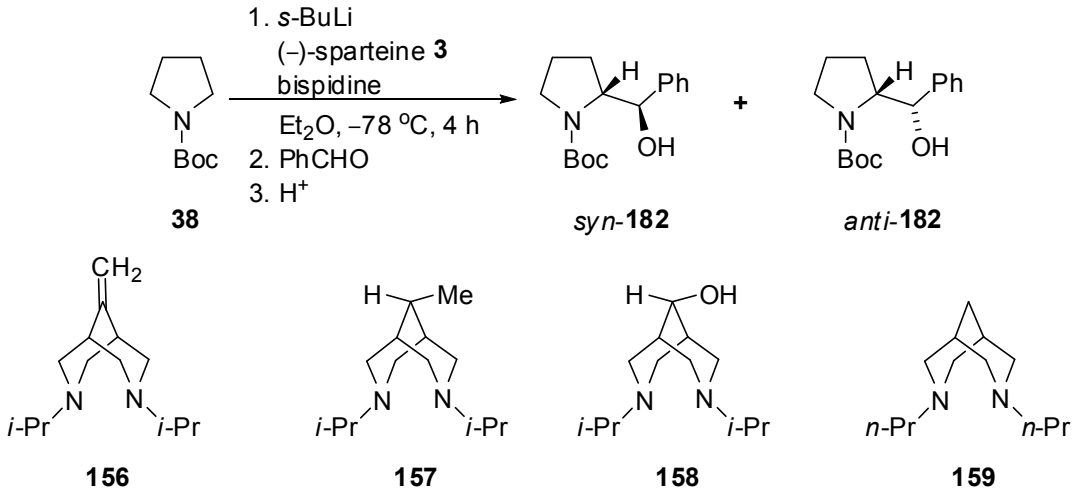
(*R*,*R*)-**8**

Entry	Eq. *s*-BuLi	Chiral Ligand (eq.)	Eq. **7**	%Yield *syn*-**182** (er)[a]	%Yield *anti*-**182** (er)[a]
1	1.0	**6** (0.25)	1.0	56 (93:7)	25 (93:7)
2	1.6	**6** (0.3)	1.3	65 (94:6)	29 (94:6)
3	1.6	(*R*,*R*)-**8** (0.3)	1.3	63 (16:84)	27 (15:85)

[a] % Yield after chromatography, er determined by CSP-HPLC.

Having optimised our catalytic lithiation conditions, and investigated three different chiral diamines using these conditions, we assayed the new bispidine ligands (table 3.3). Due to ease of use, (–)-sparteine **3** was the chiral diamine used in this investigation. Under these conditions, lithiation of *N*-Boc pyrrolidine **38** with alkene bispidine **156** gave alcohol *syn*-**182** in 61% yield and 92:8 er and alcohol *anti*-**182** in 30% yield and 88:12 er (entry 1). Methyl bispidine **157** gave poorer enantioselectivity, affording *syn*-**182** in 60% yield and 79:21 er and *anti*-**182** in 32% yield and 78:22 er (entry 2). Use of bispidol **158** required the addition of extra *s*-BuLi. Enantioselectivity was poor, giving *syn*-**182** in 54% yield and 83:17 er and *anti*-**182** in 31% yield and 77:23 er (entry 3).Unfortunately, di-*n*-Pr-bispidine **159** gave almost racemic product, with *syn*-**182** being obtained in 61% yield and 55:45 er and *anti*-**182** in 34% yield and 55:45 er (entry 4).

Table 3.3



Entry	Bispidine	%Yield *syn*-**182** (er)[a]	%Yield *anti*-**182** (er)[a]
1	**156**	61 (92:8)	30 (88:12)
2	**157**	60 (79:21)	32 (78:22)
3	**158**[b]	54 (83:17)	31 (77:23)
4	**159**	61 (55:45)	34 (55:45)

[a] % Yield after chromatography, er determined by CSP-HPLC

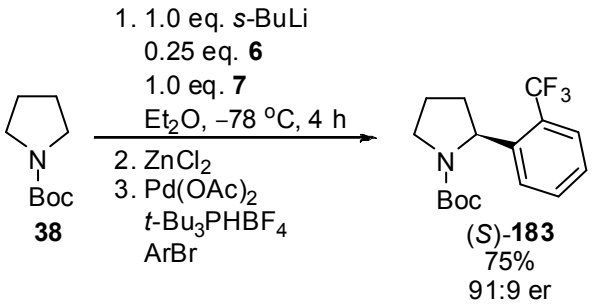
[b] 2.9 equivalents of *s*-BuLi used

None of the new achiral bispidine ligands gave higher enantioselectivities than the original bispidine **7**. Alkene bispidine **156** gave the highest er of the new ligands (92:8 er for *syn*-**182** and 88:12 er for *anti*-**182**). Use of di-*n*-Pr bispidine **159** gave nearly racemic products (55:45 er for both *syn*- and *anti*-**182**). This confirms our hypothesis that a sterically demanding ligand such as **7** is required to access products in high er.

3.4 Two-Ligand Catalytic Lithiation-Arylation of *N*-Boc Pyrrolidine

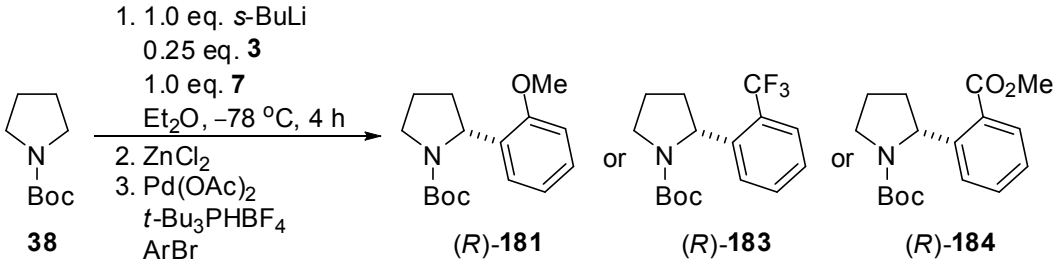
Previous work in our group and at Merck had demonstrated two-ligand catalytic lithiation-arylation with (+)-sparteine surrogate **6**.[133, 134] We wished to carry out a further example, coupling with *o*-bromobenzotrifluoride. Thus, lithiation with 1.0 equivalent of *s*-BuLi, 0.25 equivalents of (+)-sparteine surrogate **6** and 1.0 equivalent of di-*i*-Pr bispidine **7** followed by transmetallation with zinc chloride and palladium-catalysed arylation gave aryl pyrrolidine (*S*)-**183** in 75% yield and 91:9 er (scheme 3.17).

Scheme 3.17



For comparison with (+)-sparteine surrogate **6**-mediated catalytic lithiation arylations, we decided to carry out (–)-sparteine two-ligand catalytic lithiations under the same conditions, and couple with three different aryl bromides (table 3.4).

Table 3.4



Entry	Aryl Bromide	Product	%Yield[a]	er[a]
1	*o*-bromoanisole	(*R*)-**181**	50	80:20
2	*o*-bromobenzotrifluoride	(*R*)-**183**	76	80:20
3	methyl 2-bromobenzoate	(*R*)-**184**	50	81:19

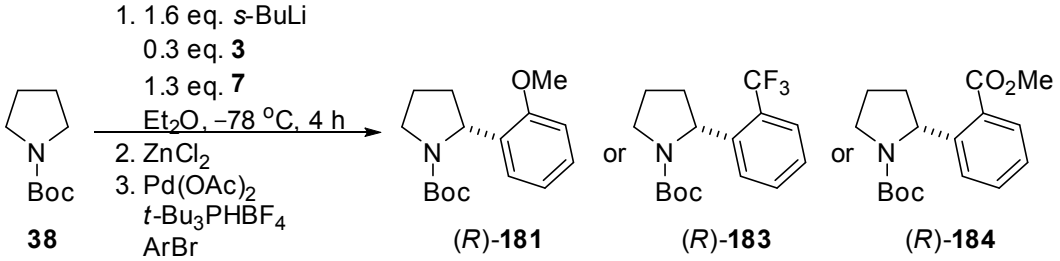
[a] % Yield after chromatography, er determined by CSP-HPLC

Thus, lithiation of *N*-Boc pyrrolidine **38** with 1.0 equivalent of *s*-BuLi, 0.25 equivalents of (–)-sparteine **3** and 1.0 equivalent of di-*i*-Pr bispidine **7** followed by tranmetallation

and coupling with *o*-bromoanisole gave aryl pyrrolidine (*R*)-**181** in 50% yield and 80:20 er (entry 1). Lithiation and transmetallation under the same conditions, followed by coupling with *o*-bromobenzotrifluoride gave (*R*)-**183** in 76% yield and 80:20 er (entry 2). Finally, coupling with methyl 2-bromobenzoate gave ester (*R*)-**184** in 50% yield and 81:19 er (entry 3).

As expected, use of these lithiation conditions did not yield aryl pyrrolidines (*R*)-**181**, (*R*)-**183** and (*R*)-**184** in as high enantioselectivity as using (+)-sparteine surrogate **6**. It was therefore decided to repeat the (–)-sparteine **3**-mediated catalytic lithiation-arylations using our optimised two-ligand catalysis conditions (table 3.5). Lithiation of *N*-Boc pyrrolidine **38** with 1.6 equivalents of *s*-BuLi, 0.3 equivalents of (–)-sparteine **3** and 1.3 equivalents of di-*i*-Pr bispidine **7** followed by transmetallation and palladium-catalysed coupling with *o*-bromoanisole gave (*R*)-**181** in 92% yield and 89:11 er (entry 1). Coupling with *o*-bromobenzotrifluoride gave aryl pyrrolidine (*R*)-**183** in 88% yield and 80:20 er (entry 2). In this case, the enantioselectivity of the reaction did not improve with our optimal lithiation conditions, despite repeated attempts. The reason for this is unknown. Finally, lithiation-transmetallation-coupling with methyl 2-bromobenzoate gave ester (*R*)-**184** in 71% yield and 89:11 er (entry 3). Thus, two-ligand catalytic lithiation-arylation using both (–)-sparteine **3** and (+)-sparteine surrogate **6** has now been demonstrated.

Table 3.5



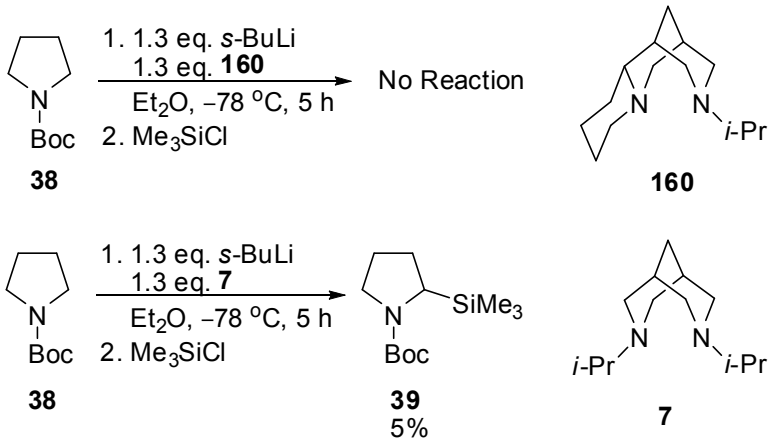
Entry	Aryl Bromide	Product	%Yield[a]	er[a]
1	*o*-bromoanisole	(*R*)-**181**	92	89:11
2	*o*-bromobenzotrifluoride	(*R*)-**183**	88	80:20
3	methyl 2-bromobenzoate	(*R*)-**184**	71	89:11

[a] % Yield after chromatography, er determined by CSP-HPLC

3.5 *In Situ* Infra-Red Spectroscopic Insights into Lithiation in the Presence of Hindered Ligands

It was believed in the group that high enantioselectivity in catalytic two-ligand lithiations was facilitated due to a lack of lithiation of *N*-Boc pyrrolidine **38** by the *s*-BuLi/di-*i*-Pr bispidine **7** complex. Previously, in collaboration with Wiberg and Bailey DFT calculations were used to show that *i*-PrLi/*N*-*i*-Pr ligand **160** would lithiate *N*-Boc pyrrolidine **38** if a prelithiation complex was formed. In fact, attempted lithiation with *s*-BuLi/**160** gave no product.[123] Similarly, attempted lithiation of *N*-Boc pyrrolidine **38** with *s*-BuLi/bispidine **7** gave trapped product **39** in only 5% yield (scheme 3.18).[5]

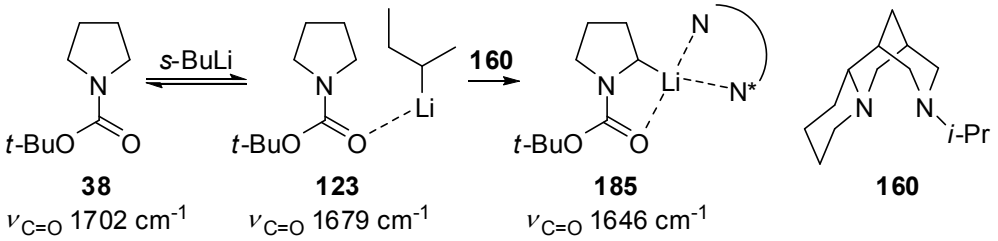
Scheme 3.18

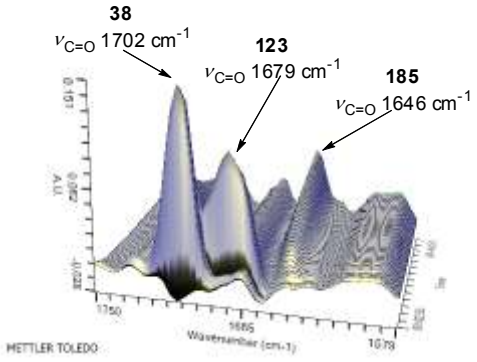


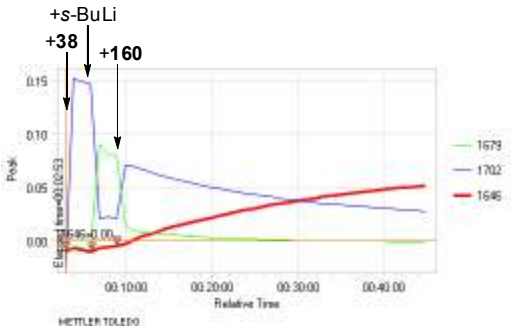
We planned to use *in situ* infra-red spectroscopic monitoring to show that the complexes *s*-BuLi/**160** and *s*-BuLi/**7** would not form a prelithiation complex in attempted lithiations of *N*-Boc pyrrolidine **38**. We also wondered whether formation of a prelithiation complex between *s*-BuLi and *N*-Boc pyrrolidine **38** followed by addition of **160** or **7** would lead to lithiation.

First, the use of *N*-*i*-Pr surrogate **160** for the *s*-BuLi-mediated lithiation of *N*-Boc pyrrolidine **38** was investigated, *via* formation of a prelithiation complex. Thus, *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1702 cm^{-1}) was stirred in diethyl ether at –78 °C and then *s*-BuLi was added. A new peak appeared, which was assigned to prelithiation complex **123** ($\nu_{C=O}$ 1679 cm^{-1}). Then, *N*-*i*-Pr surrogate **160** was added and another peak appeared, assigned to lithiated product **185** ($\nu_{C=O}$ 1646 cm^{-1}) (scheme 3.19).

Scheme 3.19



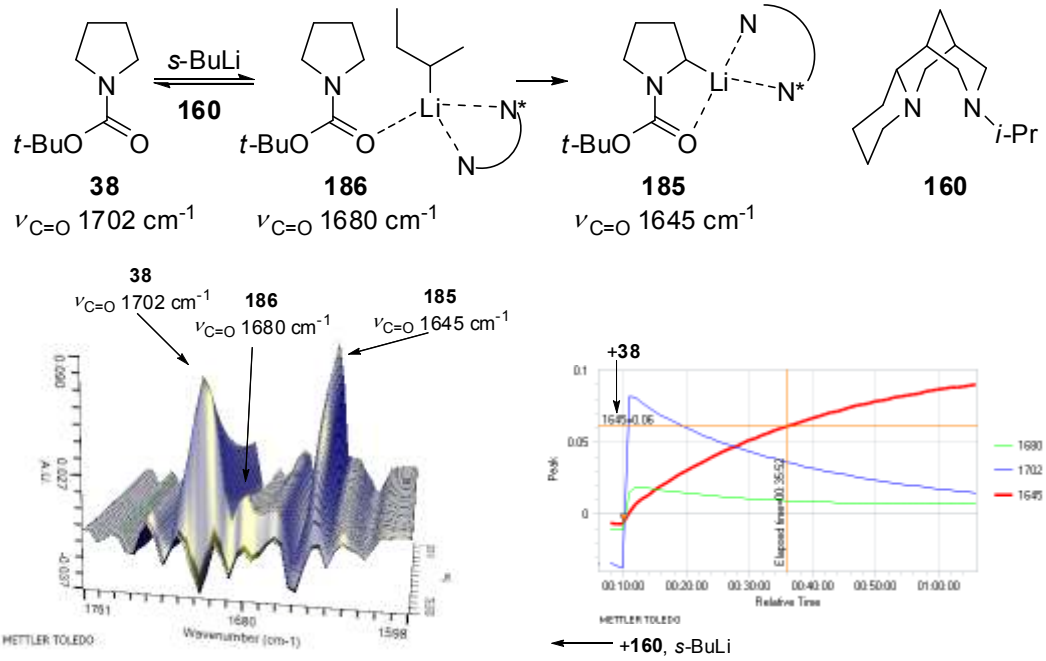




To our surprise, after addition of *N*-*i*-Pr surrogate **160**, a significant amount of lithiation of *N*-Boc pyrrolidine **38** took place. We note that after addition of the hindered diamine **160**, some of the prelithiation complex dissociated to free *N*-Boc pyrrolidine **38** and *s*-BuLi. The lithiation was slow and, after 40 min reaction time, incomplete lithiation was observed. In contrast, lithiation with *s*-BuLi/(–)-sparteine **3** has been shown to be complete in 20 min (see scheme 2.11).

Next, the lithiation of *N*-Boc pyrrolidine **38** by *s*-BuLi/*N*-*i*-Pr surrogate **160** was studied under typical experimental conditions. Thus, *N*-*i*-Pr surrogate **160** and *s*-BuLi were stirred in diethyl ether at –78 °C and *N*-Boc pyrrolidine **38** was added. Peaks corresponding to *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1702 cm^{-1}) and prelithiation complex **186** ($\nu_{C=O}$ 1680 cm^{-1}) were immediately observed. Then, slow evolution of a new peak ($\nu_{C=O}$ 1645 cm^{-1}) was noted. This peak was assigned to lithiated product **185** (scheme 3.20).

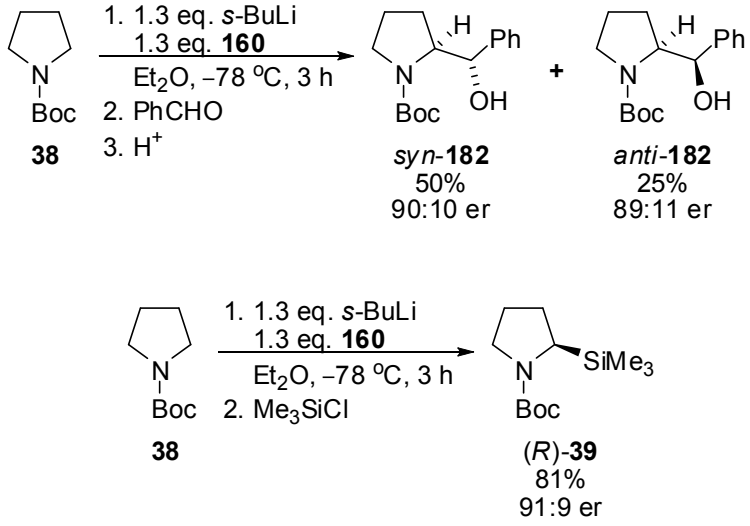
Scheme 3.20



In contrast to the previously published results from our group,[123] lithiation of *N*-Boc pyrrolidine **38** by *s*-BuLi/*N*-*i*-Pr surrogate **160** does proceed. The rate of lithiation is slow, with incomplete lithiation observed after 50 min reaction time.

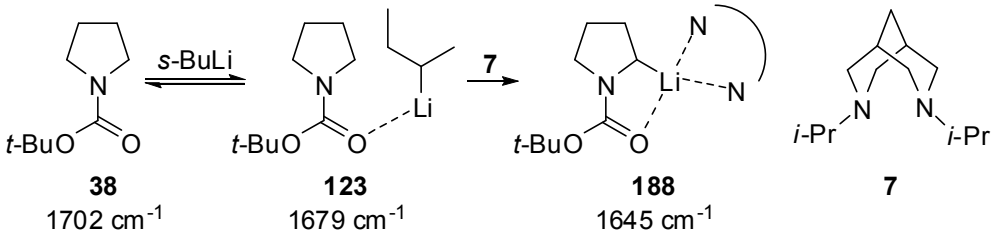
Based on this unexpected ReactIR result, two synthetic experiments were investigated with *N*-*i*-Pr surrogate **160**. It was found that lithiation of *N*-Boc pyrrolidine **38** with 1.3 equivalents of *s*-BuLi and 1.3 equivalents of *N*-*i*-Pr surrogate **160** at –78 °C in Et_2O for 3 h followed by trapping with benzaldehyde gave alcohol *syn*-**182** in 50% yield and 90:10 er and alcohol *anti*-**182** in 25% and 89:11 er. Similarly, lithiation under the same conditions and trapping with trimethylsilyl chloride led to silyl pyrrolidine (*R*)-**39** in 81% yield and 91:9 er (scheme 3.21). These results are fully consistent with the ReactIR experiments.

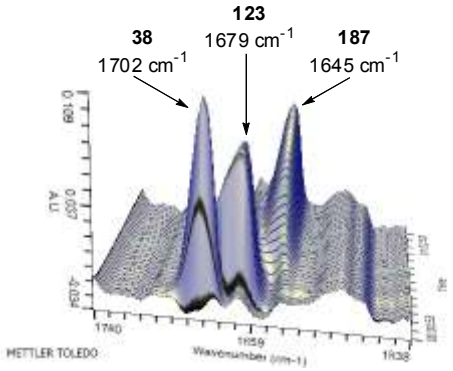
Scheme 3.21

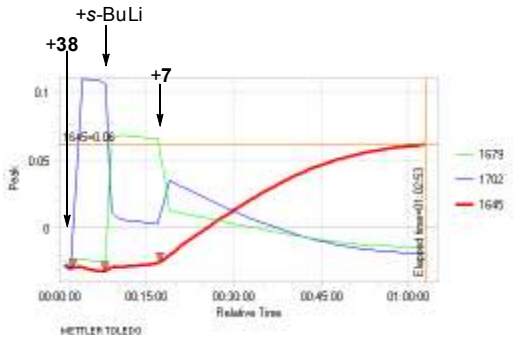


Having shown that the complex of *s*-BuLi/*N*-*i*-Pr surrogate **160** does effect lithiation of *N*-Boc pyrrolidine **38** we next investigated that use of di-*i*-Pr bispidine **7**, by first forming a prelithiation complex. Thus, *N*-Boc pyrrolidine **38** (1702 cm^{-1}) was stirred in diethyl ether at –78 °C and then *s*-BuLi was added. A new peak emerged, which was assigned to prelithiation complex **123** (1679 cm^{-1}). Then, di-*i*-Pr bispidine **7** was added and a new peak appeared, assigned to lithiated product **187** (1645 cm^{-1}) (scheme 3.22)

Scheme 3.22



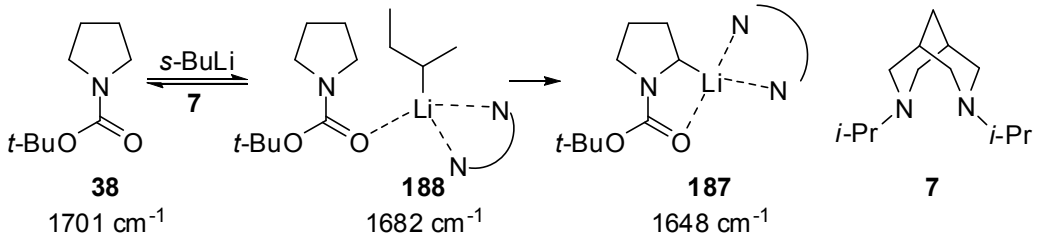


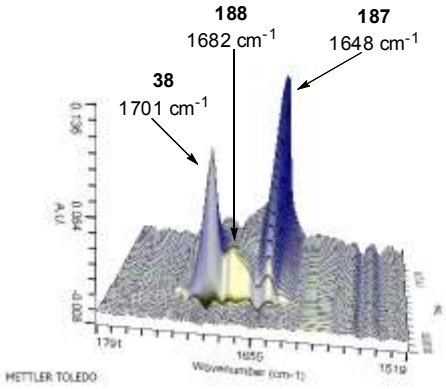


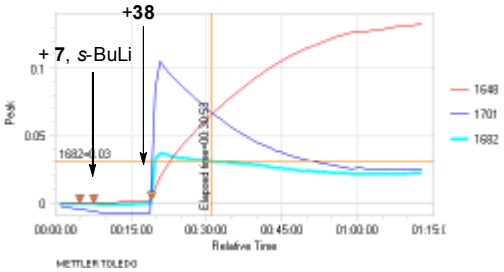
After addition of di-*i*-Pr bispidine **7**, some of prelithiation complex **123** dissociated to free *N*-Boc pyrrolidine **38** and *s*-BuLi. Then, lithiation proceeded slowly, but in this case complete formation of lithiated product **187** was observed after 45 min.

Finally, we investigated the lithiation of *N*-Boc pyrrolidine **38** by *s*-BuLi/bispidine **7** under experimental conditions. Thus, *s*-BuLi and di-*i*-Pr bispidine **7** were stirred in diethyl ether at –78 °C. Then *N*-Boc pyrrolidine **38** was added, and peaks corresponding to *N*-Boc pyrrolidine **38** (1701 cm^{-1}) and prelithiation complex **188** (1682 cm^{-1}) were observed. A new peak then slowly emerged and was assigned to lithiated product **187** (1648 cm^{-1}) (scheme 3.23).

Scheme 3.23



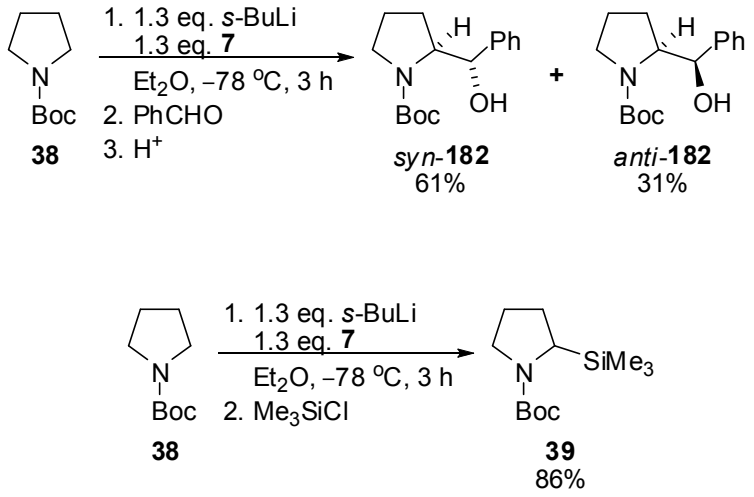




Thus, the *s*-BuLi/di-*i*-Pr bispidine **7** complex does indeed effect the lithiation of *N*-Boc pyrrolidine **38** and complete lithiation was observed after 1 h. The previously published result that *s*-BuLi/di-*i*-Pr bispidine **7**-mediated lithiation only proceeds very slowly is in error. This was confirmed by two synthetic experiments.

Lithiation of *N*-Boc pyrrolidine **38** with 1.3 equivalents of *s*-BuLi and 1.3 equivalents of di-*i*-Pr bispidine **7** at –78 °C in Et_2O for 3 h followed by trapping with benzaldehyde gave alcohol *syn*-**182** in 61% yield and alcohol *anti*-**182** in 31% yield. Lithiation under the same conditions and trapping with trimethylsilyl chloride gave silyl pyrrolidine *rac*-**39** in 86% yield (scheme 3. 24).

Scheme 3.24



The success of two-ligand catalysis with di-*i*-Pr bispidine **7** must be due to different rates of lithiation. Lower enantioselectivities compared with lithiations using a stoichiometric amount of chiral diamine are observed due to competing lithiation mediated by the *s*-BuLi/**7** complex. This observation highlights the usefulness of *in situ* infra-red spectroscopic monitoring of lithiations in determining reaction pathways.

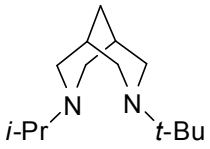
3.6 Conclusions and Future Work

Conditions for two-ligand catalytic lithiation of *N*-Boc pyrrolidine **38** using *s*-BuLi, (–)-sparteine **3** and di-*i*-Pr bispidine **7** have been optimised, and a small range of new bispidine ligands **156-159** were investigated in this reaction. It was found that none of the new ligands showed improved yields or enantioselectivity over the use of **7**. It was also shown that two-ligand lithiation with (+)-sparteine surrogate **6** gave higher enantioselectivity than (–)-sparteine **3**, while cyclohexane diamine (*R*,*R*)-**8** gave poorer enantioselectivity.

(–)-Sparteine **3**-mediated two-ligand catalytic lithiation-arylation of *N*-Boc pyrrolidine **38** has also been demonstrated under two different catalytic lithiation conditions. The best yields and enantioselectivities were obtained using the optimised lithiation conditions. An example of two-ligand lithiation-arylation with (+)-sparteine surrogate **6** was also carried out.

Finally, using ReactIR experiments, it was shown that the *s*-BuLi complexes of both di-*i*-Pr bispidine **7** and *N*-*i*-Pr surrogate **160** do in fact promote the lithiation of *N*-Boc pyrrolidine **38**, in contrast to previously published results from our group. It is possible that a more sterically hindered ligand such as *N*-*i*-Pr-*N*′-*t*-Bu bispidine **189** would promote lithiation of *N*-Boc pyrrolidine **38** to a lesser degree than **7** (figure 3.8). If this is the case, it is possible that the use of **189** in two-ligand catalytic lithiations would allow us to access products in higher er, or allow for the use of lower loadings of chiral diamine. This could form the basis of a future study.

Figure 3.8

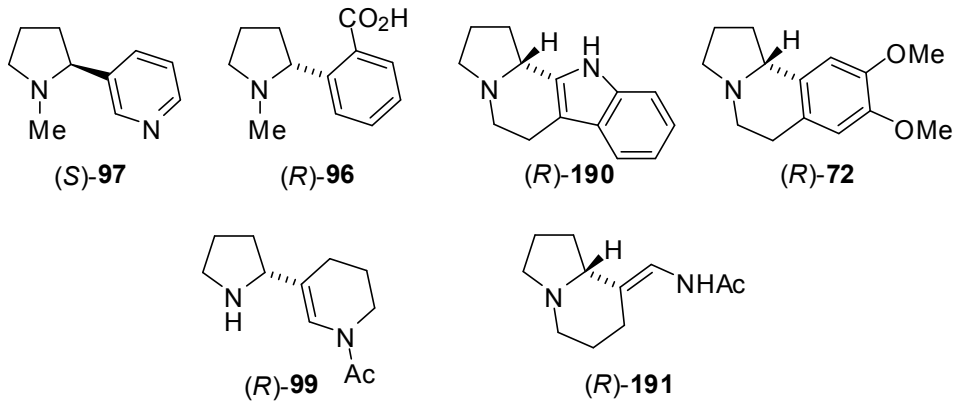


189

Chapter 4: Application of Lithiation-Negishi Coupling to the Total Synthesis of Natural Products and Drug Molecules

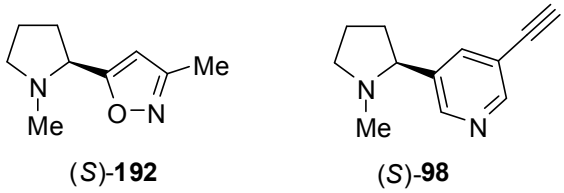
This chapter details the use of Campos' lithiation-arylation of *N*-Boc pyrrolidine **38** in total synthesis. A wide range of 2-aryl and 2-vinyl pyrrolidine natural products and drug molecules have previously been reported. 2-Aryl pyrrolidine natural products include (*S*)-nicotine (*S*)-**97**,[135] (*R*)-dihydroshihunine (*R*)-**96**,[136] (*R*)-harmicine (*R*)-**190**[137] and (*R*)-crispine A (*R*)-**72**.[81] 2-Vinyl pyrrolidine natural products have also been isolated; (*R*)-Maackiamine (*R*)-**99**[138] and (*R*)-tenuamine (*R*)-**191**[139, 140] are two such compounds (figure 4.1).

Figure 4.1



The biological activity of natural products frequently inspires the development of analogous drug molecules. For example, the activity of (*S*)-nicotine (*S*)-**97** has led to the investigation of ABT418 (*S*)-**192**[141-144] and SIB1508Y (*S*)-**98**[145] for the treatment of a range of CNS diseases (figure 4.2).

Figure 4.2

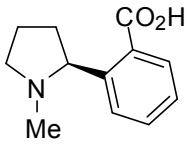


The primary aim of the results presented in this chapter was to exemplify the lithiation-arylation of *N*-Boc pyrrolidine **38** by completing a number of total syntheses. The natural products (*S*)-nicotine (*S*)-**97** and (*R*)-dihydroshihunine (*R*)-**96** were selected as targets, as was the drug molecule SIB1508Y (*S*)-**98**. Additionally, it was hypothesised that the reported lithiation-arylation procedure could be modified to effect vinylation of *N*-Boc pyrrolidine **38** and complete a total synthesis of (*R*)-maackiamine (*R*)-**99**. Our efforts on the synthesis of these four target molecules are presented in this chapter.

4.1 Dihydroshihunine

(*S*)-Dihydroshihunine (*S*)-**96** is an amino acid natural product first reported in 1982 by Kawanishi, and isolated from the Ayahuasca vine, *B. cappi* (figure 4.3).[146] Isolation of (*S*)-**96** has also been reported from *B. tenuiflora*.[147] (*R*)-dihydroshihunine has also been reported from *R. chiliantha* in 2001 by Kouno.[136]

Figure 4.3

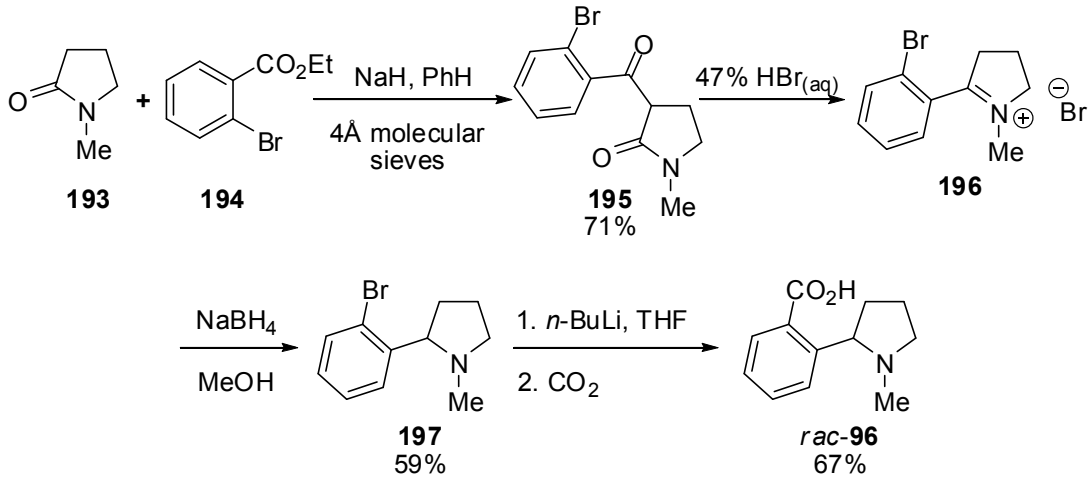


(*S*)-**96**

4.1.1 Previous Total Synthesis of Dihydroshihunine

A total synthesis of *rac*-dihydroshihunine *rac*-**96** carried out by Leete and co-workers is the only previous synthesis of which we are aware (scheme 4.1).[148] It is worth noting that this work was carried out en route to another natural product, shihunine, and was completed before dihydroshihunine had been reported from natural sources.

Scheme 4.1



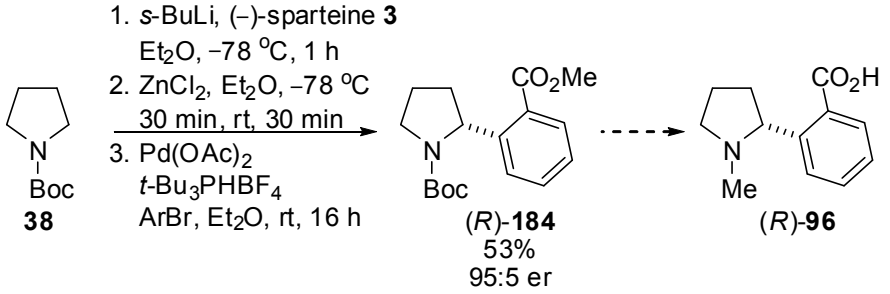
Starting from *N*-methylpyrrolidone **193**, treatment with sodium hydride and aryl ester **294** gave pyrrolidone ketone **195** in 71% yield. Then, refluxing **195** with HBr led to a decarboxylative rearrangement, affording pyrrolinium salt **196**. Subsequent reduction with sodium borohydride in one pot gave aryl pyrrolidine **197** in 59% yield. Finally,

lithium-bromine exchange with *n*-BuLi, followed by trapping with CO_2 gave *rac*-dihydroshihunine *rac*-**96** in 67% yield (scheme 4.1).[148]

4.1.2 Attempted Synthesis of (*R*)-Dihydroshihunine *via* Lithiation-Arylation of *N*-Boc Pyrrolidine

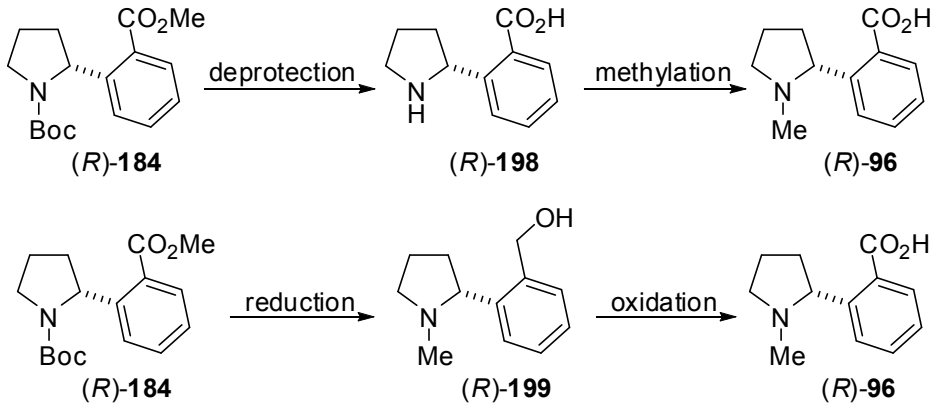
As there are no asymmetric syntheses of dihydroshihunine, we selected it as a suitable target molecule. It was proposed that the first step towards (*R*)-dihydroshihunine (*R*)-**96** would be a lithiation-arylation of *N*-Boc pyrrolidine **38**. Thus, **38** was treated with *s*-BuLi and a stoichiometric amount of (–)-sparteine **3**. Transmetallation was then effected using zinc chloride, and coupling of methyl 2-bromobenzoate was carried out using palladium(II) acetate and *t*-Bu_3PHBF_4. Aryl pyrrolidine (*R*)-**184** was obtained in 53% yield and 95:5 er (scheme 4.2).

Scheme 4.2



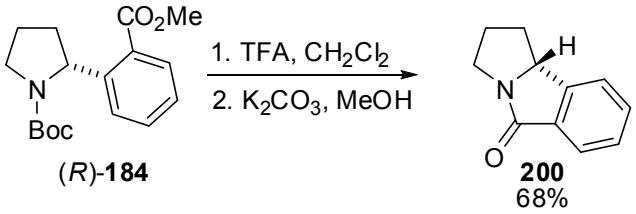
With aryl pyrrolidine (*R*)-**184** in hand, two different routes to the natural product were proposed. In the first route, global deprotection would provide amino acid (*R*)-**198**, which would then be methylated to give (*R*)-dihydroshihunine (*R*)-**96**. Alternatively, global hydride reduction would give *N*-methyl amino alcohol (*R*)-**199**, and then reoxidation would allow access to (*R*)-dihydroshihunine (*R*)-**96** (scheme 4.3).

Scheme 4.3



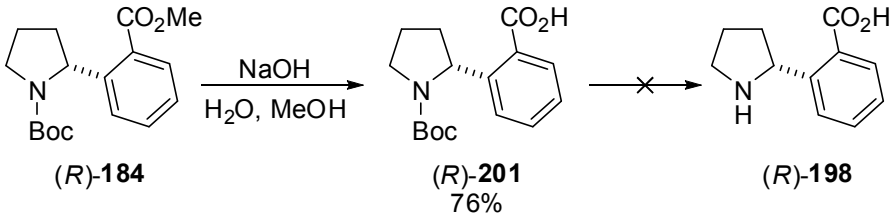
Removal of the Boc protecting group of (*R*)-**184** using TFA was successful but also led to cyclisation and formation of lactam **200**. To prove this reactivity, we optimised the synthesis of lactam **200**, using TFA-mediated Boc deprotection followed by treatment with K_2CO_3 to induce cyclisation. This gave lactam **200** in 68% yield (scheme 4.4).

Scheme 4.4



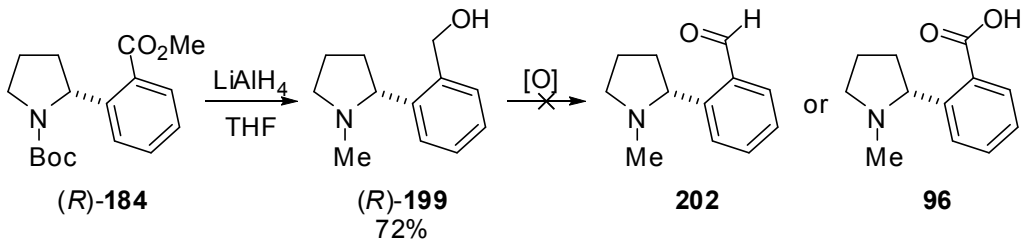
In order to prevent cyclisation following Boc deprotection, ester (*R*)-**184** was hydrolysed in 76% yield using sodium hydroxide to give acid (*R*)-**201** without the need for purification after work-up (scheme 4.5). Unfortunately, following treatment of (*R*)-**201** with TFA, it was not possible to isolate product (*R*)-**198** or starting material (*R*)-**201**. One pot deprotection-methylation to give dihydroshihunine (*R*)-**96** also met with failure.

Scheme 4.5



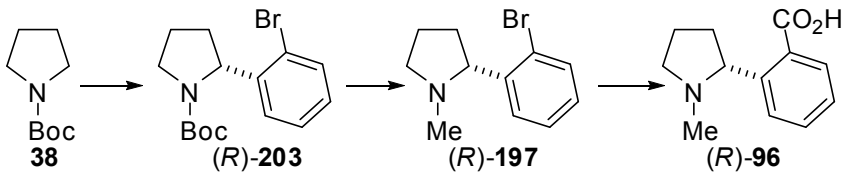
Hence, the other route to dihydroshihunine was investigated, namely global reduction then re-oxidation. Treatment of Negishi product (*R*)-**184** with $LiAlH_4$ gave amino alcohol (*R*)-**199** in 72% yield (scheme 4.6). However, we were then unable to effect oxidation to either the corresponding aldehyde **202** or acid **96** under any conditions. Oxidation was attempted using manganese dioxide in dichloromethane at room temperature and in 1,4-dioxane at reflux, pyridinium chlorochromate in dichloromethane at room temperature, pyridinium dichromate in dimethylformamide at room temperature and Swern oxidation conditions. In each case, neither the desired product nor starting material was recoverable.

Scheme 4.6



Unfortunately, neither of the proposed synthetic routes to (*R*)-dihydroshihunine (*R*)-**96** was successful in completing the synthesis. A possible alternative route that could have been investigated is shown in scheme 4.7. This would proceed *via* lithiation-arylation of *N*-Boc pyrrolidine **38** with 1,2-dibromobenzene to give aryl pyrrolidine (*R*)-**203**. Boc deprotection and then methylation would give (*R*)-**197** which is an intermediate in Leete's synthesis of *rac*-dihydroshihunine *rac*-**96**. This would then constitute a formal synthesis of (*R*)-dihydroshihunine (*R*)-**96** (scheme 4.7).

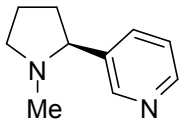
Scheme 4.7



4.2 Nicotine

(*S*)-Nicotine (*S*)-**97** is a natural product primarily associated with the tobacco plants *N. rustica* and *N. tabacum* (figure 4.4). The alkaloid can also be found in vegetables of the nightshade family *Solanaceae*, including tomato, potato, aubergine and bell peppers.[149]

Figure 4.4



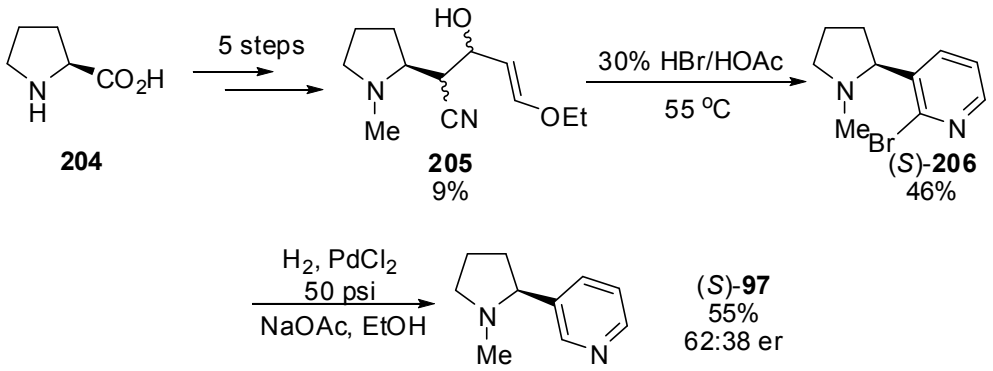
(*S*)-**97**

Interest in nicotine **97** by chemists stretches back over 150 years. The pure alkaloid was first isolated from tobacco in 1828, and the correct structure was proposed in 1893 by Pinner.[135, 150] Pictet reported the first racemic synthesis in 1904[151] and the first asymmetric synthesis was published by Chavdarian in 1982.[152] Initial chemical interest in nicotine **97** was driven by continuing widespread recreational use of tobacco products. However, nicotine **97** has also historically been used as an insecticide – as much as 2800 tons were used per year as crop protectant.[135] In recent years, further interest in nicotine **97** and its analogues has been created by the revelation that nicotine **97** is potentially active in the treatment of a wide range of CNS diseases.[135] The synthesis of nicotine **97** and the more common natural product and drug molecule analogues has been recently reviewed.[135]

4.2.1 Selected Previous Syntheses of (*S*)-Nicotine

A common theme running through previous syntheses of nicotine **97**, and indeed many 2-aryl pyrrolidines, is the need to start a synthesis with one ring system intact, and build up the other ring through two or more synthetic steps. An example is the first asymmetric synthesis of (*S*)-nicotine (*S*)-**97** reported by Chavdarian, wherein the synthesis started from L-proline and the pyridine ring was then built up (scheme 4.8).[152, 153]

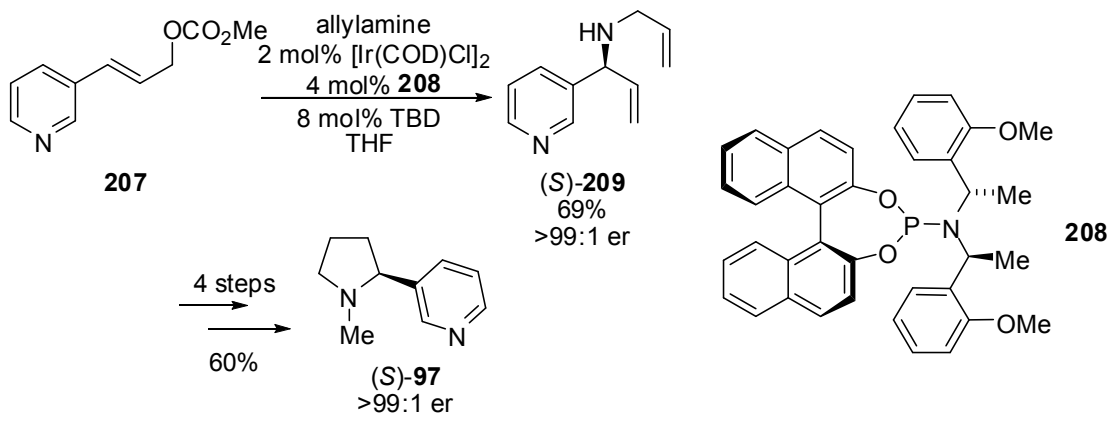
Scheme 4.8



Starting from L-proline **204**, installation of the *N*-methyl group and the pyridine ring atoms was achieved in 9% yield over 5 steps to give **205**. As the two new stereocentres in **205** would be lost in subsequent steps, the mixture of product diastereomers was used as obtained. Cyclisation was then accomplished using a route pioneered by Bryson, treating **205** with HBr in acetic acid to give (*S*)-bromonicotine (*S*)-**206** in 46% yield.[154] Finally, high pressure hydrogenation using a palladium(II) chloride catalyst removed the bromine to give (*S*)-nicotine (*S*)-**97** in 55% yield and 62:38 er (4% overall yield from L-proline). It was believed that the loss of er came during the cyclisation step, although epimerisation could also have occurred when forming **205**.[152]

In contrast to Chavdarian's synthesis is the approach reported in 2005 by Helmchen.[155] Beginning with a pyridine starting material **207**, stereochemistry was installed in the first step using an allylic amination. Using ligand **208**, first developed by Alexakis, Helmchen reported optimising this amination using an iridium/**208** catalyst which afforded product (*R*)-**209** in high yields and >99:1 er (scheme 4.9).[155, 156]

Scheme 4.9

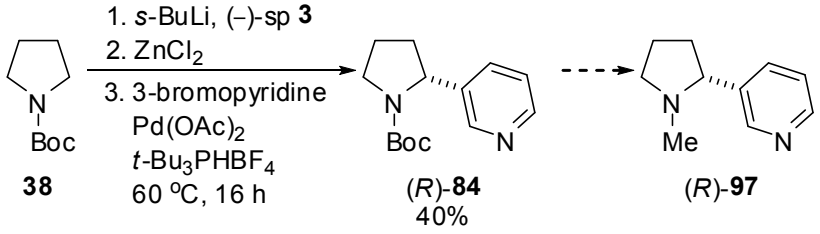


Following amination, (*S*)-nicotine (*S*)-**97** was formed in 60% yield over 4 steps. Thus, (*S*)-nicotine (*S*)-**97** was synthesised in >99:1 er in 5 steps with an overall yield of 42%.

4.2.2 Synthesis of (*S*)-Nicotine *via* Two-Ligand Catalytic Lithiation-Arylation of *N*-Boc Pyrrolidine

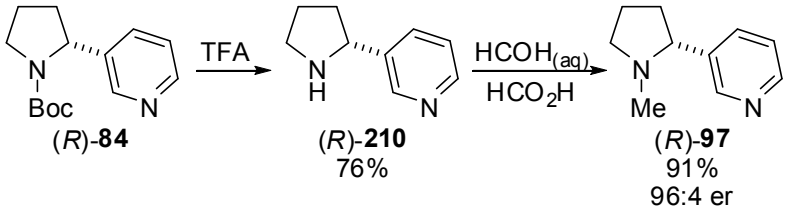
It was proposed that lithiation-arylation of *N*-Boc pyrrolidine **38** with 3-bromopyridine would provide a convenient starting point for our new synthesis of (*S*)-nicotine (*S*)-**97**. Due to ease of use and availability, the synthetic route was first optimised using (–)-sparteine **3**, which would eventually lead to unnatural (*R*)-**97**. Thus, using the conditions reported by Campos,[89] (*R*)-pyridyl pyrrolidine (*R*)-**84** was obtained in 40% yield (scheme 4.10). Determination of the er of (*R*)-**84** by CSP-HPLC did not prove possible, but we were later able to determine the er of (*R*)-nicotine (*R*)-**97** by ^{1}H NMR spectroscopy in the presence of a chiral shift reagent.

Scheme 4.10



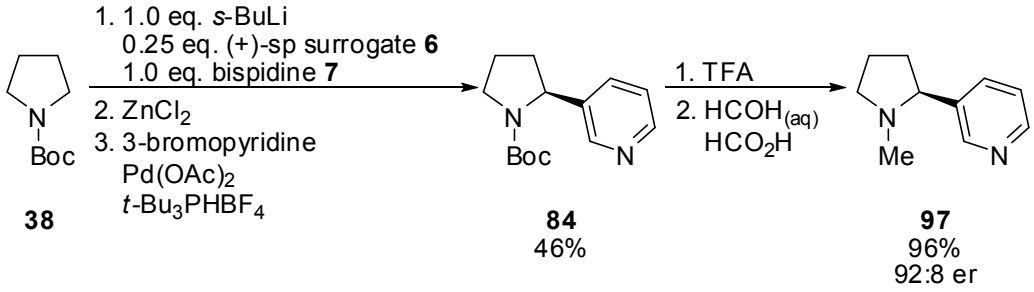
We had hoped that $LiAlH_4$ reduction of (*R*)-**84** would convert the *N*-Boc group to a *N*-Me group and thus complete the synthesis of (*R*)-nicotine (*R*)-**97**. Unfortunately, using this approach traces of an inseparable impurity remained in the resulting sample of (*R*)-nicotine (*R*)-**97**. It was then found that TFA-mediated Boc deprotection to give (*R*)-nornicotine (*R*)-**210** and then Eschweiler-Clarke methylation to give (*R*)-nicotine (*R*)-**97** both proceeded in high yields (76% and 91% respectively) (scheme 4.11). Furthermore, purification was not required after either step. The er of the sample of (*R*)-nicotine (*R*)-**97** was then determined using chiral shift ^{1}H NMR spectroscopy in the presence of Pirkle's alcohol. The er found (96:4) is that expected from the lithiation-arylation protocol, indicating that no epimerisation took place during the deprotection-methylation steps.

Scheme 4.11



With a facile synthesis of (*R*)-nicotine (*R*)-**97** in hand, we were able to turn our attention to the naturally occurring enantiomer, (*S*)-nicotine (*S*)-**97**. Thus, two-ligand catalytic lithiation of *N*-Boc pyrrolidine **38** mediated by *s*-BuLi, 0.25 equivalents of (+)-sparteine surrogate **6** and 1.0 equivalent of di-*i*-Pr bispidine **7**, followed by transmetallation with zinc chloride and finally Negishi coupling with 3-bromopyridine gave (*S*)-pyridyl pyrrolidine (*S*)-**84** in 46% yield. Deprotection-methylation then gave (*S*)-nicotine (*S*)-**97** in 96% yield and 92:8 er (scheme 4.12). In this case, we did not isolate (*S*)-nornicotine (*S*)-**210** after Boc deprotection. The er was determined by chiral shift ^{1}H NMR spectroscopy in the presence of Pirkle's alcohol.

Scheme 4.12

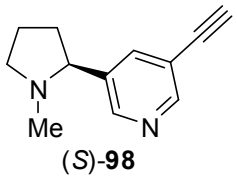


To the best of our knowledge this is the shortest and most efficient synthesis of (*S*)-nicotine (*S*)-**97** to date. It is also the first synthesis in which both rings and the stereochemistry are installed in a single synthetic step. Finally, our synthesis represents a synthetic protocol in which the two rings are joined directly, rather than requiring a ring closing step.

4.3 SIB1508Y

SIB1508Y (*S*)-**98** (Altinicline) is a nicotine analogue first reported by a group at SIBIA led by Cosford (figure 4.5).[145] Like (*S*)-nicotine (*S*)-**97**, it acts as a nicotinic acetylcholine receptor (NAChR) agonist, but displays a greater selectivity between receptor subtypes.[145]

Figure 4.5

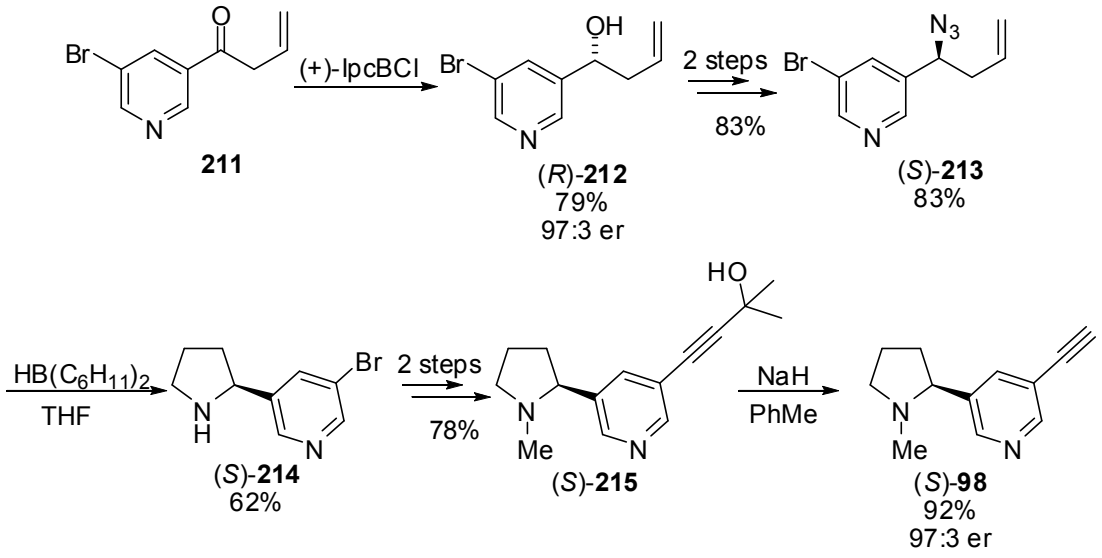


(*S*)-**98**

4.4.1 Selected Previous Syntheses of SIB1508Y

The first asymmetric synthesis of SIB1508Y (*S*)-**98** was reported by Lebreton in 2001 (scheme 4.13).[157] Ketone **211** was first formed in 61% over 3 steps from bromonicotinic acid. Then, reduction to alcohol (*R*)-**212** in 79% yield and 97:3 er using (+)-Ipc_2BCl installed the stereocentre. Quantitative mesylation then allowed nucleophilic displacement by sodium azide to give azide (*S*)-**213** in 83% yield, setting the system up for cyclisation.

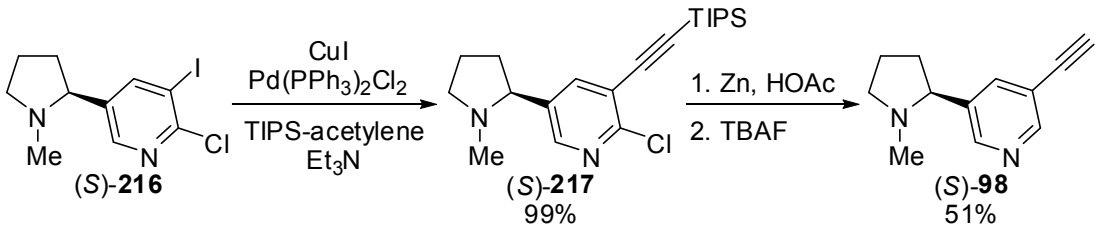
Scheme 4.13



Formation of the pyrrolidine ring was achieved by a dicyclohexyl borane-mediated hydroboration-cyclisation to give bromo nornicotine (*S*)-**214** in 62% yield. Then, methylation and installation of the alkyne motif was accomplished in 78% over two steps to give (*S*)-**215**. Deprotection using sodium hydride provided SIB1508Y (*S*)-**98** in 92% yield and 97:3 er (10 steps and 18% overall yield).[157]

In contrast to Lebreton's synthesis of SIB1508Y (*S*)-**98**, Comins has published two total syntheses of the drug molecule starting from (*S*)-nicotine (*S*)-**97**.[158, 159] The optimal synthesis afforded enantiopure SIB1508Y (*S*)-**98** in 5 steps and 32% overall yield.[159] Dihalo nicotine analogue (*S*)-**216** has previously been prepared from natural (*S*)-nicotine (*S*)-**97** in two steps.[160] Sonogashira coupling with tri-*i*-Pr-silyl acetylene installed the alkyne motif, giving (*S*)-**217** in almost quantitative (99%) yield. Removal of chlorine using zinc metal in acetic acid, and silyl deprotection using TBAF was achieved in 51% yield (scheme 4.14).[159]

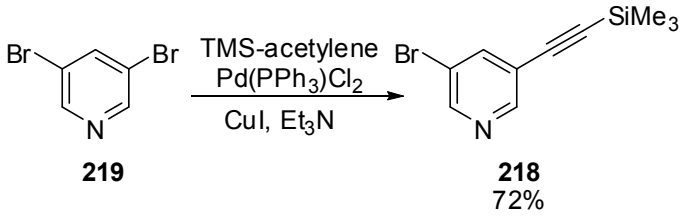
Scheme 4.14



4.3.2 Synthesis of SIB1508Y *via* Lithiation-Arylation of *N*-Boc Pyrrolidine

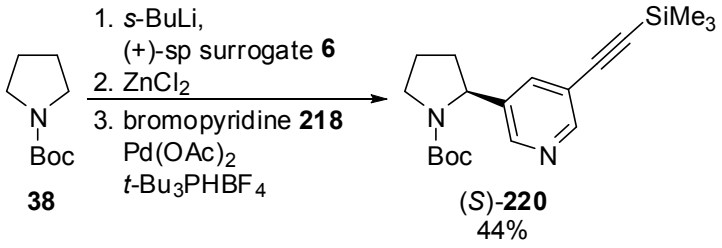
With a synthesis of (*S*)-nicotine (*S*)-**97** in hand, we decided to attempt a synthesis of the nicotine analogue SIB1508Y (*S*)-**98**. In this case, the relevant bromopyridine **218** was not commercially available and so it was synthesised in 72% yield *via* a Sonogashira coupling of 3,5-dibromopyridine **219** and trimethylsilyl acetylene, as reported by Fujita (scheme 4.15).[161]

Scheme 4.15



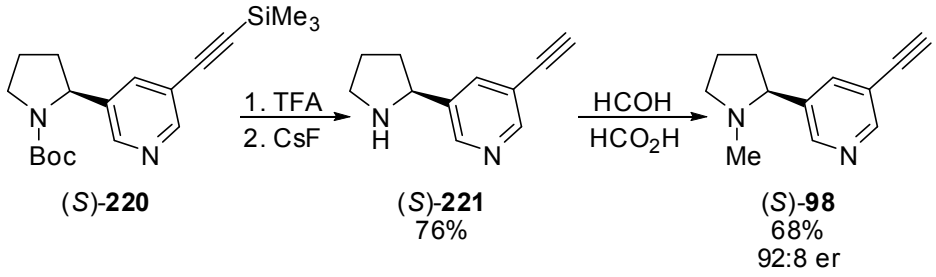
A stoichiometric lithiation of *N*-Boc pyrrolidine **38** mediated by *s*-BuLi/(+)-sparteine surrogate **6** was used to complete the synthesis. Thus, lithiation-arylation of *N*-Boc pyrrolidine **38** with alkynyl bromopyridine **218** gave (*S*)-aryl pyrrolidine (*S*)-**220** in 44% yield (scheme 4.16). Determination of the er of (*S*)-**220** by CSP-HPLC did not prove possible, but we were later able to determine the er of SIB1508Y (*S*)-**98** using ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Pirkle's alcohol.

Scheme 4.16



It was found that reduction of the Boc group with $LiAlH_4$ led to degradation of the alkyne bond – neither the expected product nor starting material were recovered. Fortunately, Boc deprotection with TFA and then removal of the trimethylsilyl group with caesium fluoride could be accomplished in one pot, giving deprotected product (*S*)-**221** in 76% yield. Eschweiler-Clarke methylation then installed the *N*-methyl group, completing the synthesis in 68% yield (scheme 4.17).

Scheme 4.17

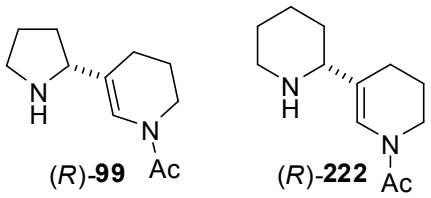


The er of the final sample of SIB1508Y (*S*)-**98** was determined as 92:8 by ^{1}H NMR spectroscopy in the presence of Pirkle's alcohol. This is the shortest (4 steps) synthesis of SIB1508Y (*S*)-**98** to date.[159]

4.4 Maackiamine

Maackiamine **99** is an alkaloid natural product isolated from the flower of the Amur Maackia tree, *M. amurensis*.[138] Although the deciduous Amur Maackia is occasionally used in central Asian folk medicine, maackiamine (*R*)-**99** has not to our knowledge been tested for biological activity – presumably due to unavailability. We are unaware of any previous asymmetric synthesis of maackiamine (*R*)-**99**. Djerassi reported a *racemic* procedure for the synthesis of maackiamine (*R*)-**99** (referred to as 'norammodendrine'), while carrying out mass spectrometry studies on ammodendrine (*R*)-**222**, before maackiamine (*R*)-**99** had been isolated from natural sources (figure 4.6).[162]

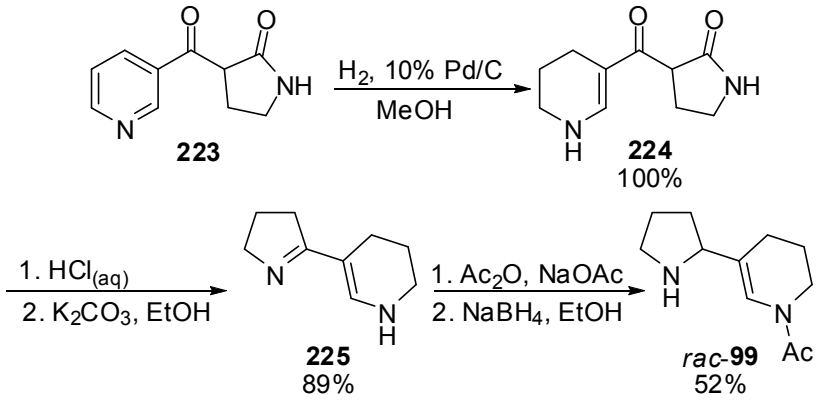
Figure 4.6



4.4.1 Previous Synthesis of *rac*-Maackiamine

Djerassi's synthesis began with a palladium-catalysed hydrogenation of nicotinoyl pyrrolidone **223** to give tetrahydropyridine **224** in quantitative yield. An acid-catalysed rearrangement then installed the two ring systems in the correct positions in 89% yield. Finally, acetylation-reduction of imine salt **225** was carried out in one pot to give *rac*-maackiamine *rac*-**99** in 52% yield (scheme 4.18).[162]

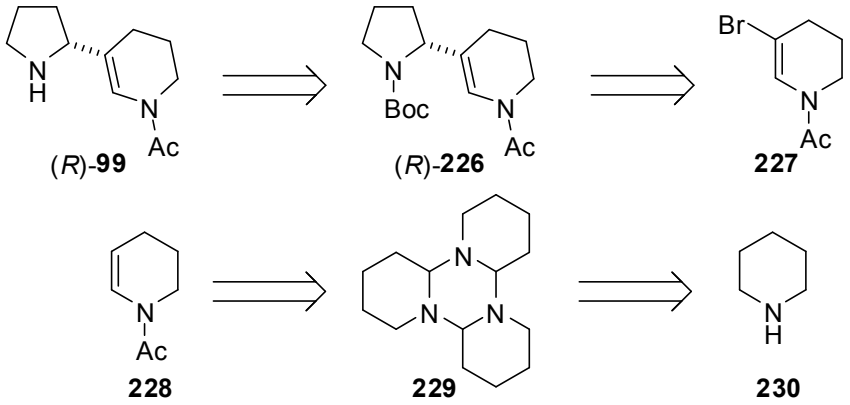
Scheme 4.18



4.4.2 Synthesis of (*R*)-Maackiamine *via* Lithiation-Vinylation of *N*-Boc Pyrrolidine

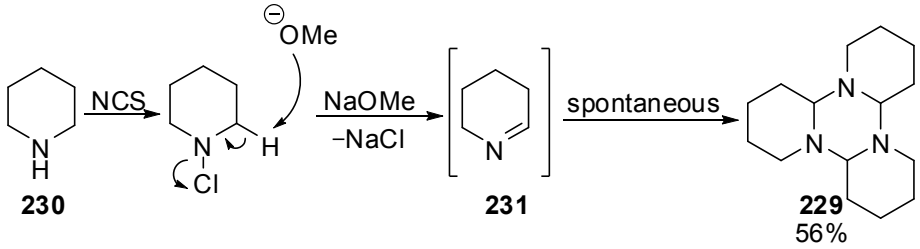
Our retrosynthetic analysis of (*R*)-maackiamine (*R*)-**99** is shown in scheme 4.19. (*R*)-Maackiamine (*R*)-**99** would be derived, by Boc deprotection, from (*R*)-**226**, itself formed from the lithiation-vinylation of *N*-Boc pyrrolidine **38**. We proposed that the relevant vinyl bromide **227** could be formed *via* bromination of enamide **228**. Enamide **228** could be formed by acetylation of the known trimer **229**, obtained from piperidine **230**. At the time this work was carried out, lithiation-vinylation of *N*-Boc pyrrolidine **38** *via* Negishi coupling had not been reported. Since then, Gawley has reported the lithiation-vinylation of *N*-Boc piperidine **44**.[100]

Scheme 4.19



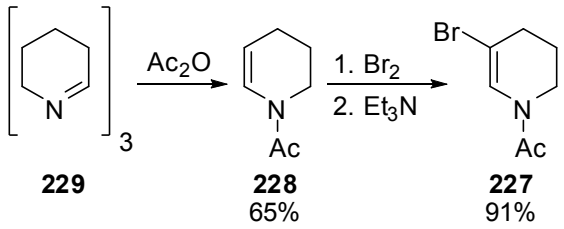
Starting from piperidine **230**, *N*-chlorination using *N*-chloro succinimide followed by base-mediated elimination using sodium methoxide gave imine **231**, which spontaneously trimerised to give **229** in 56% yield. The synthesis of trimer **229** had previously been reported by Poupon,[163] and also by de Kimpe[164] (*N*-chlorination using ClO*t*-Bu) (scheme 4.20).

Scheme 4.20



Trimer **229** was then acetylated in 65% yield by heating in acetic anhydride to give enamide **228**. Next, enamide **228** was brominated in 91% yield using a bromination procedure developed by Shipman for an analogous enamide (scheme 4.21).[165] During bromination, care had to be taken to achieve optimal yields – when adding bromine dropwise, a colour change from pale yellow to dark orange was observed. Addition of further bromine after this colour change resulted in a reduced yield of vinyl bromide **227**.

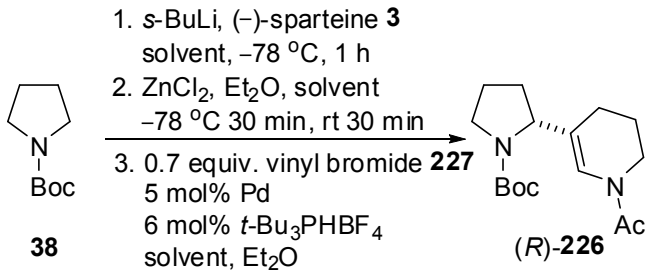
Scheme 4.21



229 **228** 65% **227** 91%

Initial results for the lithiation-vinylation of *N*-Boc pyrrolidine **38** indicated that a more detailed optimisation was required. Therefore, we decided to investigate a small range of different lithiation-transmetallation-coupling conditions. The palladium source used (palladium(II) acetate *vs.* Pd_2dba_3) was altered, as was the solvent (diethyl ether *vs. t*-butyl methyl ether). The time allowed for coupling, and the coupling temperature were also optimised (table 4.1).

Table 4.1



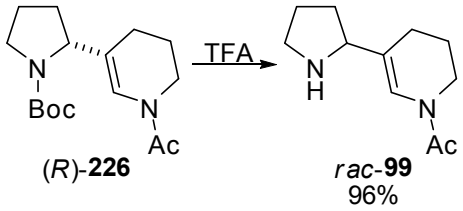
Entry	Solvent	Pd Source	Coupling Time	Coupling Temp	% Yield[a] (er)[a]
1	Et_2O	$Pd(OAc)_2$	16 h	rt	29 (94:6)
2	TBME	$Pd(OAc)_2$	16 h	rt	37 (80:20)
3	TBME	$Pd(OAc)_2$	16 h	reflux	43 (93:7)
4	TBME	Pd_2dba_3	16 h	rt	40 (92:8)
5	TBME	Pd_2dba_3	72 h	rt	56 (95:5)

[a] % Yield after chromatography, er determined by CSP-HPLC

Using Campos' conditions, lithiation of *N*-Boc pyrrolidine **38** with *s*-BuLi/(–)-sparteine **3** in diethyl ether, followed by transmetallation with zinc chloride and then coupling of vinyl bromide **227** with palladium(II) acetate at rt for 16 h gave (*R*)-*N*-Boc maackiamine (*R*)-**226** in 29% yield and 94:6 er (entry 1). Using the same conditions but exchanging diethyl ether for *t*-butyl methyl ether led to an increase in yield to 37%, but a reduction in er (80:20 *vs.* 94:6) (entry 2). Lithiation-vinylation of *N*-Boc pyrrolidine **38** in *t*-butyl methyl ether and then coupling vinyl bromide **227** with palladium(II) acetate at reflux for 16 h gave (*R*)-*N*-Boc maackiamine (*R*)-**226** in 43% yield and 93:7 er (entry 3). We then investigated the use of Pd_2dba_3 as the palladium source. Thus, lithiation of *N*-Boc pyrrolidine **38** in *t*-butyl methyl ether, transmetallation with zinc chloride and then coupling of vinyl bromide **227** with Pd_2dba_3 at rt for 16 h gave (*R*)-**226** in 40% yield and 92:8 er (entry 4). Using identical conditions, but extending the coupling time to 72 h gave (*R*)-*N*-Boc maackiamine (*R*)-**226** in 56% yield and 95:5 er (entry 5). It was decided that these conditions were adequate for the completion of the synthesis.

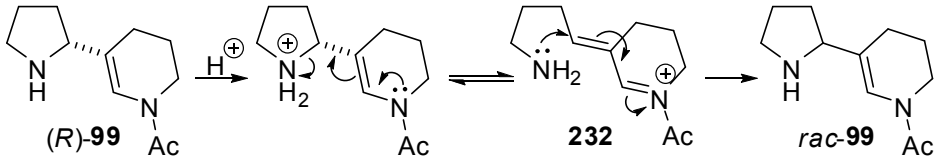
To complete the synthesis of the natural product, removal the *N*-Boc group to give the free secondary amine was necessary. Unfortunately, it was found that treatment of (*R*)-*N*-Boc maackiamine (*R*)-**226** with TFA gave a 96% yield of *racemic* maackiamine *rac*-**99** (scheme 4.22).

Scheme 4.22



We propose that the mechanism for this racemisation is that shown in scheme 4.23. Protonation of the new secondary amine and then ring opening would occur to give planar iminium **232**. Recyclisation on work-up will then lead to *rac*-maackiamine *rac*-**99**.

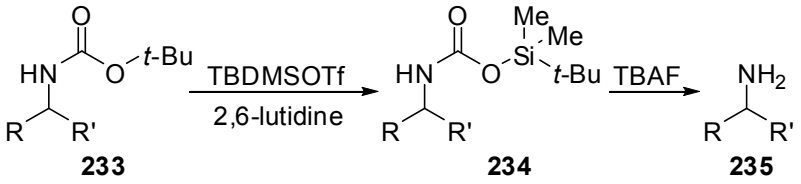
Scheme 4.23



An attempted deprotection using the Lewis acid $BF_3 \cdot OEt_2$ also led to racemisation and *rac*-maackiamine *rac*-**99** was obtained in 53% yield. Qu recently published a non-acidic Boc deprotection method using refluxing neutral H_2O.[166] Several examples of the deprotection of *N*-Boc secondary amines were described. We attempted to access (*R*)-maackiamine (*R*)-**99** under these conditions, but were unable to isolate maackiamine **99** or recover *N*-Boc maackiamine **226**.

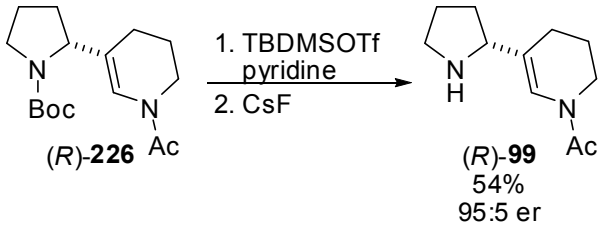
Ohfune has previously reported a two-step acid-free silylation-desilylation Boc deprotection methodology.[167, 168] One example presented by Ohfune was the deprotection of an *N*-Boc proline methyl ester. Thus, we hypothesised that this method might be of use in the deprotection of (*R*)-*N*-Boc maackiamine (*R*)-**99**. The first step of Ohfune's protocol involves treatment of an *N*-Boc amine **233** with 2,6-lutidine and a trialkylsilyl triflate. The resulting silylcarbamate **234** is then treated with TBAF. Fluoride abstraction of the trialkylsilyl group followed by loss of CO_2 leaves the deprotected amine **235** (scheme 4.24).

Scheme 4.24



In our hands, Ohfune's methodology provided a sample of maackiamine contaminated with several difficult-to-remove impurities: residual lutidine, TBAF and silyl-containing compounds. We were able to avoid some of these contaminants by slightly modifying the reaction conditions. Thus, 2,6-lutidine was replaced with pyridine, which could be removed after reaction by evaporation under high vacuum. Similarly, TBAF was replaced with caesium fluoride which could be removed by a basic aqueous wash. The residual silyl-containing compounds proved difficult to remove, but were eventually separated from the product using preperative TLC. Thus, (*R*)-maackiamine (*R*)-**99** was obtained in 54% yield (scheme 4.25).

Scheme 4.25



The sample of (*R*)-maackiamine (*R*)-**99** was shown to be 95:5 er by chiral shift ^{1}H NMR in the presence of Pirkle's alcohol. The modest (54%) yield does not reflect a lack of reactivity to deprotection on the part of *N*-Boc maackiamine **226**, but rather the difficulty of purification of the final product. To conclude, we have completed the first asymmetric synthesis of (*R*)-maackiamine (*R*)-**99**, accessing (*R*)-**99** of 95:5 er in 10% yield over 5 steps from piperidine **230**.

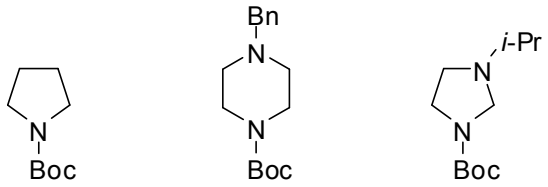
It is worth noting that although our sample was shown to be 95:5 er by ^{1}H NMR spectroscopy in the presence of a chiral shift reagent, the optical rotation ($[\alpha]_D$ +12.8 (*c* 1.0 in EtOH)) is almost an order of magnitude lower than that reported for the natural product ($[\alpha]_D$ +110 (*c* 0.01 in EtOH)). [138] The reason for this discrepancy is unknown.

To conclude, lithiation-arylation of *N*-Boc pyrrolidine has been used to complete total syntheses of (*S*)-nicotine (*S*)-**97** and SIB1508Y (*S*)-**98**. Unfortunately, we were unable to complete the synthesis of (*R*)-dihydroshihunine (*R*)-**96**. Finally, Campos' lithiation-arylation procedure was modified to allow lithiation-vinylation, and the first asymmetric synthesis of the natural product (*R*)-maackiamine (*R*)-**99** was completed.

Chapter 5: Diamine-Free Lithiation of Nitrogen Heterocycles

This chapter details the development of a new diamine-free protocol for racemic α-lithiation of *N*-Boc nitrogen heterocycles. Following optimisation of the new lithiation conditions, both lithiation-trapping and lithiation-arylation of *N*-Boc pyrrolidine **38** are reported. Then, expansion of the new methodology to effect diamine-free racemic α-lithiations of other *N*-Boc heterocycles is explored, notably on *N*-Boc-*N*′-benzyl piperazine **59** and *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (figure 5.1).

Figure 5.1

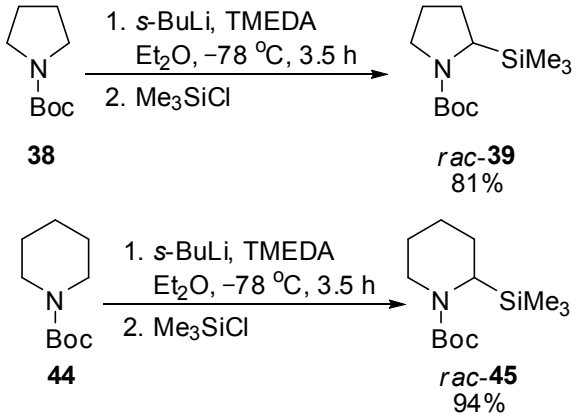


In addition to synthetic experiments, *in situ* infra-red spectroscopic monitoring of diamine-free lithiations of a range of carbamates was carried out. Issues of solvent stability to *s*-BuLi at different temperatures are also addressed.

5.1 Previous Racemic Lithiations of Carbamates

Historically, racemic lithiation-trapping of *N*-Boc nitrogen heterocycles has been carried out as reported by Beak in 1989.[29] Treatment with *s*-BuLi and TMEDA in diethyl ether at –78 °C for 3.5 h followed by electrophilic quench afforded racemic 2-substituted heterocycles in high yields. For example, lithiation of *N*-Boc pyrrolidine **38** using this protocol followed by trapping with trimethylsilyl chloride gave silyl pyrrolidine *rac*-**39** in 81% yield, while *N*-Boc piperidine **44** gave silyl piperidine *rac*-**45** in 94% yield under the same conditions (scheme 5.1).[29]

Scheme 5.1



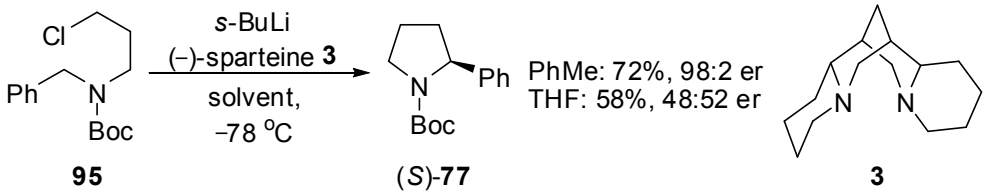
These conditions have been adopted for a range of applications in recent years.[70, 119, 169-173] Examples include Feringa's 2008 synthesis of (+)-myrtine[169] and Stoltz's synthesis of the alkaloid (–)-lobeline.[170] Indeed, TMEDA has become widely used by organometallic chemists to increase the reactivity of organolithium reagents.[2] However, the efficiency of TMEDA as a ligand for lithium was questioned as early as 1992 by Collum.[174] For example, addition of THF to a solution of the LDA/TMEDA complex caused complete dissociation of TMEDA from the organolithium.[175] Additionally, THF outcompetes TMEDA for complexation to LiHMDS.[176]

5.1.1 Displacement of Diamines from Alkyllithiums by THF

While sufficient for the research chemist, the low reaction temperature and use of TMEDA make Beak's methodology inconvenient for use on a large scale. A re-evaluation of previous literature led us to propose that a simpler racemic lithiation protocol could be developed. Specifically, it was noticed that *s*-BuLi/(–)-sparteine-

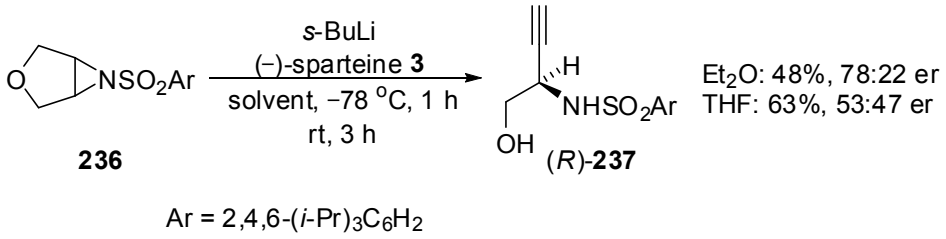
mediated asymmetric lithiations gave high enantioselectivity when carried out in non-coordinating solvents, but near racemic products when attempted in THF.[106, 177-182] This effect was first noted by Hoppe.[177] For example, Beak showed that lithiation of *N*-Boc benzylamine **95** using *s*-BuLi/(–)-sparteine **3** in toluene followed by internal electrophilic trapping to effect cyclisation gave 2-phenyl pyrrolidine (*S*)-**77** in 72% yield and 98:2 er. In contrast, lithiation using *s*-BuLi/(–)-sparteine gave (*S*)-**77** in 58% yield and 48:52 er when carried out in THF (scheme 5.2).[106]

Scheme 5.2



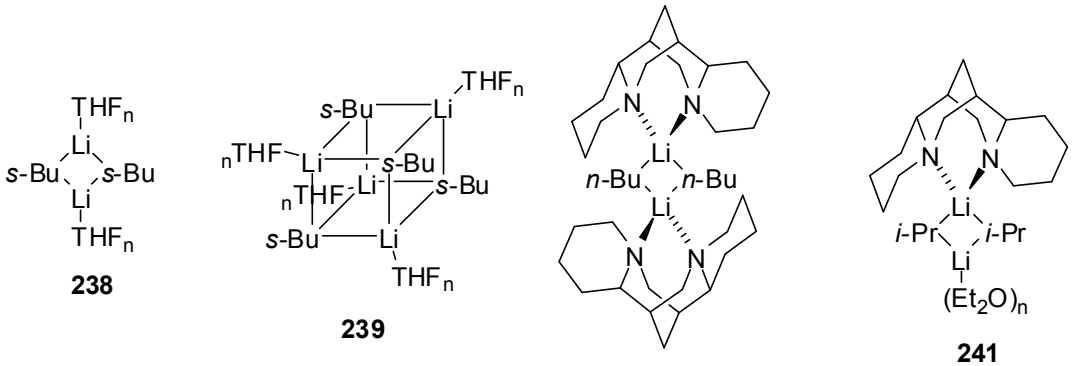
Our group presented another example of poor enantioselectivity when using *s*-BuLi/(–)-sparteine **3** in THF. Thus, treatment of aziridine **236** with *s*-BuLi and (–)-sparteine **3** in diethyl ether gave alkynyl sulfonamide (*R*)-**237** in 48% yield and 78:22 er. Alternatively, the same conditions in THF gave (*R*)-**237** in 63% yield and 53:47 er (scheme 5.3).[182]

Scheme 5.3



It is known that the coordinating solvent THF can displace (–)-sparteine **3** from alkyllithiums in solution.[183, 184] Thus, we propose that when attempting a *s*-BuLi/(–)-sparteine-mediated lithiation in THF, the active lithiating species is in fact a *s*-BuLi/THF complex such as dimer **238** or tetramer **239**. In the less strongly coordinating solvent diethyl ether, the diamine remains associated with alkyllithium. The active species in this case is presumably analogous to known dimers **240** and **241** (figure 5.2).[117, 185]

Figure 5.2



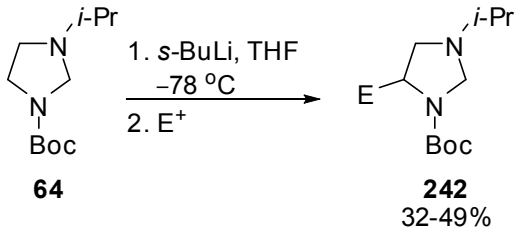
We therefore reasoned that a *s*-BuLi/THF complex was a sufficiently active lithiating agent for effecting diamine-free racemic lithiations. It was hoped that not only could such a diamine-free lithiation protocol be developed, but that the procedure could be optimised for use at temperatures more amenable for large-scale synthetic experiments.

Industrial chemists must expend their efforts not only in making large-scale syntheses economical, but also in reducing their environmental impact. Such concerns drive recent interest in "green" solvents. We hoped that a THF-mediated lithiation protocol could also be carried out using 2-Me THF. This alternative solvent is considered to be preferable to THF as it is not water-miscible, reducing contamination of the waste stream.[186] Additionally, 2-Me THF is ultimately derived from a renewable resource (2-furaldehyde from agricultural waste).[186] The use of 2-Me THF in organometallic reactions has recently been reviewed.[186]

5.1.2 Previous THF-Mediated Diamine-Free Racemic Lithiations

There have been several isolated reports of diamine-free lithiations of carbamates carried out in THF.[74, 75, 187, 188] For example, Orito reported lithiation of *N*-Boc pyrrolidine **38** using LDA in THF,[188] although it should be noted that we were unable to reproduce this result, despite several attempts. Coldham reported racemic lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** using *s*-BuLi in THF, obtaining substituted imidazolidines in modest yields (scheme 5.4).[74, 75]

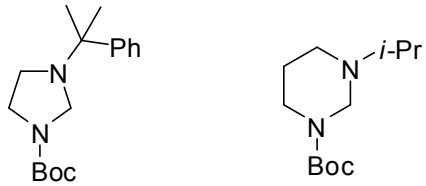
Scheme 5.4



64 **242**
32-49%

Lithiation of the analogous substrate **243** was also reported under the same conditions. It was found, however, that racemic lithiation of pyrimidine **244** required *s*-BuLi in THF with TMEDA as a co-solvent for optimal yields (figure 5.3).[75]

Figure 5.3

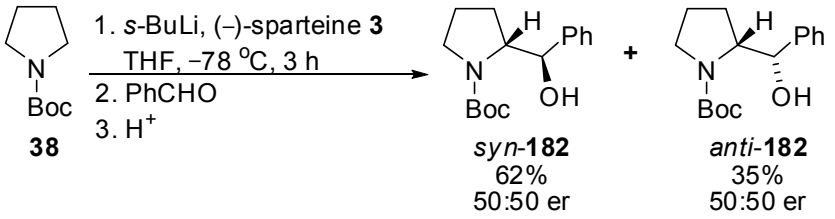


243 **244**

5.2 Diamine-Free Racemic Lithiation of *N*-Boc Pyrrolidine

First, we confirmed that *s*-BuLi/(–)-sparteine **3**-mediated lithiation of *N*-Boc pyrrolidine **38** in THF would give racemic products. Thus, **38** was lithiated using (–)-sparteine **3** and *s*-BuLi in THF at –78 °C and then benzaldehyde was added. Alcohol *syn*-**182** was obtained in 62% yield and 50:50 er, together with *anti*-**182** in 35% yield and 50:50 er (scheme 5.5). Hence, the *s*-BuLi/THF complex is presumably more reactive than any *s*-BuLi/(–)-sparteine **3** present in the solution. In collaboration with Hilmerson, our group has recently reported ^{6}Li NMR spectroscopic evidence that in THF, (–)-sparteine **3** does not coordinate to *i*-PrLi, when using 3 equivalents of diamine.[183]

Scheme 5.5

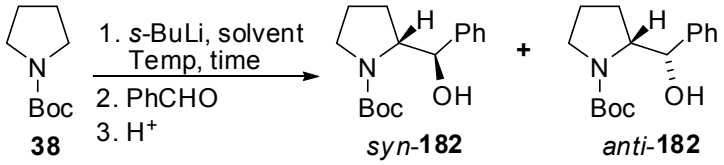


5.2.1 Diamine-Free Lithiation of *N*-Boc Pyrrolidine

To optimise the new diamine-free racemic lithiation conditions, *N*-Boc pyrrolidine **38** was treated with *s*-BuLi in THF, 2-Me THF or diethyl ether at a range of temperatures and reaction times. Due to ease of availability and efficient trapping, we selected benzaldehyde as the electrophile in these lithiations. In all cases, a roughly 75:25 mixture of *syn*:*anti* diastereomers of alcohols *syn*-**182** and *anti*-**182** were obtained. For clarity, the total combined yield of *syn*-**182** and *anti*-**182** is also shown (table 5.1).

Lithiation in diethyl ether at –78 °C for 60 min gave a low 8% yield of trapped products (entry 1) as the *s*-BuLi/Et_2O complex is not reactive enough to effect complete lithiation. In contrast, the same conditions in THF and 2-Me THF gave 89% yield and 92% yield respectively (entries 2 and 3).

Table 5.1



Entry	Solvent	Temp (°C)	Reaction Time (min)	%Yield *syn*-**182**[a]	%Yield *anti*-**182**[a]	%Yield Total[a]
1	Et_2O	–78	60	6	2	8
2	THF	–78	60	57	32	89
3	2-Me THF	–78	60	55	37	92
4	Et_2O	–40	60	18	8	26
5	THF	–40	60	43	21	64
6	2-Me THF	–40	60	57	37	94
7	Et_2O	–30	60	0	0	0
8	THF	–30	60	25	12	37
9	2-Me THF	–30	60	0	0	0
10	THF	–30	10	58	31	89
11	THF	–30	5	56	28	84
12	2-Me THF	–30	5	49	24	73
13	THF	–20	30	7	3	10
14	THF	–20	5	44	22	66
15	THF	–20	2	37	20	57
16	THF	–10	5	19	10	29
17	THF	–10	1	0	0	0
18	THF	0	30	0	0	0

a %Yield of *syn*-**182** and *anti*-**182** after chromatography

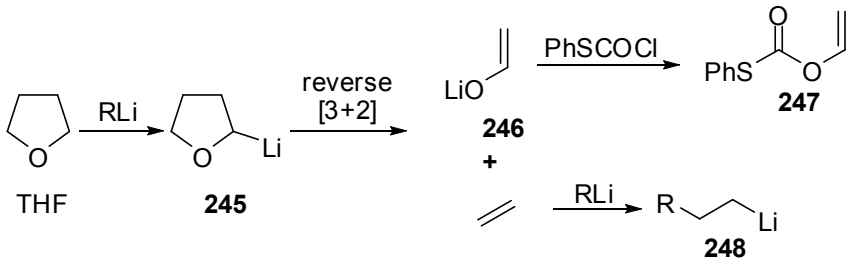
Next, lithiations at higher temperatures were investigated. Lithiation at –40 °C for 60 min gave 26% yield of trapped product when carried out in diethyl ether (entry 4), 64% yield in THF (entry 5) and 94% yield in 2-Me THF (entry 6). Then, the reaction temperature was further raised to –30 °C. Lithiation for 60 min gave no product in diethyl ether (entry 7) or 2-Me THF (entry 9) and only 37% yield in THF (entry 8). Disappointed by these low yielding lithiations, we next decided to investigate shorter lithiation times. Lithiation for 10 min in THF at –30 °C gave 89% combined yield of alcohols *syn*-**182**

and *anti*-**182** (entry 10), while a 5 min lithiation time in THF gave a total yield of 84% (entry 11). Use of 2-Me THF gave a slightly poorer result – 73% yield was obtained after 5 min (entry 12).

Lithiations at temperatures higher than –30 °C in THF gave at best modest yields. Treatment of *N*-Boc pyrrolidine **38** with *s*-BuLi in THF at –20 °C and then trapping with benzaldehyde gave 10% combined yield after a lithiation time of 30 min (entry 13), 66% yield after 5 min (entry 14) and 57% yield after 2 min (entry 15). Yields reduced even further with higher temperatures. Thus, lithiation at –10 °C for 5 min gave 29% yield of trapped products (entry 16), while no products were isolated after a 1 min reaction time at –10 °C (entry 17). As might be expected from these results, lithiation at 0 °C for 30 min also gave no products (entry 18). The conditions selected as our new optimised diamine-free racemic lithiation protocol were those shown in entry 11: treatment with *s*-BuLi in THF at –30 °C for 5 min and then electrophilic trapping.

We note that at temperatures higher than –30 °C, optimal yields could not be obtained from *s*-BuLi/THF-mediated lithiations (table 5.1, entries 13-18). It was likely that at these temperatures, low yields were obtained due to preferential lithiation of THF rather than substrate. The stability of *s*-BuLi in THF has not, to our knowledge, been reported. However, the breakdown of THF by other alkyllithiums has been studied by a number of groups, and has been shown to proceed by one of two routes. The most common is shown in scheme 5.6.[2]

Scheme 5.6

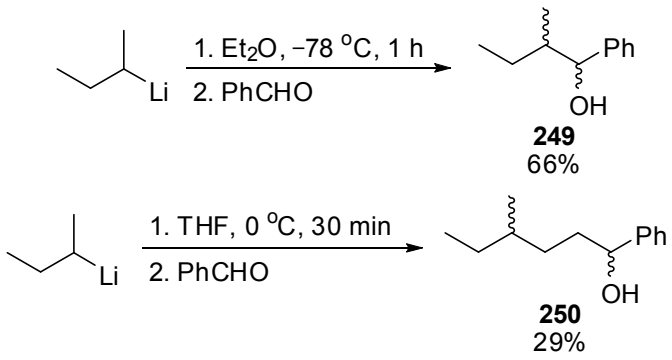


Lithiation of THF in the 2-position gives lithiated species **245**. This can then undergo a reverse [3+2]-cycloaddition to give lithium enolate **246** which can be trapped out with electrophiles.[189, 190] Cycloreversion also leads to the formation of ethene which upon carbolithiation with another equivalent of alkyllithium gives rise to homologated alkyllithiums such as **248**.[191-193] Following this solvent decomposition pathway one

molecule of solvent therefore consumes two equivalents of alkyllithium. An alternative pathway can lead to the formation of but-3-en-1-oxide *via* α-elimination from **245** or 3-lithiation of THF, but this has only been observed when using a very basic organolithium solution (*e.g. t*-BuLi/HMPA in THF).[194]

It was decided to attempt to confirm the breakdown of THF at high temperatures and thus explain the low yield we had obtained from diamine-free lithiations at > –30 °C. First, we attempted to trap *s*-BuLi with benzaldehyde under conditions which would not lead to solvent breakdown as a control reaction: *s*-BuLi was stirred in diethyl ether at –78 °C for 1 h and then the electrophile was added. Alcohol **249** was isolated in 66% yield (Scheme 5.7).

Scheme 5.7

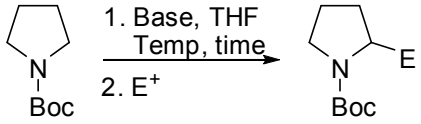


Then, *s*-BuLi was stirred in THF at 0 °C for 30 min and one equivalent of benzaldehyde was added to trap the organolithium species present. This yielded a 29% yield of alcohol **250**, derived from ethene-homologated *s*-BuLi (scheme 5.7). As two equivalents of *s*-BuLi are required to form the primary alkyllithium, *at least* 58% of the *s*-BuLi present has been consumed. It is possible that some gaseous ethene escaped the reaction solution, explaining the modest yield of **250**. We did not observe any evidence of trapped enolate **246** or trapped *s*-BuLi. We have thus determined that the cause of poor yields in diamine-free racemic lithiations at tempertures > –30 °C is breakdown of THF by *s*-BuLi.

We wondered whether diamine-free racemic lithiations of *N*-Boc pyrrolidine **38** in THF could be carried out using the bases *n*-BuLi or LDA instead of *s*-BuLi. Advantages of this would be that these bases are more stable in THF than *s*-BuLi, and are considered safer to use. A range of attempted reaction conditions is shown in table 5.2. In each case, no

product was formed – inspection of the ^{1}H NMR spectrum of the crude product revealed only unreacted starting material **38** and electrophile.

Table 5.2

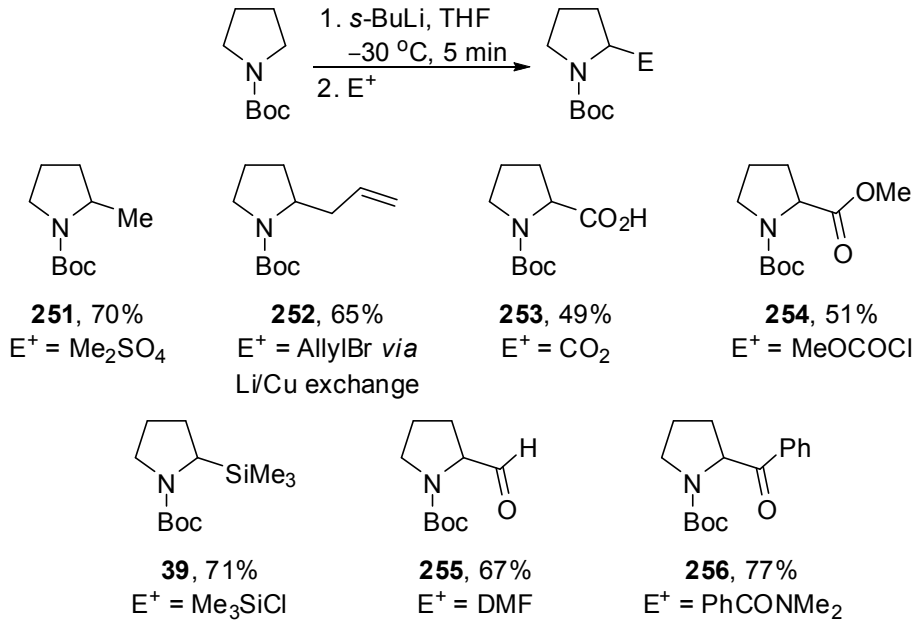


Entry	Base	Temp (°C)	Time (min)	Electrophile
1	*n*-BuLi	0	60	PhCHO
2	*n*-BuLi	rt	60	PhCHO
3	LDA	–78	60	PhCHO
4	LDA	–40	30	PhCHO
5	LDA	–20	30	PhCHO
6	LDA	0	60	PhCHO
7	LDA	0	180	PhCHO
8	LDA	rt	30	PhCHO
9	LDA	0	30	BnBr
10	LDA	rt	30	BnBr

First, lithiation using *n*-BuLi was attempted. Treatment of *N*-Boc pyrrolidine **38** with *n*-BuLi in THF for 60 min at either 0 °C or rt followed by attempted trapping with benzaldehyde gave no products (entries 1 and 2). Ortio has previously reported the lithiation of *N*-Boc pyrrolidine **38** using LDA in THF followed by trapping with benzyl bromide, but did not report the conditions used. In our hands, lithiation of **38** using LDA at –78 °C for 60 min, –40 °C for 30 min, –20 °C for 30 min, 0 °C for 60 min or 180 min or rt for 30 min followed by addition of PhCHO gave only recovered starting material and electrophile (entries 3-8). Attempted LDA-mediated lithiation of *N*-Boc pyrrolidine **38** for 30 min at either 0 °C or rt and then trapping with benzyl bromide also met with failure (entries 9 and 10).

With a set of optimised reaction conditions for diamine-free racemic lithiation of *N*-Boc pyrrolidine **38** in hand, a range of different electrophiles was assayed, giving 2-substituted pyrrolidines **39** and **251**-**256** (scheme 5.8).

Scheme 5.8

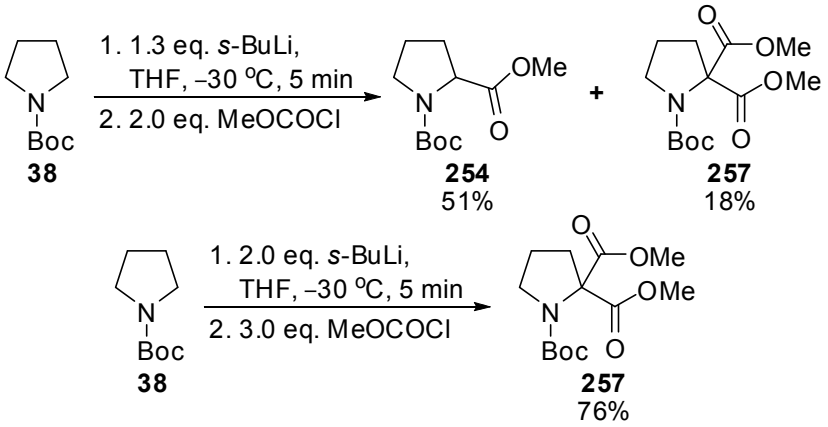


Trapping with dimethyl sulfate gave methyl pyrrolidine **251** in 70% yield. When trapping with allyl bromide, the lithiated pyrrolidine intermediate was first transmetallated to an organocuprate species using a CuCN/2LiCl complex, as it has previously been shown that this procedure gives higher yields of trapped *N*-heterocycles than a direct trap.[67] A lithium-zinc-copper double transmetallation procedure has since been shown to give even higher yields.[195] Allyl pyrrolidine **252** was obtained in 65% yield. Use of carbon dioxide as electrophile gave *N*-Boc proline **253** in 49% yield, while methyl chloroformate gave *N*-Boc methyl prolinate **254** in 51% yield. Silyl pyrrolidine **39** was accessed in 71% yield when trapping with trimethylsilyl chloride. Finally, two dimethyl amide electrophiles were used. DMF gave **255** in 67% yield, while dimethyl benzamide gave ketone **256** in 77% yield (scheme 5.8)

When trapping with methyl chloroformate, product **254** was obtained in only 51% yield. The disubstituted pyrrolidine **257** was also obtained (18% yield). This indicated that after trapping once, residual *s*-BuLi would preferentially deprotonate **254** to give the enolate which would then trap to give disubstituted product **257**, rather than undergoing nucleophilic attack on excess electrophile. Thus, we were able to optimise the synthesis of product **257**. Treatment of *N*-Boc pyrrolidine **38** with 2 equivalents of *s*-BuLi in THF at –78 °C for 1 h and then adding 3 equivalents of methyl chloroformate gave disubstituted pyrrolidine **257** in 76% yield (scheme 5.9). We note that Coldham had

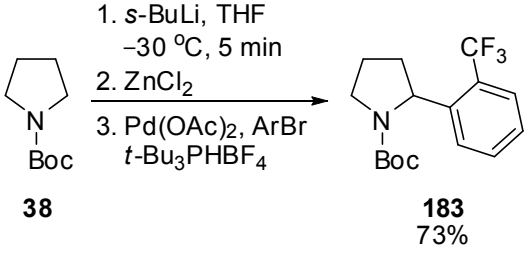
observed a similar disubstitution when trapping lithiated imidazolidine **64** with ethyl chloroformate.[74, 75]

Scheme 5.9



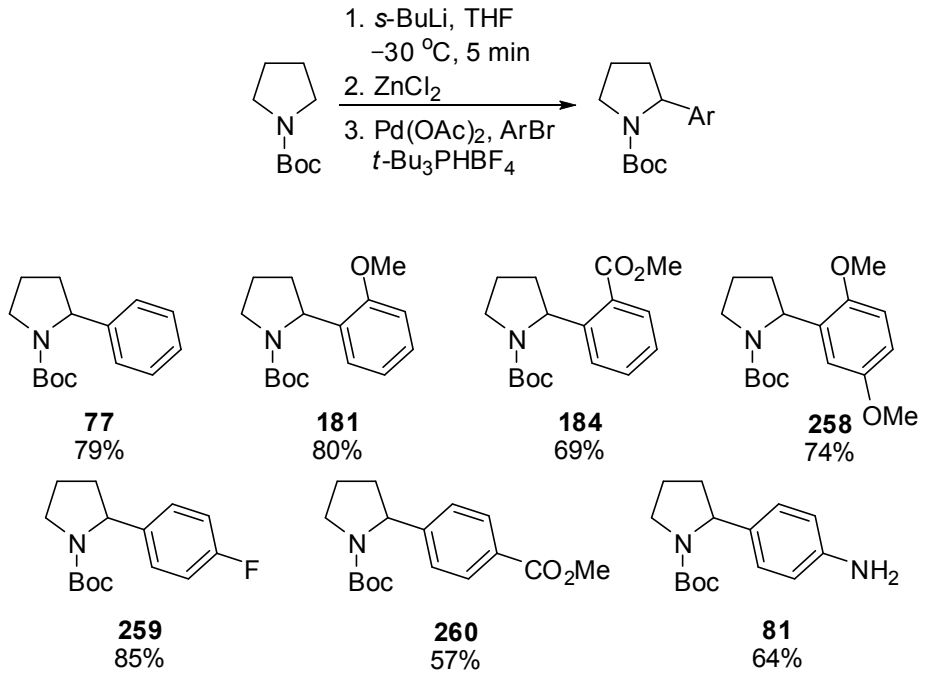
Although Campos had reported the *s*-BuLi/(–)-sparteine **3**-mediated enantioselective lithiation-arylation of *N*-Boc pyrrolidine **38**, *racemic* lithiation-arylation has not previously been reported. It was hoped that our new racemic lithiation procedure could be used to access such products. Gratifyingly, lithiation of *N*-Boc pyrrolidine **38** using our optimised conditions followed by transmetallation using zinc chloride and then palladium-catalysed Negishi coupling with 2-bromobenzotrifluoride gave aryl pyrrolidine **183** in 73% yield (scheme 5.10).

Scheme 5.10



Next, racemic lithiation-arylation was demonstrated with a range of different aryl bromides. For convenience, lithiation of *N*-Boc pyrrolidine **38** and then transmetallation to the organozinc species was carried out on a large scale. Then, aliquots of this stock solution were taken and used to carry out seven parallel Negishi couplings (scheme 5.11).

Scheme 5.11



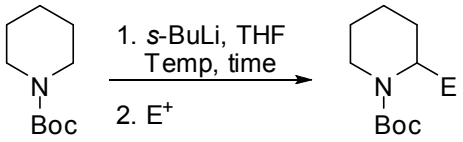
Coupling with bromobenzene gave 2-phenyl pyrrolidine **77** in 79% yield. 2-Bromoanisole gave product **181** in 80% yield while methyl 2-bromobenzoate gave **184** in 69% yield. Aryl pyrrolidines **258** and **259** were obtained in 74% yield and 85% yield, respectively, while coupling methyl 4-bromobenzoate gave **260** in 57% yield. Campos has previously shown that the lithiation-Negishi coupling strategy is compatible with aryl bromides containing unprotected amine; 4-bromoaniline was coupled to give **81** in 64% yield.

We have thus developed a new protocol for the lithiation-trapping and lithiation-arylation of *N*-Boc pyrrolidine **38**. Compared to the existing procedure (*s*-BuLi, TMEDA, 3.5 h in Et_2O at –78 °C), our new lithiation conditions (*s*-BuLi in THF at –30 °C for 5 min) are simpler, less time consuming and more suitable for use on a large scale. We have demonstrated both lithiation followed by trapping with a range of electrophiles, and the previously unreported racemic lithiation-arylation of *N*-Boc pyrrolidine **38**.

5.3 Diamine-Free Lithiation of Other *N*-Boc Heterocycles

Having demonstrated diamine-free lithiation-trapping and lithiation-arylation of *N*-Boc pyrrolidine **38**, we turned our attention to other *N*-Boc heterocycles. Unfortunately, we were unable to effect diamine-free lithiation-trapping of *N*-Boc piperidine **44** (attempted lithiation-trapping conditions shown in table 5.3). In each case, the ^{1}H NMR spectrum of the crude product showed only unreacted starting material and electrophile.

Table 5.3

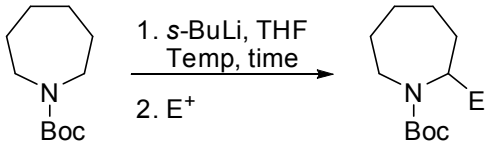


Entry	Reaction Temp (°C)	Reaction Time	Electrophile
1	–78	3 h	MeOCOCl
2	–78	6 h	MeOCOCl
3	–40	3 h	DMF
4	–40	1 h	DMF
5	–40	1 h	MeOCOCl
6	–40	30 min	DMF
7	–30	5 min	DMF
8	–30	5 min	MeOCOCl

We first attempted to effect lithiation in THF at –78 °C. Disappointingly, after lithiating for 3 or 6 h followed by addition of methyl chloroformate, no trapped product could be isolated (entries 1 and 2). Then, lithiation under our optimised conditions and then trapping with methyl chloroformate and DMF was attempted (entries 7 and 8). Finally, lithiation at –40 °C was attempted. Treatment of *N*-Boc piperidine **44** with *s*-BuLi in THF for 3 h and 1 h followed by addition of DMF gave only recovered starting material (entries 3 and 4). Lithiation for 1 h then addition of methyl chloroformate gave no product (entry 5), as did lithiation for 30 min then addition of DMF (entry 6).

Next, we attempted diamine-free lithiation-trapping of *N*-Boc homopiperidine **56**. Unfortunately, we were unable to isolate trapped products under any of the conditions which were attempted (table 5.4).

Table 5.4

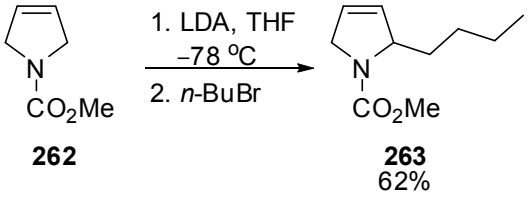


Entry	Reaction Temp (°C)	Reaction Time	Electrophile
1	–78	6 h	MeOCOCl
2	–78	6 h	DMF
3	–40	3 h	MeOCOCl
4	–40	3 h	DMF
5	–40	1 h	MeOCOCl
6	–40	1 h	DMF
7	–40	30 min	DMF
8	–30	5 min	MeOCOCl
9	–30	5 min	DMF

Attempted lithiation of *N*-Boc homopiperidine **56** in THF at –78 °C for 6 h using *s*-BuLi followed by addition of methyl chloroformate or DMF gave no products (entries 1 and 2). Lithiation-trapping under our optimised diamine-free lithiation conditions, then trapping with methyl chloroformate or DMF also gave only recovered starting material (entries 8 and 9). We also attempted to carry out lithiation of *N*-Boc homopiperidine **56** at –40 °C. After lithiation for 3 h or 1 h, then addition of methyl chloroformate or DMF we were unable to isolate any trapped products (entries 3-6). Lithiation also did not take place after treatment of *N*-Boc homopiperidine **56** with *s*-BuLi in THF at –40 °C for 30 min, then trapping with DMF (entry 7).

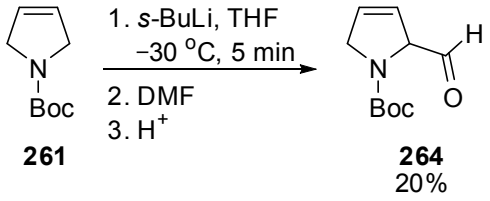
Instead, the diamine-free lithiation of *N*-Boc pyrroline **261** was investigated. It was proposed that in this substrate, substitution could be effected in the 2- and 5-positions using lithiation-trapping, and then the alkene motif could act a synthetic "handle" for installation of substituents in the 3- and 4-positions. In 1977, Pandit reported the LDA-mediated trapping of *N*-CO_2Me pyrroline **262** (scheme 5.12).[187] In this case, the activated allylic α-protons can be removed by LDA, a weaker base than BuLi. Use of the less nucleophilic LDA in turn allowed the use of the less sterically demanding methoxy carbonyl directing group rather than the Boc group which is required to prevent nucleophilic attack when using *s*-BuLi or *n*-BuLi.

Scheme 5.12



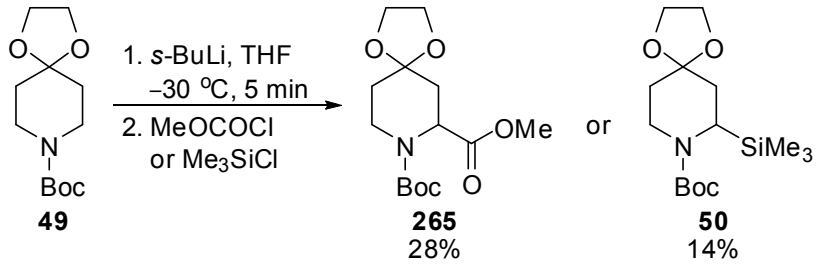
Unfortunately, lithiation of *N*-Boc pyrroline **261** in THF at –30 °C for 5 min followed by trapping with DMF gave aldehyde **264** in only 20% yield (scheme 5.13). Attempted lithiation-trapping with trimethylsilyl chloride and methyl chloroformate did not give rise to the desired products.

Scheme 5.13



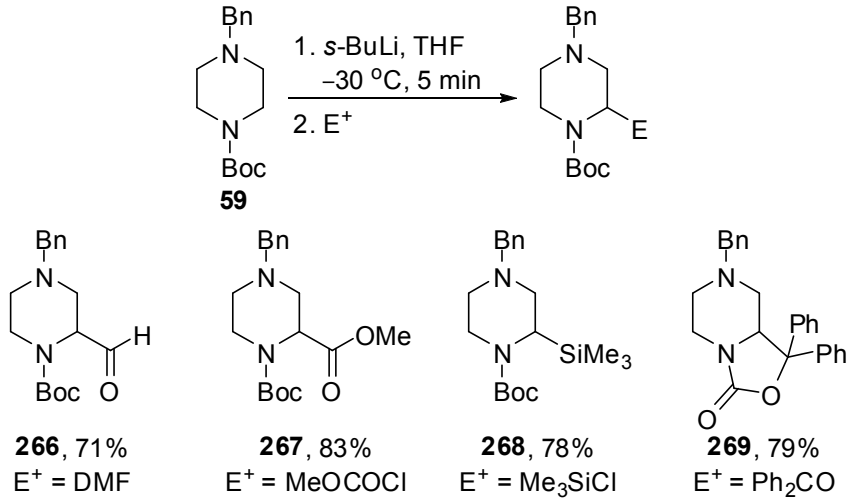
As discussed in chapter 2, *N*-Boc acetal piperidine **49** has been shown to be easier to lithiate than *N*-Boc piperidine **44**.[65] We therefore hoped that racemic lithiation of **49** could be effected using the optimised diamine-free lithiation conditions. Unlike *N*-Boc piperidine **44**, lithiation of *N*-Boc acetal piperidine **49** did take place using *s*-BuLi in THF at –30 °C followed by trapping with methyl chloroformate, but unfortunately product **265** was obtained in only 28% yield. Alternatively, lithiation under the same conditions and then trapping with trimethylsilyl chloride gave silyl piperidine **50** in 14% yield (scheme 5.14)

Scheme 5.14



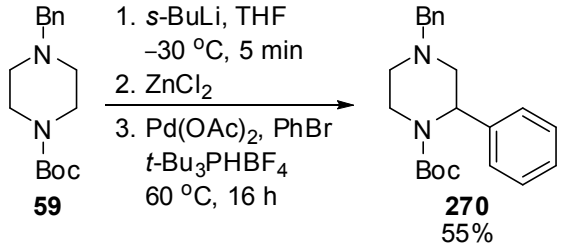
Better results were achieved from diamine-free lithiations of *N*-Boc-*N*′-benzyl piperazine **59** (scheme 5.15). Thus, lithiation using the optimised conditions followed by trapping with DMF gave aldehyde **266** in 71% yield. Trapping with methyl chloroformate and trimethylsilyl chloride gave products **267** and **268** in 83% yield and 78% yield, respectively. Lithiation-trapping using benzophenone as the electrophile led to cyclisation of the resultant alkoxide onto the Boc group and oxazolidinone **269** was obtained in 79% yield. The comparative ease of lithiation of *N*-Boc-*N*′-benzyl piperazine **59** compared to *N*-Boc piperidine **44** has been discussed in chapter 2.

Scheme 5.15



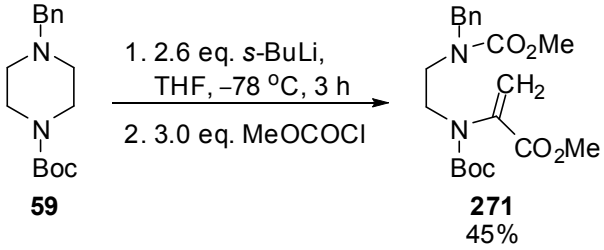
Next, we carried out the first example of lithiation-arylation of *N*-Boc-*N*′-benzyl piperazine **59**. After lithiation-transmetallation and then palladium-catalysed Negishi coupling with bromobenzene, phenyl piperazine **270** was obtained in 55% yield (scheme 5.16). In this case, palladium-catalysed Negishi coupling was carried out under reflux for 16 h since attempted arylation at rt for 16 h did not result in the formation of phenyl piperazine **270**.

Scheme 5.16



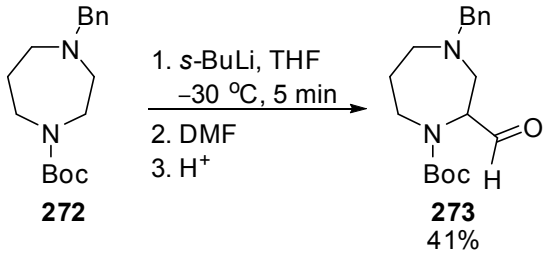
Additionally, we attempted to carry out a 2,2-disubstitution of *N*-Boc-*N*′-benzyl piperazine **59** under the same conditions as *N*-Boc pyrrolidine **38** – treatment with 2.6 equivalents of *s*-BuLi in THF at –78 °C and then addition of 3 equivalents of methyl chloroformate. Under these conditions, ring opening of the piperazine occurred together with vinyl lithiation-trapping, and alkene **271** was isolated in 45% yield (scheme 5.17).

Scheme 5.17



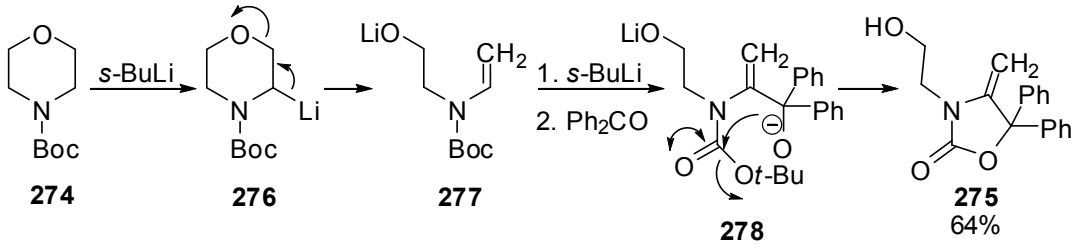
Having demonstrated diamine-free lithiation-trapping of *N*-Boc-*N*′-benzyl piperazine **59**, we investigated lithiation of *N*-Boc-*N*′-benzyl homopiperazine **272**. Unfortunately, lithiation under our optimised conditions followed by trapping with DMF gave aldehyde **273** in only 41% yield, and we were subsequently unable to repeat this reaction (scheme 5.18). The regioselectivity of this lithiation has not been established unequivocally. Attempted lithiation-trapping with methyl chloroformate, trimethylsilyl chloride or benzophenone as electrophile gave 0% yields.

Scheme 5.18



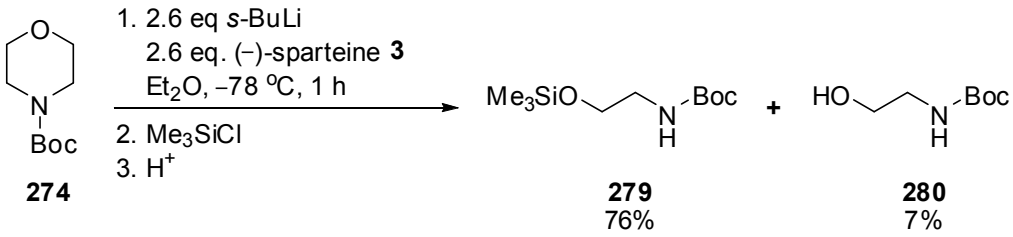
For comparison to piperazine **59**, we also investigated the lithiation-trapping of *N*-Boc morpholine **274**. Lithiation using the optimised conditions followed by trapping using benzaldehyde gave an inseparable mixture of products. Instead, lithiation using 2 equivalents of *s*-BuLi in THF at –30 °C for 5 min followed by trapping with benzophenone gave oxazolidinone **275** in 64% yield (scheme 5.17). In this case, lithiation gave organolithium species **276**, which underwent ring opening to give alkene **277**. Then, a second lithiation at the vinyl position followed by trapping gave alkoxide **278**. Cyclisation then gave product **275**. Lautens has previously reported a similar lithiation-induced ring opening of an analogous bicyclic system.[196]

Scheme 5.19



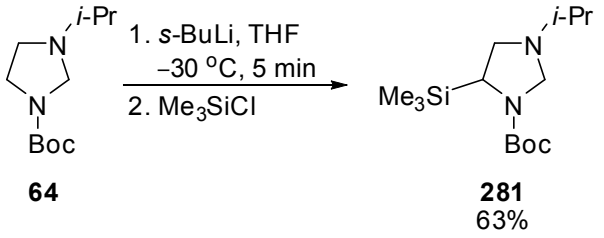
For comparison, we also wished to verify whether ring opening of *N*-Boc morpholine would occur after a *s*-BuLi/(–)-sparteine **3**-mediated lithiation. *N*-Boc morpholine **274** was treated with *s*-BuLi and (–)-sparteine in diethyl ether at –78 °C for 1 h, and then trimethylsilyl chloride was added. Silyl ether **279** (76% yield) and amino alcohol **280** (7% yield) were isolated (scheme 5.20). Presumably, the enamine part of the molecule is hydrolysed during the work up to account for the loss of the C_2 unit.

Scheme 5.20



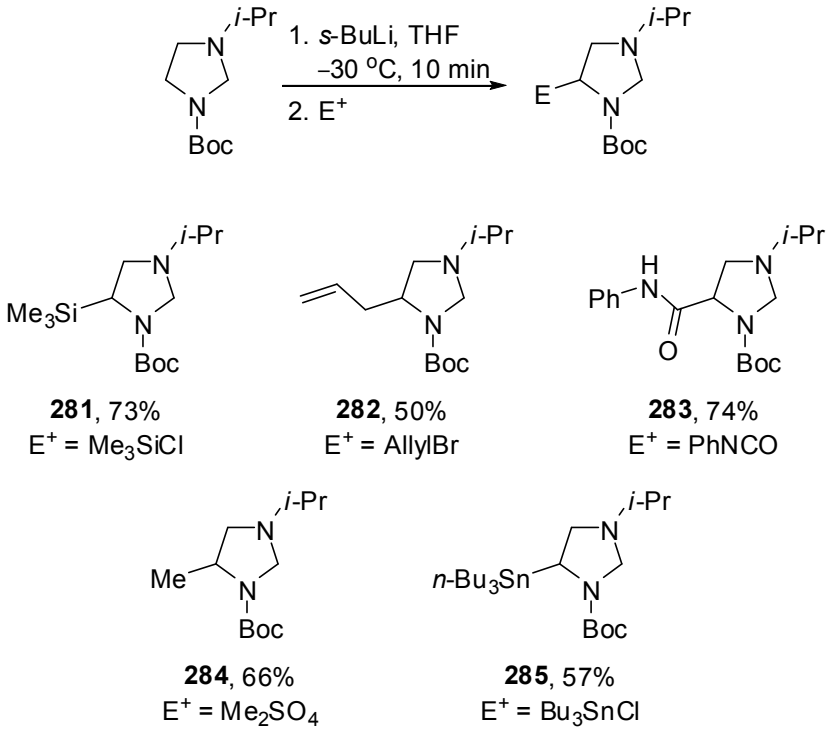
For our final example, we investigated the diamine-free lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64**. Lithiation under our optimised conditions and then trapping with trimethylsilyl chloride gave silyl imidazolidine **281** in 63% yield (scheme 5.21).

Scheme 5.21



The 63% yield of silyl imidazolidine **281** obtained suggested that interconversion of the *N*-Boc rotamers was taking place at –30 °C, overcoming the maximum of 50% yield obtained by Coldham (see scheme 1.28).[74, 75] We hypothesised that a longer lithiation time would allow for more rotamer interconversion and so furnish us with substituted imidazolidines in higher yields. Indeed, lithiation with *s*-BuLi in THF at –30 °C for 10 min followed by trapping with trimethylsilyl chloride gave silyl imidazolidine **281** in 73% yield (scheme 5.22).

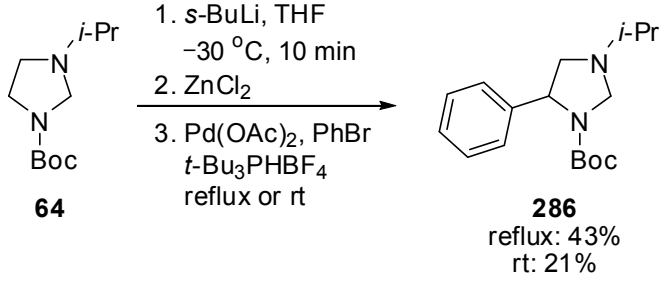
Scheme 5.22



Imidazolidine **64** was then lithiated using these conditions and trapped with a range of electrophiles (scheme 5.22). Direct trapping with allyl bromide gave **282** in 50% yield without transmetallation to an organocuprate species. Trapping with phenyl isocyanate gave amide **283** in 74% yield. Finally, trapping with dimethyl sulfate gave **284** in 66% yield, and tri-*n*-butyltin chloride gave stannane **285** in 57% yield.

The first example of lithiation-arylation of imidazolidine **64** was also demonstrated. Lithiation using *s*-BuLi in THF at –30 °C for 10 min followed by transmetallation with zinc chloride and then palladium-catalysed Negishi coupling with bromobenzene gave phenyl imidazolidine **286** in 43% yield (scheme 5.23). Heating at reflux during the coupling step was required for optimal yields; when coupling was carried out at rt, phenyl imidazolidine **286** was isolated in only 21% yield.

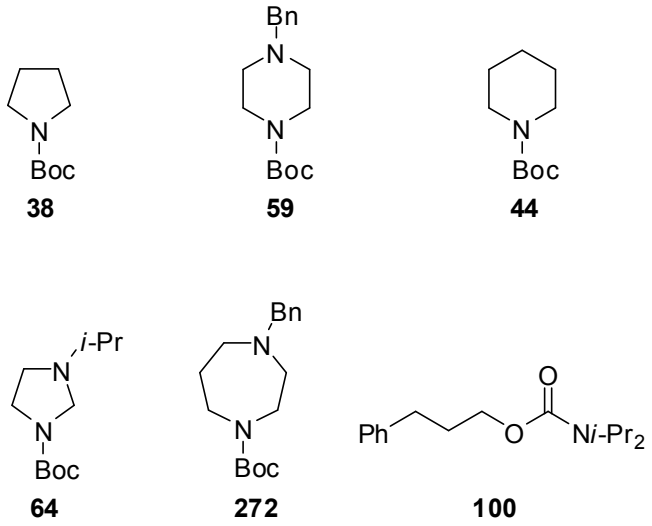
Scheme 5.23



5.4 *In Situ* Infra-Red Spectroscopic Monitoring of Diamine-Free Lithiations

To complete our study of diamine-free lithiations of carbamates, we wished to follow such lithiations using *in situ* infra-red spectroscopic monitoring. Six substrates were chosen to be investigated (figure 5.5).

Figure 5.5

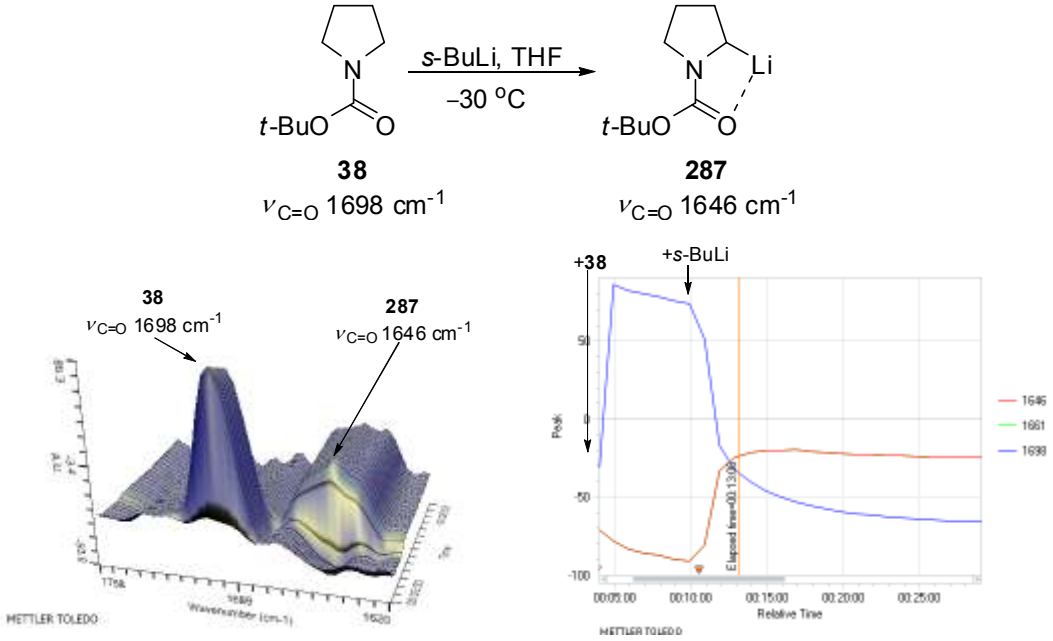


We studied the lithiations of *N*-Boc pyrrolidine **38** and *N*-Boc-*N*′-benzyl piperazine **59** at –30 °C and at –78 °C. It has been found that *s*-BuLi-mediated lithiation of *N*-Boc piperidine **44** does not proceed in THF, even in the presence of TMEDA or (+)-sparteine surrogate **6**.[197] We wished to confirm this lack of reactivity. Interested in the interconversion of *N*-Boc rotamers at different temperatures, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** and *N*-Boc-*N*′-benzyl homopiperazine **272** were also chosen to be monitored using *in situ* infra-red spectroscopy. Finally for comparison to the *N*-Boc heterocycles, lithiation of *O*-alkyl carbamate **100** was also investigated.

5.4.1 *N*-Boc Pyrrolidine

First, diamine-free lithiation of *N*-Boc pyrrolidine **38** under the optimised conditions was observed. Thus, *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1698 cm^{-1}) was stirred in THF at –30 °C and then *s*-BuLi was added. A new peak emerged, corresponding to lithiated product **287** ($\nu_{C=O}$ 1646 cm^{-1}) (scheme 5.24).

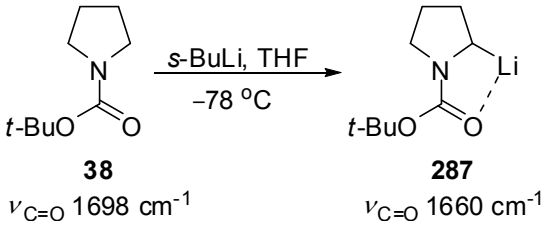
Scheme 5.24

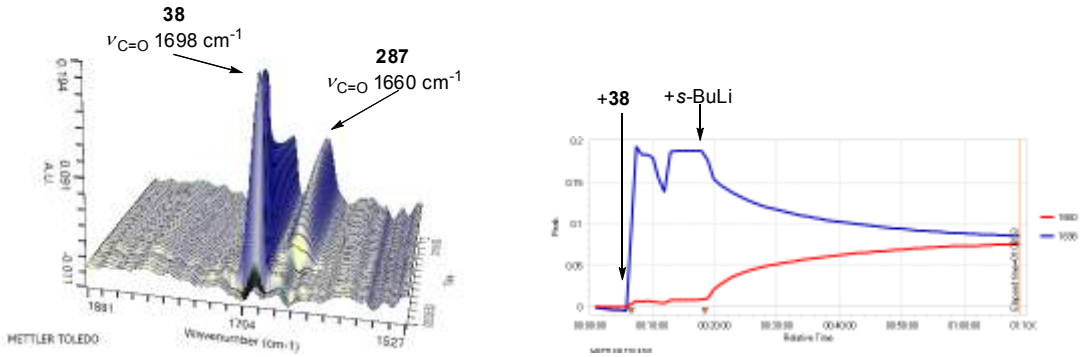


Confirming our optimal yields after 5 min at –30 °C in THF, lithiation of *N*-Boc pyrrolidine **38** was fast: complete lithiation was observed after 3 min. No peak corresponding to a prelithiation complex was observed.

For comparison, we next investigated the diamine-free lithiation of *N*-Boc pyrrolidine **38** in THF at –78 °C. Thus, *N*-Boc pyrrolidine **38** ($\nu_{C=O}$ 1698 cm^{-1}) was stirred in THF at –78 °C and then *s*-BuLi was added. A new peak emerged at 1660 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated product **287** (scheme 5.25).

Scheme 5.25



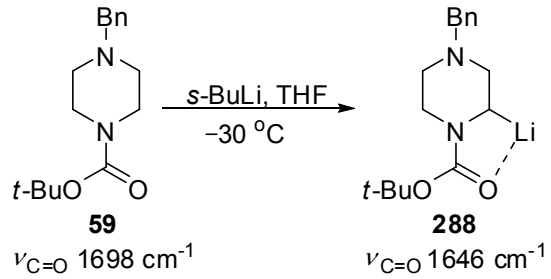


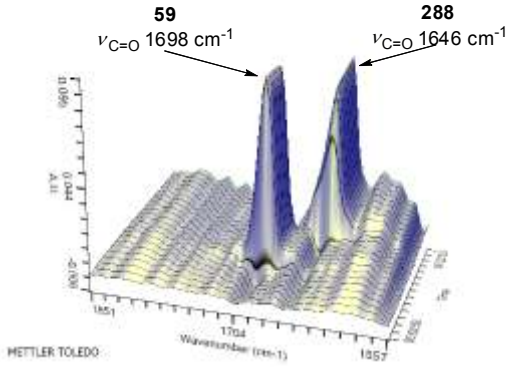
As expected, lithiation of *N*-Boc pyrrolidine **38** by *s*-BuLi/THF at –78 °C was slower than at –30 °C. After 45 min, lithiation of *N*-Boc pyrrolidine **38** was still incomplete. No peak corresponding to a prelithiation complex was observed, despite the slow lithiation. Two possible hypotheses can be proposed to explain the lack of prelithiation complex in this case. Only a small amount of prelithiation complex could form in solution due to preferential coordination of the THF to the *s*-BuLi. Subsequent lithiation then takes place quickly to give product **287**, preventing direct observation of the prelithiation complex. Alternatively, the *s*-BuLi/THF complex may directly abstract an α-proton without any pre-complexation.

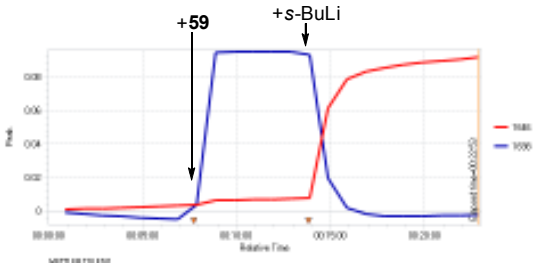
5.4.2 *N*-Boc-*N*′-Benzyl Piperazine

Next, *s*-BuLi/THF-mediated lithiation of *N*-Boc-*N*′-benzyl piperazine **59** under the optimised diamine-free lithiation conditons was monitored. Thus, piperazine **59** ($\nu_{C=O}$ 1698 cm^{-1}) was stirred in THF at –30 °C and *s*-BuLi was added. Lithiated piperazine **288** formed, indicated by a peak at 1646 cm^{-1} (scheme 5.26).

Scheme 5.26



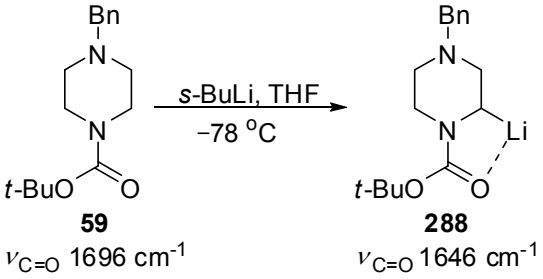


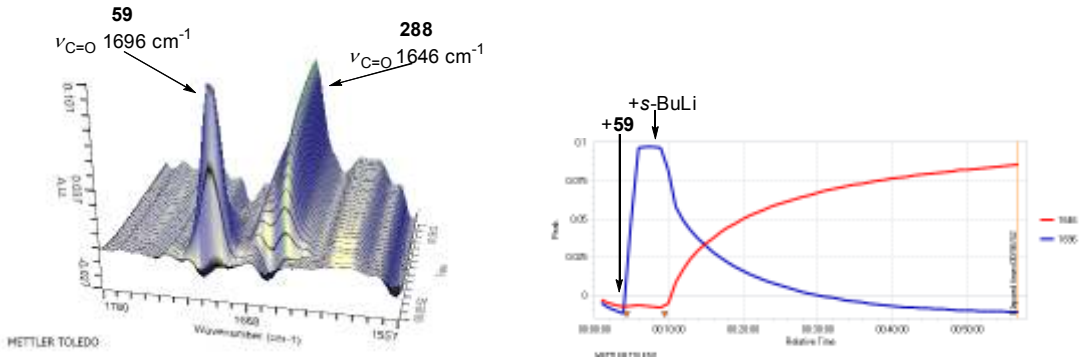


In common with the lithiation of *N*-Boc pyrrolidine **38** under these conditions, lithiation proceeded quickly and complete formation of product **288** was observed within 3 min. No peak corresponding to a prelithiation complex could be observed.

For comparison, *s*-BuLi-mediated lithiation of *N*-Boc-*N*′-benzyl piperazine **59** in THF at –78 °C was next investigated. Thus, **59** ($\nu_{C=O}$ 1696 cm^{-1}) was stirred in THF at –78 °C and then *s*-BuLi was added. Lithiated product **288** ($\nu_{C=O}$ 1646 cm^{-1}) formed more slowly (scheme 5.27).

Scheme 5.27





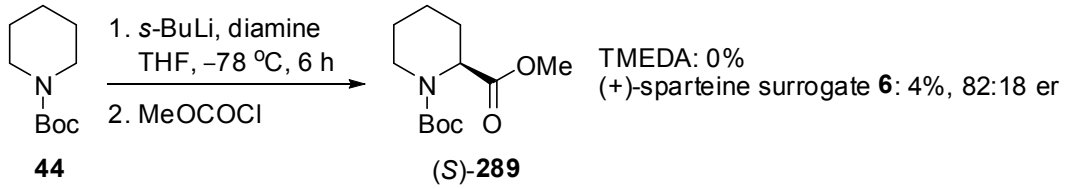
Complete conversion to give **288** was observed in 45 min. Despite the slow lithiation, no prelithiation complex could be detected.

5.4.3 *N*-Boc Piperidine

It had been found that attempted lithiation-trapping of *N*-Boc piperidine **44** under the optimised diamine-free lithiation conditions gave no yield of substituted products. To verify this result, the lithiation was observed using *in situ* infra-red spectroscopic monitoring. Thus, *N*-Boc piperidine **44** ($\nu_{C=O}$ 1694 cm^{-1}) was stirred in THF at –30 °C and then *s*-BuLi was added. As expected, no new peaks emerged – neither prelithiation complex nor lithiated product was formed over 20 min.

Additionally, we had found that attempted lithiation-trapping of *N*-Boc piperidine **44** using *s*-BuLi and TMEDA or (+)-sparteine surrogate **6** in THF at –78 °C gave no products; treatment of *N*-Boc piperidine **44** with *s*-BuLi and TMEDA in diethyl ether at –78 °C for 6 h followed by addition of methyl chloroformate gave only recovered **44**. Additionally, treatment of *N*-Boc piperidine **44** with *s*-BuLi and (+)-sparteine surrogate **6** in diethyl ether at –78 °C for 6 h and then trapping with methyl chloroformate gave trapped product (*S*)-**289** in only 4% yield and 82:18 er (scheme 5.28).[197] For comparison, lithiation of *N*-Boc piperidine **44** with *s*-BuLi and (+)-sparteine surrogate **6** in diethyl ether followed by electrophilic trapping gives substituted piperidines in up to 92% yield and 88:12 er (electrophile = CO_2).[67]

Scheme 5.28



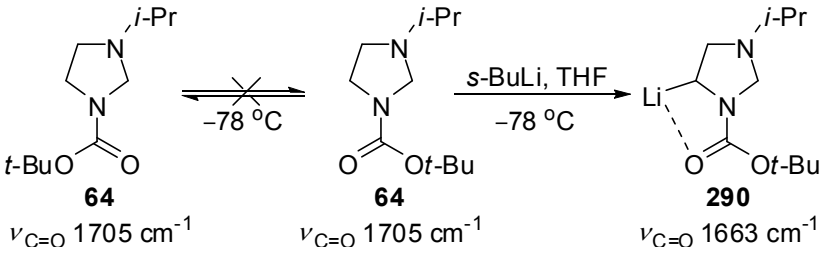
44 (*S*)-**289**

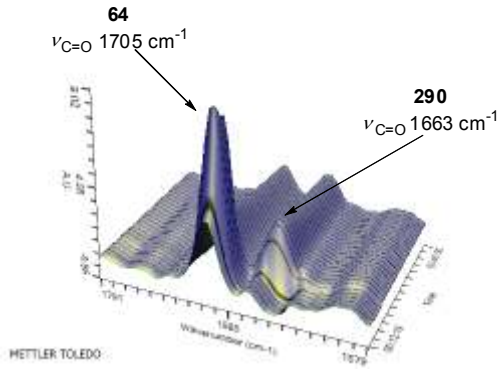
This result was also confirmed using the ReactIR set-up. *N*-Boc piperidine **44** ($\nu_{C=O}$ 1695 cm^{-1}) and TMEDA or (+)-sparteine surrogate were stirred in THF at –78 °C and then *s*-BuLi was added. Neither prelithiation complex nor lithiated products were formed over 20 min.

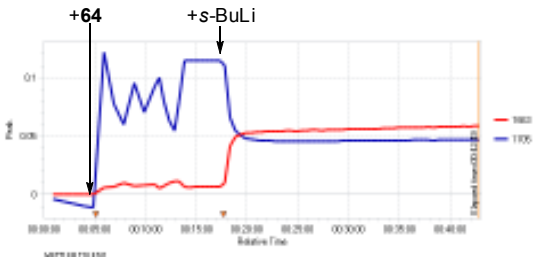
5.4.4 Unsymmetrical *N*-Boc Heterocycles

Using *s*-BuLi/THF-mediated lithiation-trapping of *N*-Boc-*N*′-isopropylimidazolidine **64** at –30 °C, access to trapped products in yields > 50% is possible (scheme 5.22). In contrast, Coldham had shown that at –78 °C, maximum yields were deteremined by the ratio of *N*-Boc rotamers in solution.[74, 75] We wished to observe this phenomenon using *in situ* infra-red spectroscopic monitoring. First, **64** ($\nu_{C=O}$ 1705 cm^{-1}) was stirred in THF at –78 °C and then *s*-BuLi was added. The lithiated product **290** peak appeared at 1663 cm^{-1} (scheme 5.29).

Scheme 5.29



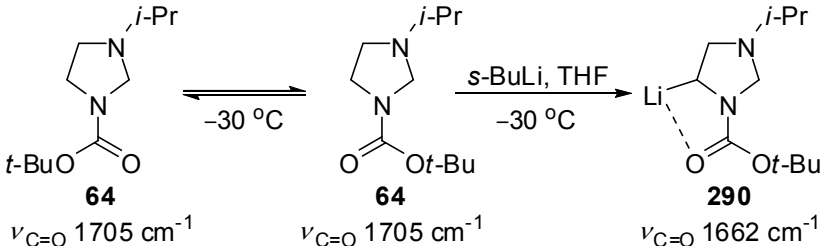


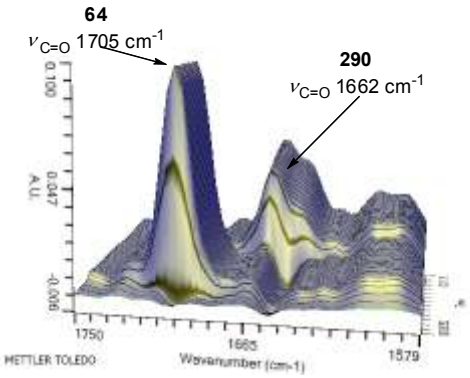


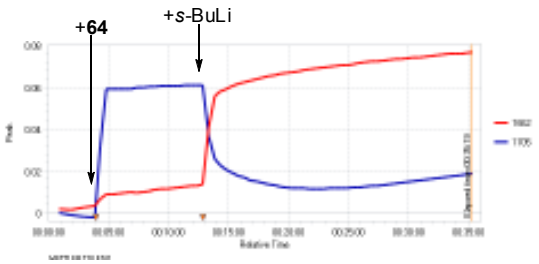
After addition of *s*-BuLi, partial lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** took place within 3 min, after which no further lithiation took place. This is a faster lithiation than that of *N*-Boc pyrrolidine **38** at –78 °C. This would be consistent with a fast lithiation of one rotamer and then no further lithiation as the unreactive rotamer could not convert into the reactive rotamer. No IR stretch for a prelithiation complex was observed.

Then, the lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** was repeated under our optimised conditions. Thus, **64** ($\nu_{C=O}$ 1705 cm^{-1}) was stirred in THF at –30 °C and then *s*-BuLi was added. A new peak emerged, corresponding to lithiated product **290** ($\nu_{C=O}$ 1662 cm^{-1}) (scheme 5.30).

Scheme 5.30



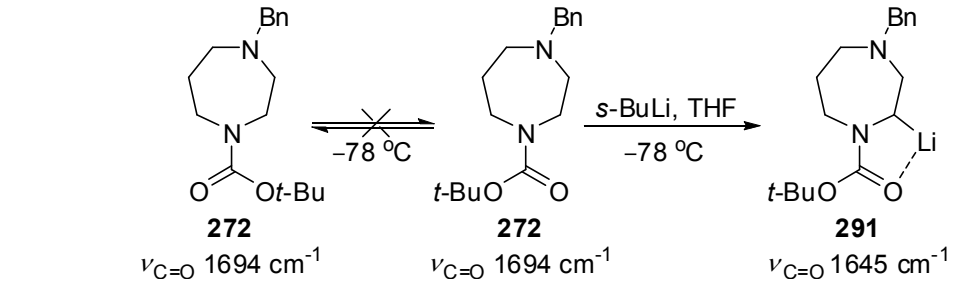


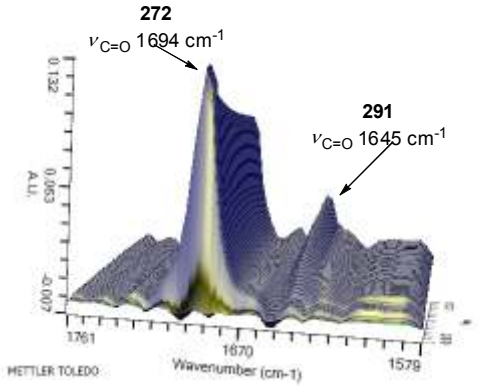


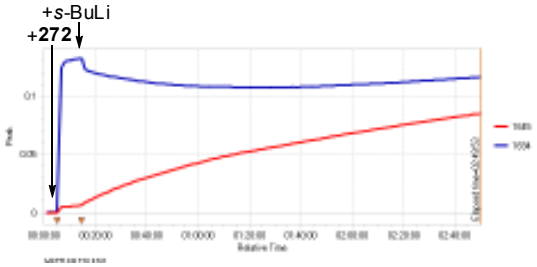
At –30 °C, it was found that the *N*-Boc rotamers did interconvert, allowing >50% lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** to take place. Complete conversion of **64** to lithiated product **290** was observed in 10 min. No IR stretch for a prelithiation complex was observed.

Another non-symmetrical *N*-Boc heterocycle is *N*-Boc-*N*′-benzyl homopiperazine **272**. We wondered whether diamine-free lithiation could be affected on this substrate, and if *N*-Boc rotamers would influence the outcome of lithiation. First, lithiation at –78 °C was investigated. Thus, *N*-Boc-*N*′-benzyl homopiperazine **272** ($\nu_{C=O}$ 1694 cm^{-1}) was stirred in THF and *s*-BuLi was added. A new peak, corresponding to lithiated product **291** ($\nu_{C=O}$ 1645 cm^{-1}) emerged (scheme 5.31).

Scheme 5.31



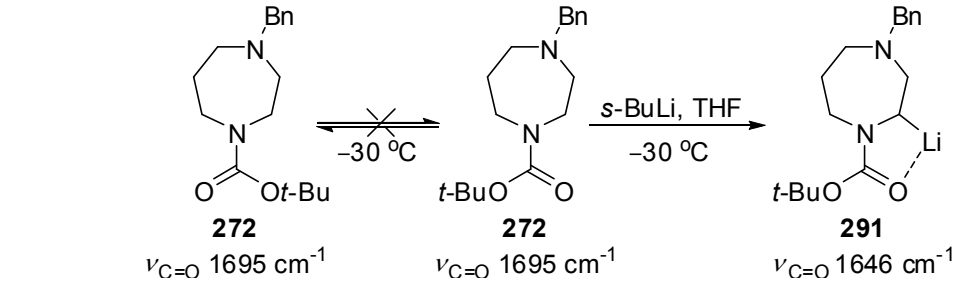


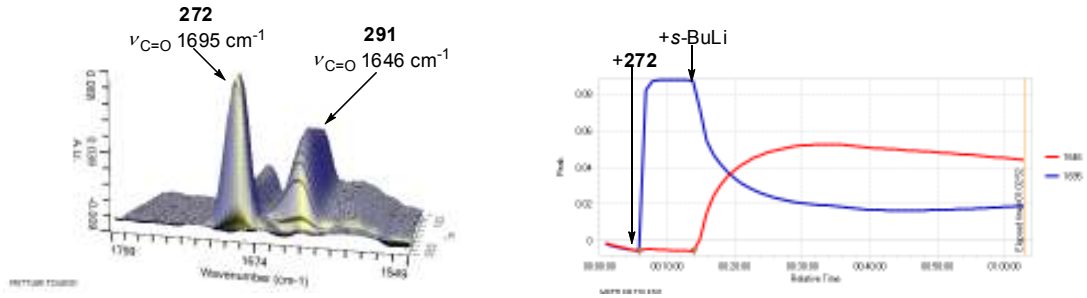


Lithiation of substrate **272** was slow: only partial conversion to lithiated product **291** was observed after 60 min. No prelithiation complex was observed. Due to the slow lithiation, it is hard to determine whether the *N*-Boc rotamers are interconverting. Note that lithiation of susbtrate **272** under these conditions followed by electrophilic trapping with DMF gives rise to a 44% yield of substituted product (Scheme 5.18).

Lithiation of *N*-Boc-*N*′-benzyl homopiperidine **272** at –30 °C gave a clearer insight into the conversion of *N*-Boc rotamers. **272** ($\nu_{C=O}$ 1695 cm^{-1}) was stirred in THF at –30 °C and then *s*-BuLi was added. The lithiated product peak at $\nu_{C=O}$ 1646 cm^{-1} then emerged (Scheme 5.32).

Scheme 5.32



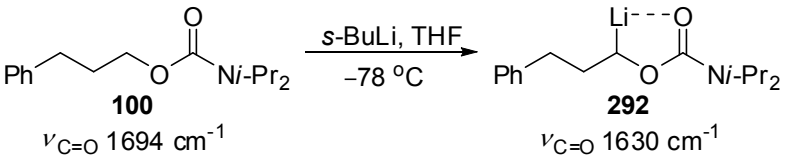


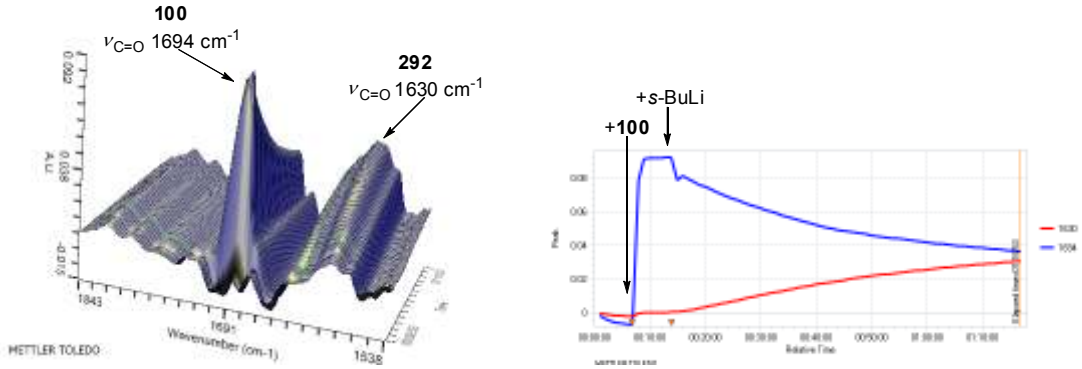
After addition of *s*-BuLi, fast but incomplete lithiation to give product **291** took place within 20 min. After a further 40 min of incubation, no further lithiation was observed. We thus conclude that in the case of *N*-Boc-*N*′-benzyl homopiperazine **272**, the *N*-Boc rotamers do not interconvert at –30 °C.

5.4.5 *O*-Alkyl Carbamate

For comparison to the *N*-Boc heterocycles that had previously been studied, we wished to monitor the diamine-free lithiation of *O*-alkyl carbamate **100** using *in situ* infra-red spectroscopy. Additionally, we wondered whether a prelithiation complex could be observed during this lithiation as such a complex had not been seen during *s*-BuLi/THF-mediated lithiations of *N*-Boc heterocycles. Thus, *O*-alkyl carbamate **100** ($\nu_{C=O}$ 1694 cm^{-1}) was stirred in THF at –78 °C and then *s*-BuLi was added. A peak at 1630 cm^{-1} emerged and was assigned to $\nu_{C=O}$ of lithiated product **292** (scheme 5.33).

Scheme 5.33





In common with the diamine-free lithiation of *N*-Boc heterocycles, no prelithiation complex was observed in the *s*-BuLi/THF-mediated lithiation of *O*-alkyl carbamate **100**. Lithiation was slow at –78 °C, and only partial lithiation was observed after 1 h.

5.5 Conclusions and Future Work

A new diamine-free racemic lithiation procedure has been developed for *N*-Boc pyrrolidine **38**, *N*-Boc-*N*′-benzyl piperazine **59** and *N*-Boc-*N*′-*i*-Pr imidazolidine **64**. Substituted products of lithiation-trapping and lithiation-arylations were obtained in high yields. In the case of **64**, products were obtained in yields greater than the 50% yield limit previously reported. The new racemic lithiation conditions which have been developed are both simpler, as no diamine is required, and more suitable for use on a large scale, as cooling to –78 °C is not necessary; –30 °C is sufficient. Additionally, our new conditions can also be carried out using the "green" solvent 2-Me THF as opposed to diethyl ether, which had previously been used.

Unfortunately, lithiation-trapping of other *N*-Boc heterocycles under the same conditions gave low yields of products, or no products at all. Future work may include testing lithiation of a wider range of substrates under the new conditions. Additionally, *s*-BuLi/THF-mediated lithiation of *O*-alkyl carbamates may be investigated.

Diamine-free lithiations of carbamates have been monitored using *in situ* infra-red spectroscopy. The results obtained confirmed the synthetic results already obtained on different substrates. In addition, it was shown that *O*-alkyl carbamate **100** underwent *s*-BuLi/THF-mediated lithiation.

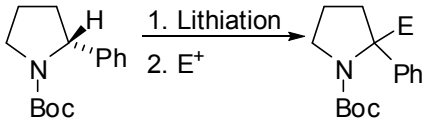
We were unable to observe any peak corresponding to a prelithiation complex using ReactIR spectroscopic monitoring. A further investigation of these reactions with a view to determining whether complexation of alkyllithium to the carbonyl group takes place prior to lithiation could be carried out.

Chapter Six: Benzylic Lithiation-Trapping of

N-Boc-2-Phenyl Pyrrolidine

This chapter concerns the development of a new synthetic route to 2,2-disubstituted pyrrolidines *via* lithiation-trapping of *N*-Boc-2-phenyl pyrrolidine (*R*)-**77** (scheme 6.1). The aim was to identify suitable conditions for lithiation at the more acidic benzylic position. There are several issues to consider including rotamer interconversion and maintaining the er through the lithiation-trapping process.

Scheme 6.1



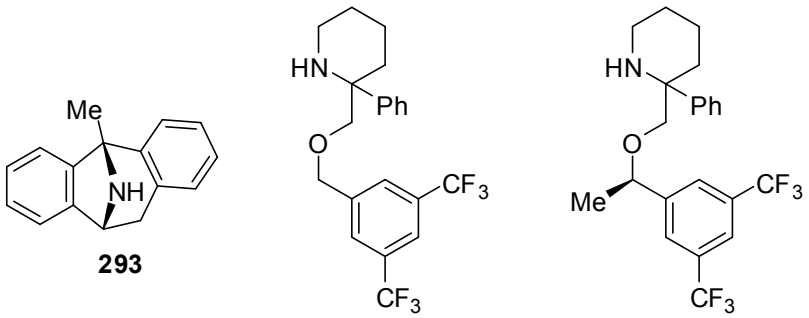
(*R*)-**77**

The development of an efficient lithiation-trapping protocol on *rac*-**77** is described, and the optimised conditions are illustrated with a range of electrophiles. Then, lithiation-trapping of enantioenriched (*R*)-**77** is described. The use of *in situ* infa-red spectroscopic monitoring would be used to gain insight into the progress of the lithiation reaction, and to observe the interconversion of the *N*-Boc rotamers at different temperatures.

6.1 Synthesis of 2,2-Disubstituted Nitrogen Heterocycles

As discussed so far in this thesis, 2-substituted nitrogen heterocycles are an important substructure in drug molecules and natural products. Of the examples reported in the chemical literature, several are 2,2-disubstituted heterocycles. Examples include MK-801 (dizocilpine) **293**, a ligand for the PCP receptor[198] which possesses both anti-convulsant[199] and neuroprotective[200, 201] properties, and NK_1 antagonists **294**[202] and **295**[203] (figure 6.1).

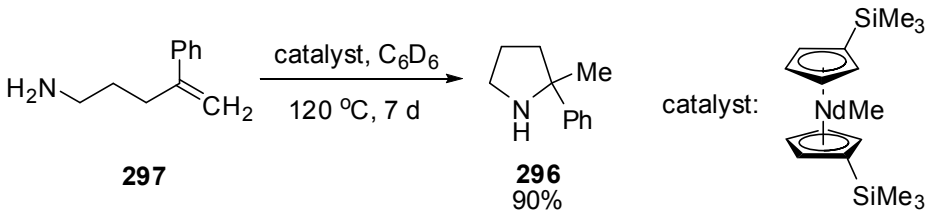
Figure 6.1



293 **294** **295**

Several synthetic approaches to 2,2-disubstituted nitrogen heterocycles in which one substituent is an aryl group using metal-catalysed processes have been reported. An early example is the lanthanide-catalysed intramolecular hydroamination reported by Molander in 1998. A range of different 2,2-disubstituted heterocyclic skeletons was formed from secondary alkenes. For example, 2-phenyl-2-methyl pyrrolidine **296** was obtained in 90% yield from alkene **297** (scheme 6.2).[204]

Scheme 6.2

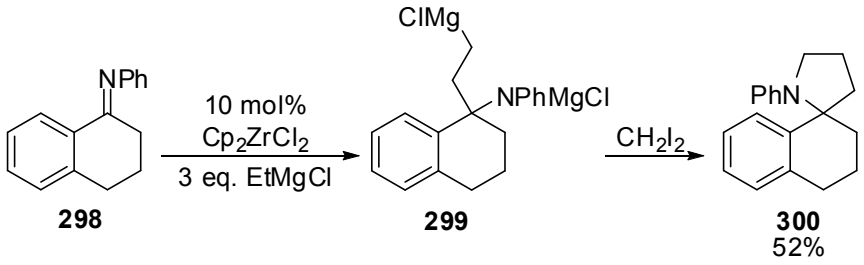


297 **296** 90%

Another example of intramolecular hydroamination has recently been reported by Liu.[205] Using a palladium-based catalyst, an isolated example of formation of a 2,2-disubstituted pyrrolidine in modest yield was reported. Szymoniak used an unusual zirconium-catalysed reaction of imines to access 2,2-disubstituted pyrrolidines and azetidines. The reaction proceeded *via* complexation of Cp_2ZrCl_2 with ethyl magnesium

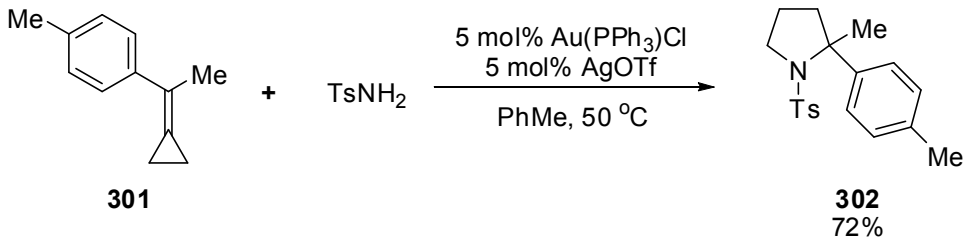
chloride to give a zirconocene-ethylene species. Then, the C_2 unit was inserted into the imine C=N bond. Displacement of zirconium with two more equivalents of the Grignard reagent then released dimagnesium species **299**. Addition of a double electrophile such as diiodomethane then allowed trapping and cyclisation to give spirocyclic products such as **300** (scheme 6.3).[206]

Scheme 6.3



An alternative metal-catalysed route to 2,2-disubstituted pyrrolidines involves the gold-catalysed ring opening of a methylene cyclopropane reported by Shi. For example, treatment of cyclopropane-alkene **301** with *p*-toluene sulfonamide and an *in situ* prepared $Au(PPh_3)OTf$ catalyst gave disubstituted pyrrolidine **302** in 72% yield (scheme 6.4).[207]

Scheme 6.4

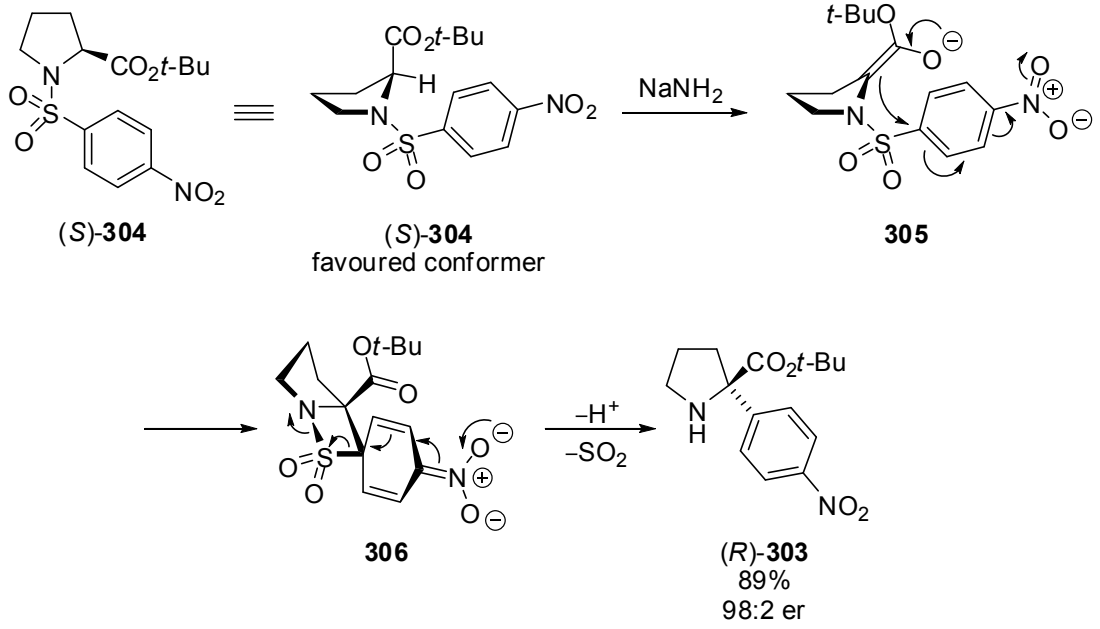


Isolated examples of gold-catalysed ring opening of cyclopropanes to give 2,2-disubstituted pyrrolidines have also been reported by Togni[208] and Chan.[209] Limitations of the metal-catalysed procedures discussed so far are the unusual catalysts employed, and the need for both substituents in the final product to be present in the starting material. Thus, a range of different products cannot be accessed from a common starting point. Additionally, these methodologies all provide racemic products.

Recently, Penso and Tagliabue have reported the rearrangement of *N*-aryl sulfonyl proline esters as a route to 2,2-disubstituted pyrrolidines. Building on earlier work on an acyclic system, 2,2-disubstituted pyrrolidines such as **303** were accessed in good yields

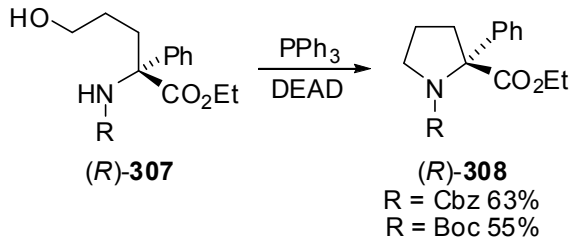
and ers.[210] The mechanism of the reaction proceeds *via* sodium amide-mediated enolisation of starting material **304**. Deprotonation of the favoured (less sterically crowded) conformer of **304** gave enolate **305** which then underwent S-C_α aryl migration with loss of SO_2 *via* spiro-Meisenheimer complex **306**. Thus, 2-aryl prolines were accessed with retention of stereochemistry (scheme 6.5). The methodology suffers from the limitation that in order to form complex **306**, electron-withdrawing substituents on the aryl portion are required; without such groups, only starting material was recovered.[211]

Scheme 6.5



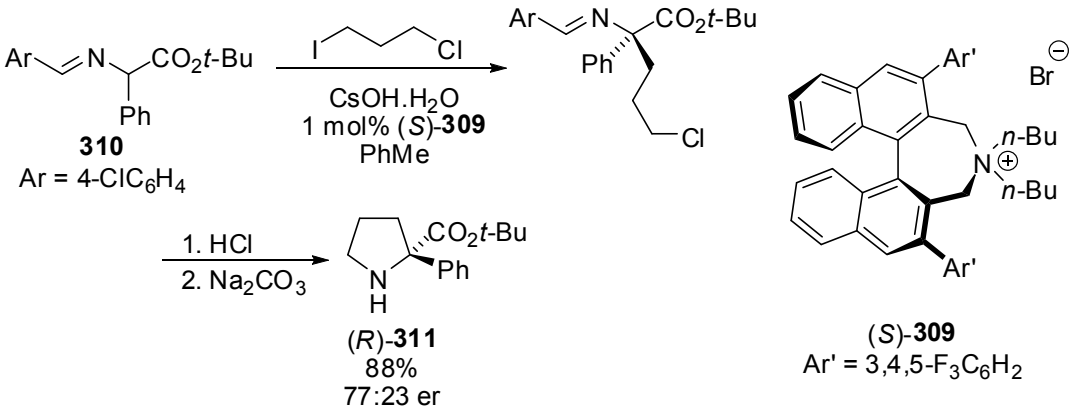
In 1997, Tourwé reported using a Mitsunobu cyclisation to form 2-phenyl prolines. Thus, treatment of *N*-Boc amine (*R*)-**307** of 98:2 er with triphenylphosphine and DEAD gave *N*-Boc-2-phenyl ethyl prolinate (*R*)-**308** in 55% yield. Replacement of the Boc group with Cbz gave an increase in yield to 63% (scheme 6.6). Unfortunately, formation of amine (*R*)-**307** used an enzymatic resolution. Hence, synthesis of the other enantiomeric series could not be achieved in high er. Additionally, 2-phenyl ethyl prolinates were the only examples reported.[212]

Scheme 6.6



Maruoka recently reported another synthesis of 2-substituted prolines. Using caesium hydroxide and phase transfer catalyst (*S*)-**309**, alkylation of imine ester **310** with 1-chloro-3-iodo propane took place with high enantioselectivity. Imine hydrolysis and accompanying cyclisation then gave 2-substituted prolines in high yield and er. For example, 2-phenyl-*t*-Bu prolinate (*R*)-**311** was obtained in 88% yield and 77:23 er (scheme 6.7). Replacing the phenyl substituent with alkyl groups gave an increase in enantioselectivity. For example, 2-methyl-*t*-Bu prolinate was obtained in 87% yield and >99:1 er. Using other dihalo alkanes, examples with larger ring analogues was also described.[213]

Scheme 6.7



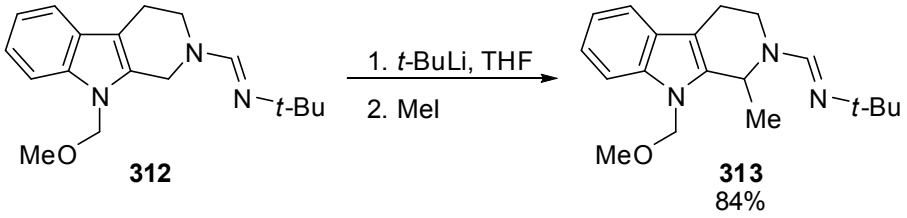
In summary, no general strategy to 2,2-disubstituted pyrrolidines with one aryl group has been reported. The methods reported here all require both α-substituents in the final product to be present in the starting material.

6.2 Overview of Benzylic Lithiation Methodology

Our proposed approach to 2,2-disubstituted pyrrolidines would rely on lithiation at the benzylic position of *N*-Boc-2-phenyl pyrrolidine **77**. Benzylic lithiation α to a heteroatom

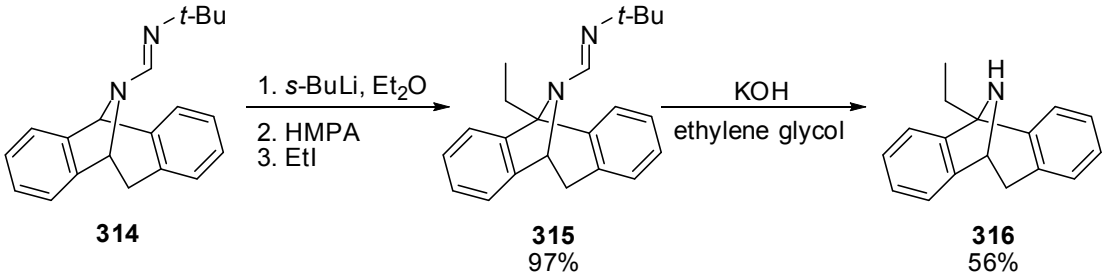
on other systems has been reported by a number of different groups. Early examples focused on benzylic lithiation of formamidine-protected *N*-heterocycles. In the first such example of which we are aware, Meyers reported lithiation of indole derivative **312** using *t*-BuLi and then electrophilic trapping. For example, trapping with methyl iodide gave **313** in 84% yield (scheme 6.8).[21]

Scheme 6.8



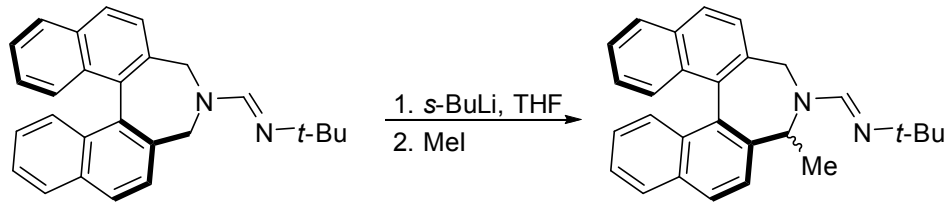
Subsequently, Rice used this methodology to prepare a range of analogues of the drug molecule MK-801. Thus, for example, treatment of formamidine-protected heterocycle **314** with *s*-BuLi in diethyl ether and then trapping with ethyl iodide gave product **315** in 97% yield (scheme 6.9).[214] The formamide group was then removed to give **316** in 56% yield. A range of secondary amine analogues were investigated as PCP receptor ligands.[215]

Scheme 6.9



Meyers later reported the benzylic lithiation of a formamidine-protected amine. Lithiation of C_2 symmetric azepine **317** using *s*-BuLi in THF and then trapping with methyl iodide gave trapped product **318** in 90% yield as a mixture of diastereomers (scheme 6.10).[216]

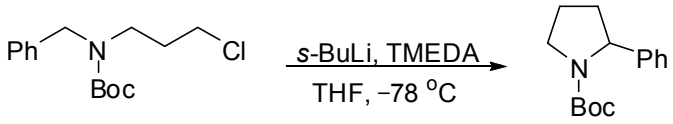
Scheme 6.10



317 **318** 90%

Benzylic lithiation of *N*-Boc substrates was first investigated by Beak wherein the lithiation of *N*-Boc benzylamines was used as a route to 2-aryl nitrogen heterocycles, *via* internal electrophilic trapping.[106, 173] For example, *s*-BuLi/TMEDA-mediated lithiation of *N*-Boc amine **95** followed by internal trapping gave *N*-Boc-2-phenyl pyrrolidine *rac*-**77** in 82% yield (scheme 6.11).[173] Subsequently it was found that enantioselective lithiation using *s*-BuLi/(–)-sparteine **3** gave access to enantioenriched 2-aryl pyrrolidines (see scheme 1.41).[106]

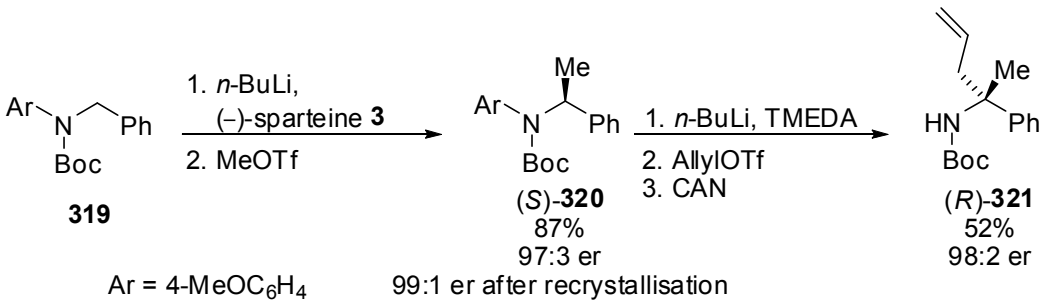
Scheme 6.11



95 *rac*-**77** 82%

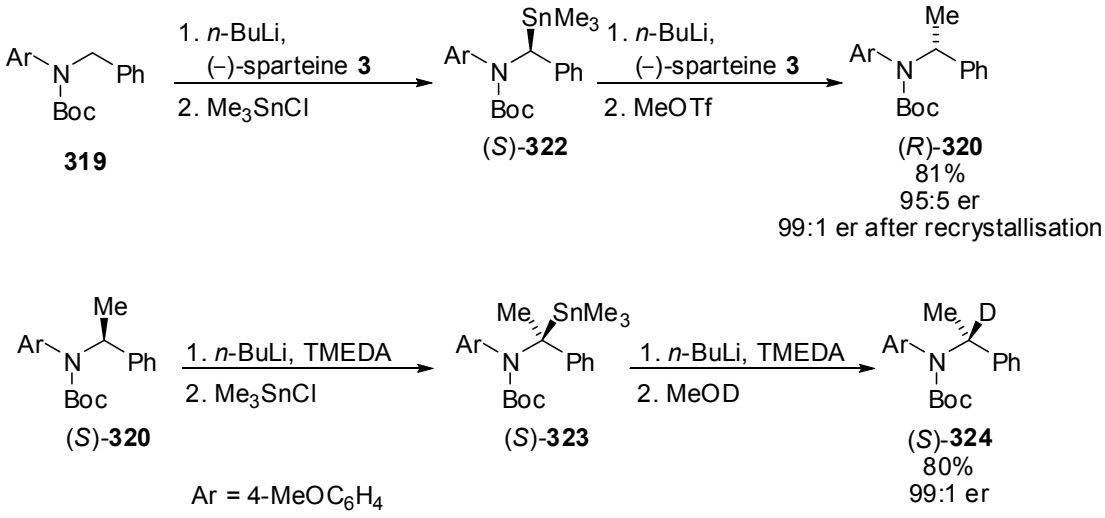
Beak then investigated enantioselective benzylic lithiations as a route to α-substituted primary amines.[178, 217] In this case, the chloroalkyl substituent was replaced with a *para*-methoxyphenyl group, which could subsequently be removed using CAN. Thus, for example, treatment of *N*-Boc benzylamine **319** with *n*-BuLi and (–)-sparteine **3** and then trapping with methyl triflate gave methyl benzylamine (*S*)-**320** in 87% yield and 97:3 er, which was then recrystallised to 99:1 er. Treatment of (*S*)-**320** with *n*-BuLi/TMEDA followed by addition of allyl triflate then installed another benzylic substituent. The *para*-methoxy phenyl group was then removed using CAN in one pot to give *N*-Boc benzylamine (*R*)-**321** in 52% yield and 98:2 er (scheme 6.12).[178]

Scheme 6.12



Interestingly, lithiation-trapping using trimethyltin chloride to give stannane (*S*)-**322** followed by *n*-BuLi/(–)-sparteine **3**-mediated tin-lithium exchange and then trapping with methyl triflate gave product (*R*)-**320** in 81% yield and high er (scheme 6.13). Thus, both enantiomers of **320** and **321** could be obtained using (–)-sparteine **3**.[178] Additionally, during the second lithiation, direct lithiation-trapping proceeded with retention of configuration (see scheme 6.12), whereas lithiation-trapping with trimethyltin chloride and then tin-lithium exchange-electrophilic trapping gave products of the opposite enantiomeric series. For example, treatment of (*S*)-**320** with *n*-BuLi and TMEDA and then trapping with trimethyltin chloride gave stannane (*S*)-**323**. Then, treatment with *n*-BuLi and TMEDA and trapping with MeOD gave deuterated product (*R*)-**324** in 80% yield and 99:1 er (scheme 6.13).[217]

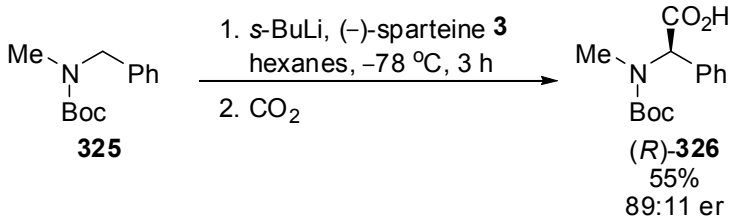
Scheme 6.13



Clayden recently reported the use of Beak's protocol to provide enantioenriched samples of isotopically labelled anilines.[218] Concurrent with Beak's research, Voyer reported *s*-BuLi/(–)-sparteine **3**-mediated lithiation of *N*-methyl-*N*-Boc benzylamine **325**

and trapping with carbon dioxide to effect a simple synthesis of *N*-Boc phenyl sarcosine (*R*)-**326** (scheme 6.14). However, yields and enantioselectivity were modest (55% yield, 89:11 er) and only two electrophiles were used: carbon dioxide and trimethylsilyl chloride.[219]

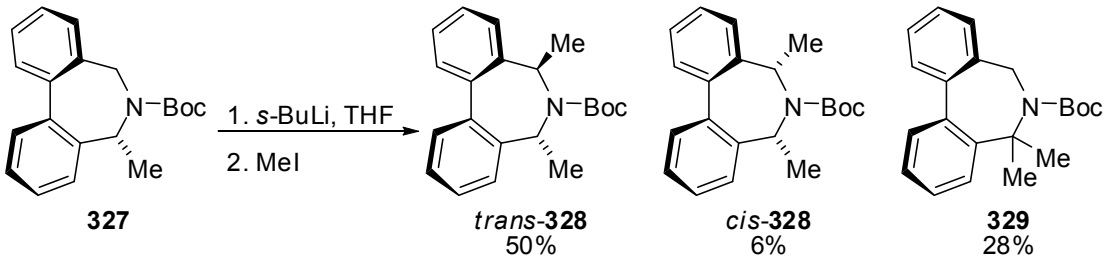
Scheme 6.14



(–)-Sparteine-mediated lithiation of *N*-methyl-*N*-Boc benzylamine **325** has also been studied by Schlosser and co-workers.[220]

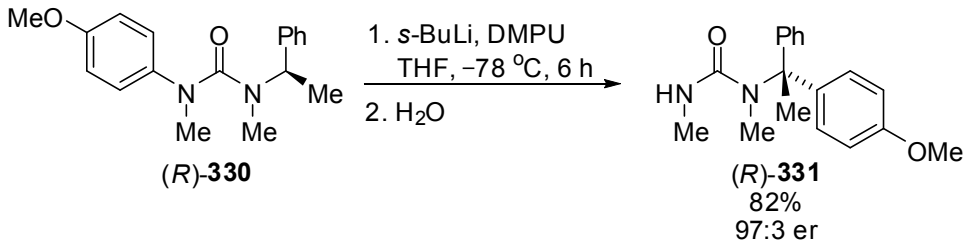
Another example of the benzylic lithiation of *N*-Boc amines was reported by Wallace in 2009.[221] Thus, treatment of methyl *N*-Boc azepine **327** with *s*-BuLi in THF and then trapping with methyl iodide gave a 50% yield of *trans*-**328**, a 6% yield of *cis*-**328** and a 28% yield of *gem*-dimethyl product **329** (scheme 6.15).

Scheme 6.15



Clayden has reported a number of interesting benzylic lithiation-aryl migration protocols. In the first such example, benzylic lithiation of ureas was used to gain access to compounds containing tertiary and quaternary nitrogen bearing stereocentres. For example, treatment of urea (*R*)-**330** with *s*-BuLi and DMPU in THF followed by quenching with water gave product (*R*)-**331** in 82% yield and 97:3 er (scheme 6.16).[222]

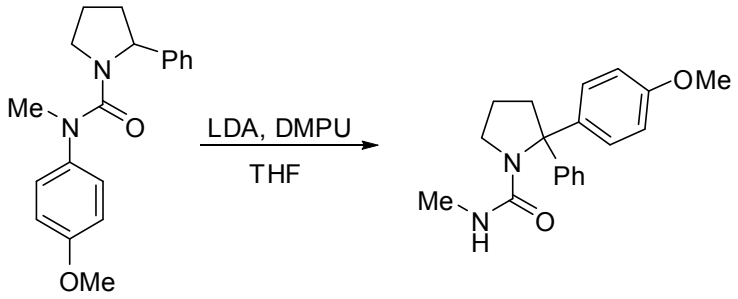
Scheme 6.16



(*R*)-**330** (*R*)-**331** 82% 97:3 er

The same group also reported similar benzylic lithiation-aryl migration procedures on carbamates, giving access to α-arylated benzylic alcohols,[223] and thiocarbamates, forming the analogous thiols.[224] More relevant to our work, it was also found that lithiation-aryl migration could be effected on cyclic ureas. For example, treatment of pyrrolidine urea *rac*-**332** with LDA and DMPU and then quenching resulted in the isolation of 2,2-biaryl pyrrolidine urea *rac*-**333** in 89% yield (scheme 6.17). Lithiation-aryl migration was also reported on other cyclic ureas, but not on enantioenriched substrates.[225]

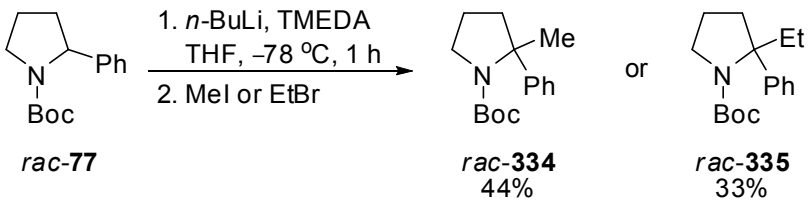
Scheme 6.17



rac-**332** *rac*-**333** 89%

Xiao and co-workers at Schering-Plough have reported the *n*-BuLi/TMEDA-mediated lithiation of racemic *N*-Boc-2-phenylpyrrolidine *rac*-**77**.[226] Lithiation of *rac*-**77** using *n*-BuLi/TMEDA followed by trapping with methyl iodide or ethyl bromide gave products *rac*-**334** and *rac*-**335** in 44% yield and 33% yield respectively (scheme 6.18). No other electrophiles or lithiation conditions were investigated. While not discussed by the authors, we believe that the modest yields obtained may due to a lack of interconversion of the *N*-Boc rotamers under the lithiation conditions used (*n*-BuLi/TMEDA in THF at –78 °C for 1 h and then electrophilic trapping).[226]

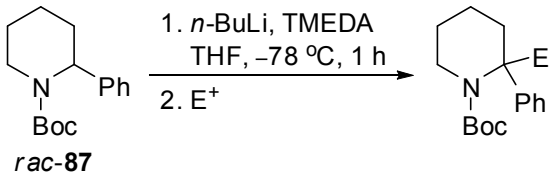
Scheme 6.18



rac-**77** *rac*-**334** 44% *rac*-**335** 33%

Using the same conditions, lithiation-trapping of racemic 2-phenylpiperidine was also carried out. The results are summarised in table 6.1.

Table 6.1



rac-**87**

Entry	Electrophile	Product	%Yield
1	MeOD	*rac*-**336**	94[a]
2	MeI	*rac*-**337**	51
3	AllylBr	*rac*-**338**	43
4	DMF	*rac*-**339**	52
5	MeCHO	*rac*-**340**	59[b]

a 2 h lithiation time used.

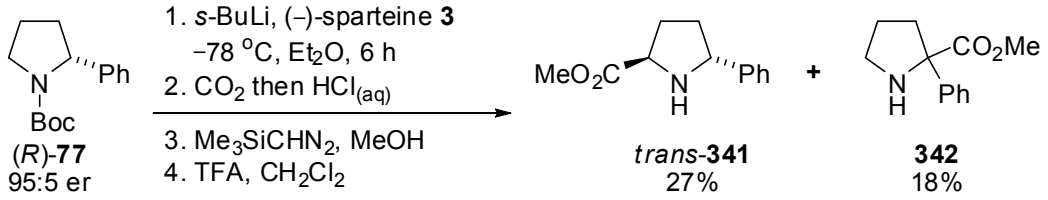
b 1:1.4 mixture of diastereomers obtained

Higher yields of trapped products were obtained from lithiation trapping of *N*-Boc-2-phenyl piperidine *rac*-**87** than from *N*-Boc-2-phenylpyrrolidine *rac*-**77**. For example, deuteration *via* quench with MeOD gave *rac*-**336** in 94% yield (entry 1). Lower yields were obtained with other electrophiles. Trapping with methyl iodide gave *rac*-**337** in 51% yield (entry 2), while allyl bromide gave *rac*-**338** in 43% yield (entry 3). Carbonyl electrophiles were also investigated. Use of DMF gave *rac*-**339** in 52% yield (entry 4), while trapping with acetaldehyde gave *rac*-**340** in 59% yield in a 1:1.4 mixture of unresolved diastereomers (entry 5). The high yield obtained when trapping with MeOD suggests that *N*-Boc rotamer interconversion is not an issue for this substrate.

Finally, our group has published an isolated example of a benzylic lithiation-derived disubstituted pyrolidine obtained as an unwanted side-product. Thus, *s*-BuLi/(–)-sparteine

3-mediated lithiation of *N*-Boc-2-phenyl pyrrolidine (*R*)-**77** followed by trapping with carbon dioxide and then *in situ* methylation of the resultant acid and TFA-mediated Boc deprotection gave desired product *trans*-**341** in 27% yield, and **342** in 18% yield. The er of **342** was not determined (scheme 6.19).[59]

Scheme 6.19

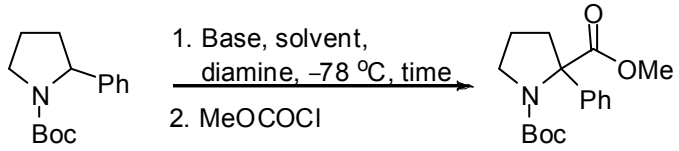


The aim of this part of the project was to build on the results reported by the Schering-Plough group and attempt to obtain higher yields of trapped products, with a wider range of electrophiles. Additionally, it was hoped that lithiation-trapping of enantioenriched starting material (prepared by asymmetric lithiation-arylation of *N*-Boc pyrrolidine **38**) would provide us with products bearing quaternary stereocentres in high ers.

6.3 Benzylic Lithiation-Trapping of Racemic Phenylpyrrolidine

To begin our investigations, racemic *N*-Boc-2-phenylpyrrolidine *rac*-**77** (prepared using the racemic lithiation-arylation procedure developed in chapter 5) was treated with *s*-BuLi or *n*-BuLi in THF or diethyl ether at –78 °C for a range of different lithiation times. TMEDA was added as a ligand in some examples. The lithiated phenyl pyrrolidine thus obtained was then trapped with methyl chloroformate to give disubstituted product *rac*-**343**. The results of this optimisation study are shown in table 6.2.

Table 6.2



rac-**77** *rac*-**343**

Entry	Base	Solvent	Diamine	Time(min)	%Yield[a]
1	*s*-BuLi	THF	None	30	17
2	*n*-BuLi	THF	None	60	33
3	*n*-BuLi	THF	None	180	39
4	*n*-BuLi	THF	TMEDA	60	31
5	*n*-BuLi	THF	TMEDA	180	33
6	*n*-BuLi	Et_2O	TMEDA	60	29
7	*n*-BuLi	Et_2O	TMEDA	180	32

[a] %Yield after chromatography

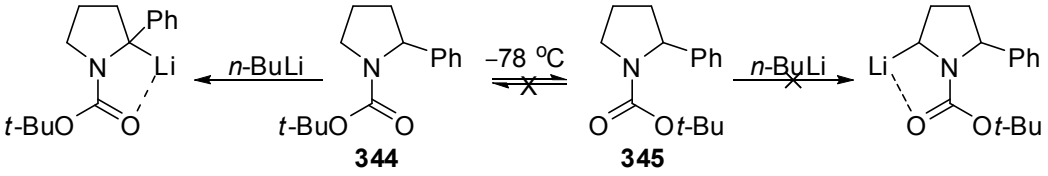
Lithiating *N*-Boc-2-phenylpyrrolidine *rac*-**77** with *s*-BuLi in THF at –78 °C for 30 min followed by trapping gave only a 17% yield of 2,2-disubstituted product *rac*-**343** (entry 1). No starting material was recovered. We believe that the low yield can be accounted for by competing lithiation in the 5-position, but it was not possible to adequately purify the 2,5-disubstituted products.

Changing the base led to an increase in yield. Treating starting material *rac*-**77** with *n*-BuLi in THF at –78 °C and then trapping gave 33% yield of *rac*-**343** after a lithiation time of 60 min (entry 2) and 39% yield after 180 min (entry 3). Addition of TMEDA did not improve the yield. After lithiation with *n*-BuLi and TMEDA in THF at –78 °C, disubstituted product *rac*-**343** was obtained in 31% yield after 60 min (entry 4) and in 33% yield after 180 min. Next, we investigated changing the solvent. Lithiation-trapping with *n*-BuLi and TMEDA in diethyl ether at –78 °C for 60 min and then addition of methyl chloroformate gave a 29% yield of *rac*-**343** (entry 6). Extending the lithiation

time to 180 min resulted in a 32% yield of disubstituted product *rac*-**343** being obtained (entry 7). These results are essentially the same as those in THF alone or in THF with TMEDA.

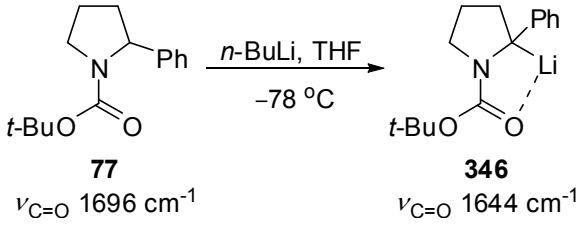
We hypothesised that the modest yields observed when lithiating at –78 °C were due to a lack of interconversion of *N*-Boc rotamers. Thus, *n*-BuLi-mediated lithiation of rotamer **344** was facile, whereas rotamer **345** was unreactive to *n*-BuLi, as noted by Beak for *N*-Boc pyrrolidine **38** (scheme 6.20).[52]

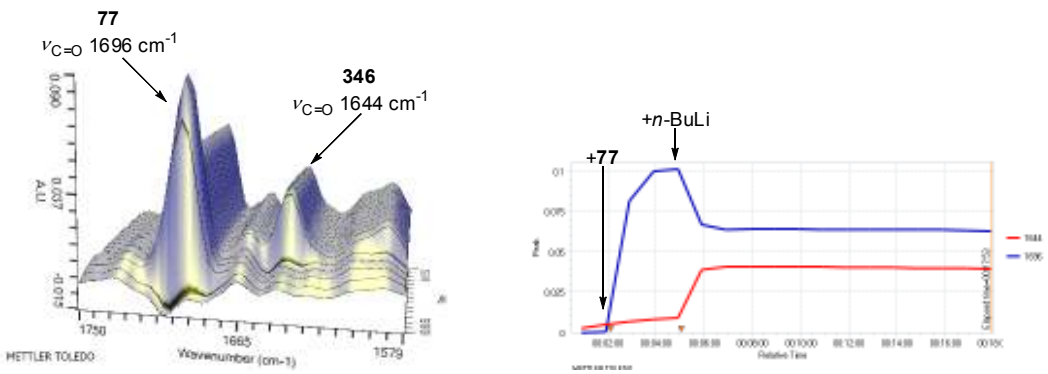
Scheme 6.20



To probe the behaviour of the *N*-Boc rotamers, we decided to monitor the progress of the benzylic lithiation using *in situ* infra-red monitoring. First, *n*-BuLi/THF-mediated lithiation at –78 °C was investigated. *N*-Boc-2-phenyl pyrrolidine **77** ($\nu_{C=O}$ 1696 cm^{-1}) was stirred in THF at –78 °C and then *n*-BuLi was added. Lithiation to give lithiated product **346** ($\nu_{C=O}$ 1644 cm^{-1}) took place (scheme 6.21).

Scheme 6.21



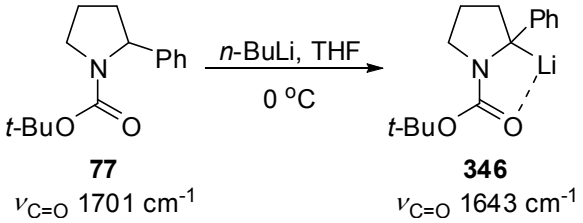


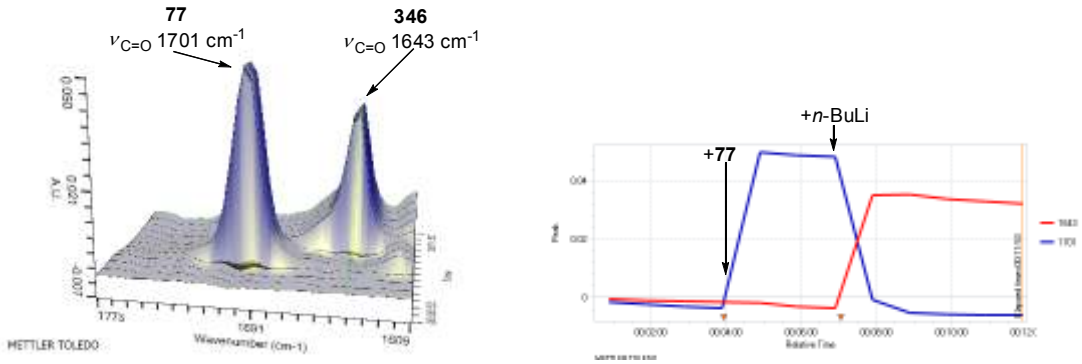
Lithiation of the reactive *N*-Boc rotamer **344** was fast, and complete within 2 min. Then, no further formation of lithiated product was observed since, presumably, the

unreactive rotamer **345** was not interconverting to the reactive one. The roughly 60:40 mixture of starting material **77** and lithiated product **346** observed after reaction of one rotamer would explain the 33% yield of trapped product **343** obtained from synthetic experiments carried out at –78 °C (Table 6.2).

Then, lithiation at 0 °C was followed using ReactIR. Thus, *N*-Boc-2-phenylpyrrolidine **77** ($\nu_{C=O}$ 1701 cm^{-1}) was stirred in THF at 0 °C and then *n*-BuLi was added. A new peak appeared at $\nu_{C=O}$ 1643 cm^{-1} and was assigned to lithiated species **346** (scheme 6.22).

Scheme 6.22

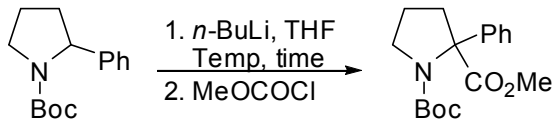




After addition of *n*-BuLi, complete lithiation to give lithiated product **346** was observed within 2 min, confirming that the *N*-Boc rotamers were interconverting. We thus concluded that lithiation-trapping of *N*-Boc-2-phenylpyrrolidine **77** at 0 °C should allow us to isolate 2,2-disubstituted products in high yields.

To determine whether high yields of trapped products could be obtained, *N*-Boc-2-phenyl pyrrolidine *rac*-**77** was lithiated using *n*-BuLi in THF at 0 °C and rt and then trapped with methyl chloroformate to give *rac*-**343**. The results are shown in table 6.3.

Table 6.3



rac-**77** *rac*-**343**

Entry	Temperature(°C)	Time(min)	%Yield[a]
1	–78	180	39
2	–78	60	33
3	0	10	72
4	0	5	77
5	rt	5	41

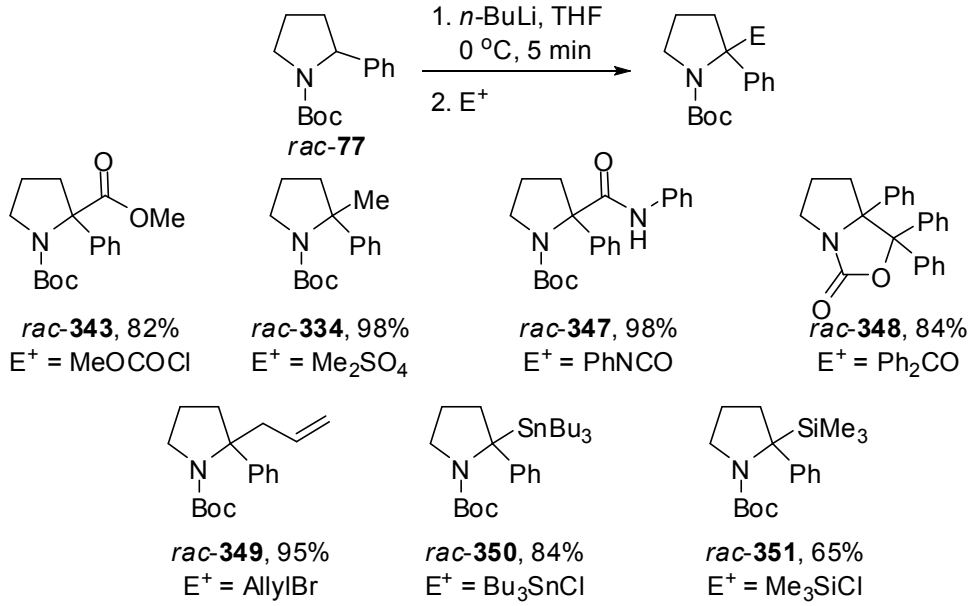
a %Yield after chromatography

Thus, *N*-Boc-2-phenylpyrrolidine *rac*-**77** was treated with *n*-BuLi in THF at 0 °C for 5 min and then trapped with methyl chloroformate. A 77% yield of product **343** was obtained (entry 4). Lithiation under the same conditions for 10 min gave a 72% yield of **343** (entry 3). These yields compare favourably with the previously discussed lithiations at –78 °C (entries 1 and 2). Raising the temperature even further led to reduced yields: a 41% yield of **343** was obtained after lithiation of starting material **77** with *n*-BuLi in THF at rt for 5 min followed by trapping (entry 5). The conditions shown in entry 4 (lithiation with *n*-BuLi for 5 min in THF) were chosen for our optimal racemic benzylic lithiation procedure.

With an optimised route to racemic 2,2-disubstituted pyrrolidine *rac*-**343** in hand, the synthesis of a range of products using different electrophiles was studied (scheme 6.23).

A 98% yield of disubstituted products *rac*-**334** and *rac*-**347** was obtained when trapping with dimethyl sulfate and phenyl isocyanate. Use of benzophenone as an electrophile gave oxazolidinone *rac*-**348** in 84% yield *via* cyclisation of the alkoxide onto the Boc group. Direct trapping with allyl bromide gave *rac*-**349** in 95% yield. An 84% yield of stannane *rac*-**350** was obtained when using tri-*n*-butyltin chloride. Slightly reduced yield was observed when trapping with trimethylsilyl chloride: silyl pyrrolidine *rac*-**351** was obtained in 65% yield.

Scheme 6.23

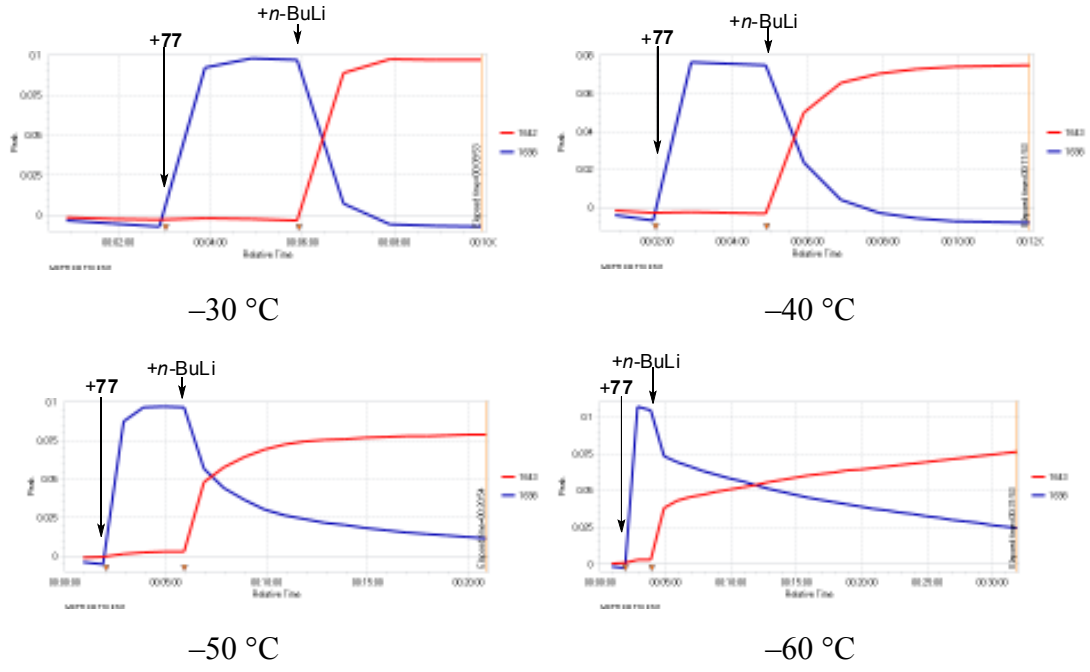


Our racemic benzylic lithiations are an improvement on the results reported by the Schering-Plough group. For example, methylation was achieved in 98% yield under our conditions (electrophile = Me_2SO_4) but in only 44% yield as reported by Xiao and Lavey (electrophile = MeI).[226] The development of a high temperature lithiation protocol to overcome the yield limitation imposed by the lack of *N*-Boc rotamer interconversion was informed by the lithiation of *N*-Boc-*N*′-*i*-Pr imidazolidine **64** discussed in chapter 5. Using our racemic lithiation-arylation of *N*-Boc pyrrolidine **38** and then our new high temperature benzylic lithiation-trapping method, we have developed a 2-step route to 2,2-disubstituted pyrrolidines in high yields, without the need for carrying out either reaction at –78 °C.

6.4 Benzylic Lithiation-Trapping of Enantioenriched Phenylpyrrolidine

Having successfully developed racemic benzylic lithiation of *N*-Boc-2-phenylpyrrolidine *rac*-**77**, we next investigated lithiation of enantioenriched (*R*)-**77**. We were concerned that at high temperatures (*e.g.* 0 °C), racemisation of lithiated *N*-Boc-2-phenyl pyrrolidine (*R*)-**77** would take place. On the other hand, at low temperatures (*e.g.* –78 °C), low yields would be obtained due to a lack of *N*-Boc rotamer interconversion. Thus, we first decided to use *in situ* infra-red spectroscopy to monitor the progress of lithiations at –30 °C, –40 °C, –50 °C and –60 °C to determine the temperature at which *N*-Boc rotamer interconversion became too slow for synthetically useful conversions. *N*-Boc-2-phenyl pyrrolidine **77** ($\nu_{C=O}$ 1698 cm^{-1}) was stirred in THF at –30 °C, –40 °C, –50 °C or –60 °C and then *n*-BuLi was added. The peak corresponding to $\nu_{C=O}$ in the lithiated product **346** appeared at 1642 or 1643 cm^{-1}. The results are shown in figure 6.2.

Figure 6.2

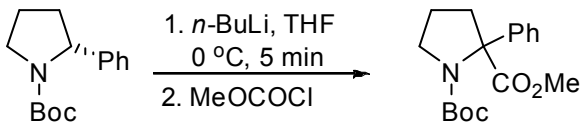


At –30 °C and –40 °C, interconversion of the *N*-Boc rotamers was fast, and complete lithiation was observed in 3 min. At –50 °C, rotamer interconversion began to slow down. Fast lithiation of the reactive rotamer in 1 min was observed, and then interconversion and lithiation of the remaining rotamer took another 5 min. Further cooling to –60 °C slowed *N*-Boc C-N bond rotation further still. Lithiation of the reactive

rotamer was complete in 1 min, but then conversion and lithiation of the remaining starting material was still incomplete after 30 min.

Next, we carried out a lithiation of enantioenriched starting material under our optimised conditions racemic conditions. Thus, *N*-Boc-2-phenylpyrrolidine (*R*)-**77** of 97:3 er (synthesised using an asymmetric Negishi reaction using (–)-sparteine **3**) was treated with *n*-BuLi in THF at 0 °C for 5 min and then methyl chloroformate was added. After work-up and purification, product **343** was obtained in 82% yield and 50:50 er: complete racemisation had not surprisingly taken place (scheme 6.24).

Scheme 6.24

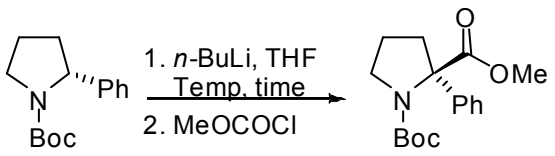


(*R*)-**77**
97:3 er

rac-**343**
82%
50:50 er

Instead, lithiation of (*R*)-**77** of 97:3 er using *n*-BuLi in THF and then trapping with methyl chloroformate was investigated at a range of different temperatures. The results of this study are shown in table 6.4.

Table 6.4



(*R*)-**77**
97:3 er

(*R*)- or (*S*)-**343**

Entry	Temperature (°C)	Time (min)	%Yield[a]	Product er[a]
1	–78 °C	60	31	97:3
2	–50 °C	10	74	90:10
3	–50 °C	5	78	94:6
4	–40 °C	5	69	85:15
5	–30 °C	5	79	65:35

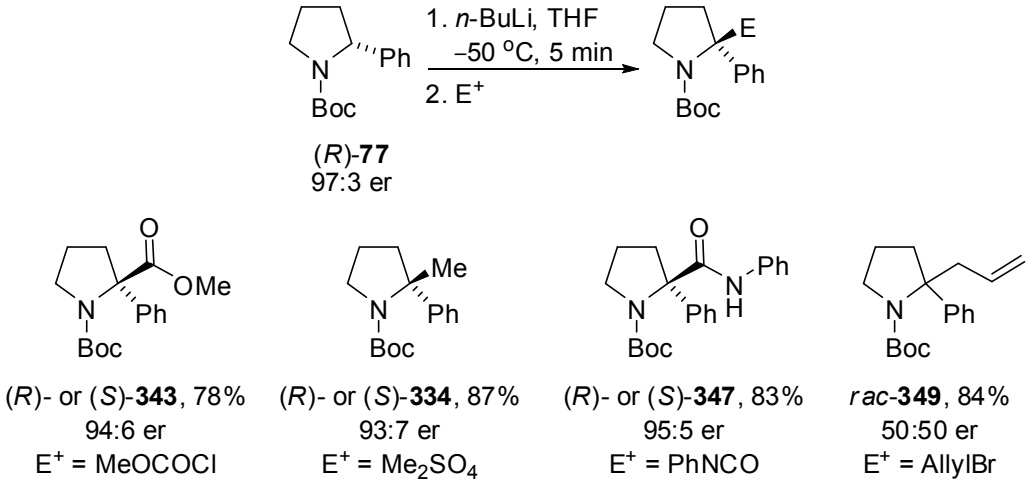
[a] %Yield after chromatography, er determined by CSP-HPLC

First, we verified that no epimerisation would take place at low temperature. Lithiation of (*R*)-**77** of 97:3 er using *n*-BuLi in THF at –78 °C for 1 h gave a 31% yield of product (*R*)- or (*S*)-**343** in 97:3 er (entry 1). Next, we investigated lithiations at –30 °C, –40 °C

and –50 °C. Significant racemisation took place at –30 °C. Lithiation of (*R*)-**77** of 97:3 er in THF at –30 °C for 5 min gave product (*R*)- or (*S*)-**343** in 79% yield but 65:35 er (entry 5). At –40 °C, lithiation of phenylpyrrolidine (*R*)-**77** of 97:3 er for 5 min in THF gave (*R*)- or (*S*)-**343** in 69% yield and 85:15 er (entry 4). Finally, lithiation at –50 °C was investigated. Treatment of *N*-Boc-2-phenylpyrrolidine (*R*)-**77** of 97:3 er in THF at –50 °C for 5 min followed by trapping with methyl chloroformate afforded product (*R*)- or (*S*)-**343** in 78% yield and 94:6 er (entry 3). These were found to be the optimal conditions. Enantiomerisation still took place slowly at –50 °C, as lengthening the lithiation time to 10 min gave product (*R*)- or (*S*)-**343** in 74% yield and 90:10 er (entry 2).

With an optimal set of conditions for lithiation of *N*-Boc-2-phenylpyrrolidine (*R*)-**77** in hand, lithiation-trapping was carried out with a small range of electrophiles using a sample of (*R*)-*N*-Boc-2-phenyl pyrrolidine of 97:3 er (scheme 6.25).

Scheme 6.25



Trapping with dimethyl sulfate gave *N*-Boc-2-methyl-2-phenylpyrrolidine (*R*)- or (*S*)-**334** in 87% yield and 93:7 er. Use of phenyl isocyanate yielded amide (*R*)- or (S)-**347** in 83% yield and 95:5 er. Trapping with allyl bromide gave an 84% yield of *racemic* product *rac*-**349**. We propose that trapping occurs *via* a single electron transfer process, leading to racemisation. Future work may include attempting to access enantioenriched allylated products *via* lithium-copper exchange.

These products have been drawn assuming retention of stereochemistry through lithiation-trapping. However, at present, the absolute configuration of **334**, **343** or **347** has not been unequivocally established.

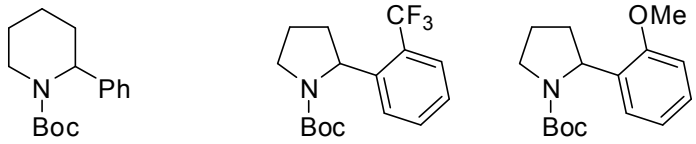
6.5 Conclusions and Future Work

A successful procedure for the lithiation-trapping of *N*-Boc-2-phenylpyrrolidine **77** has been developed. Lithiation trapping of racemic **77** was optimised, and use of a range of electrophiles was demonstrated under the optimal conditions (5 min at 0 °C in THF). It was found that lithiation of enantioenriched starting material (97:3 er) under these conditions gave racemic product. Instead, lithiation at lower temperatures (5 min in THF at –50 °C) gave products of ≥93:7 er in high yields. A small range of different electrophiles was then assayed under these conditions. The use of *in situ* infra-red spectroscopic monitoring of lithiations was of crucial importance in developing both lithiation procedures.

Future work will focus on trapping with different electrophiles to access solid products and thus ascertain the product configuration by X-ray crystallography, determining whether lithiation-trapping of enantioenriched *N*-Boc-2-phenyl pyrrolidine (*R*)-**77** proceeds with retention or inversion of stereochemistry.

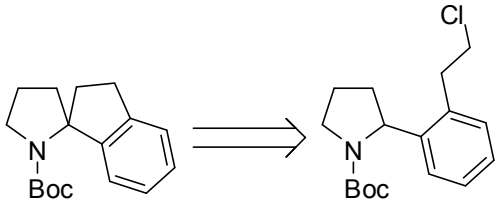
Other potential future work may involve benzylic-lithiation trapping of *N*-Boc-2-phenyl piperidine **87**, or substituted 2-aryl pyrrolidines such as **181** and **183** (figure 6.3). Another potential future development could be the synthesis of spirocyclic compounds (*e.g.* **352**) *via* benzylic lithiation and internal electrophilic trap of aryl pyrrolidines such as **353** (scheme 6.26).

Figure 6.3



87 **183** **181**

Scheme 6.26



352 **353**

Chapter Seven: Experimental

7.1 General Methods

All non-aqueous reactions were carried out under oxygen free Ar using flame-dried glassware. Et_2O and THF were dried on a Pure Solv MD-7 solvent purification system or distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[227] 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 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. Preparative thin layer chromatography was carried out using Analtech alumina matrix TLC uniplates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) 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 given for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. For compounds purified by fractional distillation, boiling points correspond to the vapor temperature at the top of the Vigreaux column. Infra-red spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recored at room temperature on a Jasco DIP-370 polarimeter (using sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. Chiral stationary phase GC was performed on either an Agilent 6890 gas chromatograph using the column indicated for individual compounds, or a Perkin Elmer Autosystem XL gas chromatograph. *In situ* ReactIR infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer equipped with a silicon-tipped (SiComp) probe.

7.2 General Procedures

General Procedure A: Stoichiometric lithiation-trapping of *N*-Boc pyrrolidine 38

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (342 mg, 350 μL, 2.0 mmol) and diamine (1.3 eq.) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 or 3 h. Then, the electrophile (2.0 eq.) was added and the resulting solution was stirred at –78 °C for 10 min and allowed to warm to rt. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: Catalytic two-ligand lithiation-trapping of *N*-Boc pyrrolidine 38

s-BuLi (1.3 M solution in hexanes, 1.0-1.6 eq.) was added dropwise to a stirred solution of chiral diamine (0.2-0.3 eq.) and achiral diamine (1.0-1.3 eq.) in Et_2O (6 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *N*-Boc pyrrolidine **38** (161 mg, 165 μL, 0.94 mmol) in Et_2O (1 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 4 h. Then, benzaldehyde (2.0 eq.) was added and the resulting solution was allowed to warm to rt over 16 h. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: Catalytic two-ligand lithiation-Negishi trapping of *N*-Boc pyrrolidine 38

s-BuLi (1.3 M solution in hexanes, 1.0-1.6 eq.) was added dropwise to a stirred solution of chiral diamine (0.25-0.3 eq.) and achiral diamine (1.0-1.3 eq.) in Et_2O (6 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *N*-Boc pyrrolidine **38** (493 mg, 493 μL, 2.88 mmol) in Et_2O (1 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 4 h. Then, $ZnCl_2$ (1.0 M solution in Et_2O, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min. Then, the aryl bromide (0.7 eq.) was added. A mixture of *t*-Bu_3PHBF_4 (6.25 mol%) and $Pd(OAc)_2$ (5 mol%) was added in one portion

and the resulting mixture was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (2 × 10 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure D: Stoichiometric lithiation-arylation of *N*-Boc pyrrolidine 38

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and (–)-sparteine (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, $ZnCl_2$ (1.0 M solution in Et_2O, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min. Then, the aryl bromide (0.7 eq.) was added. A mixture of *t*-Bu_3PHBF_4 (6.25 mol%) and $Pd(OAc)_2$ (5 mol%) was added in one portion and the resulting mixture was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure E: Lithiation-vinylation of *N*-Boc pyrrolidine 38

s-BuLi (1.3 M solution in hexanes, 1.0 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (219 mg, 225 μL, 1.28 mmol, 1.0 eq.) and (–)-sparteine (1.3 eq.) in Et_2O or TBME (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, $ZnCl_2$ (1.0 M solution in Et_2O, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, a solution of vinyl bromide **227** (0.7 eq.) in Et_2O or TBME (1 mL) was added. A mixture of $Pd(OAc)_2$ (5 mol%) or Pd_2dba_3 (2.5 mol%) and *t*-Bu_3PHBF_4 (6.25 mol%) was added in one portion and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.5 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (20 mL). The filtrate was washed with 10% $NH_4Cl_{(aq)}$, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure F: TFA-mediated Boc deprotection

TFA (5-20 eq.) was added dropwise to a stirred solution of *N*-Boc amine (750 mg, 3.02 mmol) in CH_2Cl_2 (40 mL) at rt under Ar. The resulting solution was stirred at rt for 4-16 h. The resulting solution was evaporated under reduced pressure. 5 M $NaOH_{(aq)}$ (20 mL) and Et_2O (45 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (7 × 45 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure G: Eschweiler-Clarke methylation

A solution of unprotected pyrrolidine (169 mg, 1.14 mmol), paraformaldehyde (5 eq.) and formic acid (5 eq.) in H_2O (15 mL) under air was stirred and heated at reflux for 16 h. Then, the solvent was evaporated under reduced pressure. 5 M $NaOH_{(aq)}$ (10 mL) and Et_2O (25 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (8 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure H: Lithiation-benzaldehyde trapping of *N*-Boc pyrrolidine 38

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 **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in Et_2O, THF or 2-methyl THF (7 mL) at –78 °C, –40 °C, –30 °C, –20 °C, –10 °C or 0 °C under Ar. The resulting solution was stirred at the specified temperature for 1 min, 2 min, 5 min, 10 min, 30 min or 60 min. Then, benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at the specified temperature for 10 min and allowed to warm to rt. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure I: Attempted lithiation-trapping of *N*-Boc pyrrolidine 38 with *n*-BuLi or LDA

n-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) or LDA (1.0 mL of a 1.3 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C, –40 °C, –20 °C, 0 °C or rt under Ar. The resulting

solution was stirred at the specified temperature for 30 min, 60 min or 180 min. Then, benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) or benzyl bromide (342 mg, 238 μL, 2.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at the specified temperature for 10 min and allowed to warm to rt. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure J: Attempted lithiation-trapping of *N*-Boc piperidine 44 and *N*-Boc homopiperidine 56

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 piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) or *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C, –40 °C or –30 °C under Ar. The resulting solution was stirred at the specified temperature for 5 min, 30 min, 60 min, 180 min or 360 min. Then, DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) or methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at the specified temperature for 10 min and allowed to warm to rt. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure K: Optimised lithiation-trapping of *N*-Boc heterocycles using *s*-BuLi in THF

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 heterocycle (1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, the electrophile (2.0 mmol) was added and the resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 15 min. 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) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure L: Racemic arylation of *N*-Boc pyrrolidine 38

s-BuLi (10 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 **38** (1.71 g, 1.75 mL, 10.0 mmol) in THF (70 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, $ZnCl_2$ (6.0 mL of a 1.0 M solution in Et_2O, 6.0 mmol, 0.6 eq.) was added and the resulting solution was stirred at –30 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min.

Aryl bromide (0.7 mmol) was added to a stirred 7.0 mL aliquot of arylzinc reagent at rt. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%) and *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) were added in one portion and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ was added and the solution was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (20 mL). The filtrate was washed with a 1 M $HCl_{(aq)}$ (20 mL) and saturated brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure M: Lithiation-trapping of imidazolidine 64

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′*-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 or 10 min. Then, the electrophile (2.0 mmol) was added and the resulting solution was stirred at –30 °C for 10 min and then allowed to warm to rt over 15 min. Saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure N: Diamine free lithiation-methyl chloroformate trapping of phenyl pyrrolidine *rac*-77

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) or *n*-BuLi (2.5 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-2-phenylpyrrolidine *rac*-**77** (100 mg, 0.4 mmol) in THF (4 mL) at –78 °C, 0 °C or rt under Ar. The resulting solution was stirred at the specified temperature for 5 min, 10 min, 30 min, 60 min or 180 min. Then, methyl chloroformate (2.0 eq.) was added dropwise and the resulting solution was stirred at the specified temperature for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (6

mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure O: TMEDA-mediated lithiation-methyl chloroformate trapping of phenyl pyrrolidine *rac*-77

n-BuLi (2.5 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-2-phenylpyrrolidine *rac*-**77** (100 mg, 0.4 mmol) and TMEDA (1.3 eq.) in THF (4 mL) or Et_2O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 60 min or 180 min. Then, methyl chloroformate (2.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (6 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure P: Lithiation-trapping of phenyl pyrrolidine *rac*-77

n-BuLi (2.5 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-2-phenylpyrrolidine *rac*-**77** (110 mg, 0.44 mmol) in THF (4 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 min. Then, the electrophile (2.0 eq.) was added dropwise and the resulting solution was stirred at 0 °C for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (6 mL) as added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure Q: Lithiation-methyl chloroformate trapping of phenyl pyrrolidine (*R*)-77

n-BuLi (2.5 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-2-phenylpyrrolidine (*R*)-**77** (70 mg, 0.28 mmol, 97:3 er) in THF (4 mL) at –78 °C, –50 °C, –40 °C, –30 °C or 0 °C under Ar. The resulting solution was stirred at the specified temperature for 5 min, 10 min or 60 min. Then, the electrophile (2.0 eq.) was added dropwise and the resulting solution was stirred at the specified temperature for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (6 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the

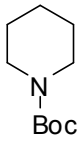
combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure R: Lithiation-trapping of phenyl pyrrolidine (*R*)-77

n-BuLi (2.5 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-2-phenylpyrrolidine (*R*)-**77** (46 mg, 0.18 mmol, 97:3 er) in THF (4 mL) at –50 °C under Ar. The resulting solution was stirred at –50 °C for 5 min. Then, the electrophile (2.0 eq.) was added dropwise and the resulting solution was stirred at –50 °C for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (6 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

7.3 Experimental for Chapter 2

N-Boc Piperidine 44[119]

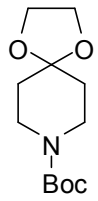


44

Piperidine (11.7 g, 11.7 mL, 137.5 mmol) was added dropwise to a stirred solution of di-*t*-butyl dicarbonate (20.0 g, 91.64 mmol) in THF (100 mL) at 0 °C under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 30 min. Then, 10% $NaHCO_{3(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with saturated brine (300 mL), dried (K_2CO_3) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc piperidine **44** (14.55 g, 86%) as a colourless oil, bp 100-110 °C/0.2 mmHg (lit.,[119] bp 60-70 °C/1.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46-3.23 (m, 4H, NCH_2), 1.69-1.43 (m, 6H, CH_2), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 78.8 (*C*Me$_3$), 44.2 (br s, NCH_2), 28.2 (C*Me*$_3$), 25.5 (NCH_2CH_2), 24.3 ($NCH_2CH_2CH_2$). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book Reference GB6/489

1,4-Dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester 49

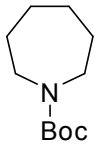


49

A solution of *N*-Boc-4-piperidone (6.03 g, 30.26 mmol), *p*-toluenesulfonic acid monohydrate (4.22 mg, 2.22 mmol) and diethylene glycol (18.78 g, 16.88 mL, 302.6 mmol) in toluene (150 mL) was stirred and heated at reflux under Dean-Stark conditions for 72 h. After cooling to rt, the solvent was evaporated under reduced pressure and CH_2Cl_2 (60 mL) was added. The organic solution was washed with

saturated $NaHCO_{3(aq)}$ (60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave the acetal piperidine **49** (5.10 g, 69%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.6; bp180-190 °C/0.4 mmHg; IR($CHCl_3$) 3010, 2978, 2882, 1683 (C=O), 1426, 1366, 1244, 1171, 1114, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 4H, OCH_2), 3.48 (t, J = 5.5 Hz, 4H, NCH_2), 1.63 (t, J = 5.5 Hz, 4H, NCH_2CH_2), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.0 (C=O), 107.1 (OCO), 79.5 (CMe_3), 64.3 (OCH_2), 41.6 (NCH_2), 34.8 (NCH_2CH_2), 28.3 (CMe_3); MS (ESI) *m/z* 266 [$(M + Na)^+$, 24], 244 [$(M + H)^+$, 5], 188 (16), 144 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_4$ $(M + Na)^+$ 266.1363, found 266.1360 (–2.9 ppm error).
Lab Book Reference GB6/516

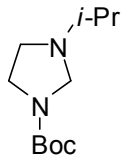
Azepane-1-carboxylic acid *tert*-butyl ester 56[119]



56

A solution of hexamethylene imine (5.82 g, 6.75 mL, 58.69 mmol) in THF (15 mL) was added dropwise to a stirred solution of di-*t*-butyl dicarbonate (12.2 g, 55.9 mmol) at 0 °C under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 30 min. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc azepine **56** (8.93 g, 80%) as a colourless oil, bp 110-115 °C/1.0 mmHg; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 3.36 (t, J = 6.0 Hz, 1H, NCH_2), 3.29 (t, J = 6.0 Hz, 1H, NCH_2), 3.32-3.24 (m, 2H, NCH_2), 1.71-1.55 (m, 4H, NCH_2CH_2), 1.55-1.47 (m, 4H, $NCH_2CH_2CH_2$), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.5 (C=O), 78.6 (CMe_3), 46.8 (NCH_2), 46.4 (NCH_2), 28.3 (CMe_3), 27.3 (CH_2), 26.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[119]
Lab Book Reference GB6/490

3-Isopropyl imidazolidine-1-carboxylic acid *tert*-butyl ester 64[74]

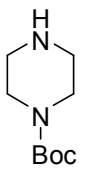


64

N-*i*-Pr-ethylene diamine (5.0 g, 6.1 mL, 48.93 mmol) was added dropwise to a stirred suspension of paraformaldehyde (1.47 g, 48.93 mmol), K_2CO_3 (22.8 g, 165.0 mmol) and $MgSO_4$ (22.75 g, 189.0 mmol) in $CHCl_3$ (165 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, di-*t*-butyl dicarbonate (10.68 g, 48.93 mmol) 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 **64** (9.12 g, 87%) as a colourless oil, bp 165-167 °C/12.0 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 3.97 (s, 1H, NCH_2N), 3.90 (s, 1H, NCH_2N), 3.41 (t, J = 6.5 Hz, 1H, $BocNCH_2$), 3.37 (t, J = 6.5 Hz, 1H, $BocNCH_2$), 2.76 (t, J = 6.5 Hz, 1H, NCH_2), 2.75 (t, J = 6.5 Hz, 1H, NCH_2), 2.37 (septet, J = 6.5 Hz, 0.5 H, NCH), 2.36 (septet, J = 6.5 Hz, 0.5 H, NCH), 1.39 (s, 9H, CMe_3), 1.05 (br d, J = 6.5 Hz, 6H, NCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.3 (C=O), 153.2 (C=O), 79.4 (*C*Me_3), 79.3 (*C*Me_3), 66.5 (NCH_2N), 66.5 (NCH_2N), 53.1 (NCH), 53.0 (NCH), 50.9 ($BocNCH_2$), 50.1 ($BocNCH_2$), 44.8 (NCH_2), 44.3 (NCH_2), 28.3 (C*Me*$_3$), 28.3 (C*Me*$_3$), 21.5 (NCH*Me*$_2$). Spectroscopic data consistent with those reported in the literature.[75]

Lab Book Reference GB7/597

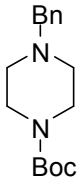
Piperazine-1-carboxylic acid *tert*-butyl ester[228]



A solution of di-*t*-butyl dicarbonate (7.62 g, 34.9 mmol) in CH_2Cl_2 (95 mL) was added dropwise to a stirred solution of piperazine (6.0 g, 69.6 mmol) in CH_2Cl_2 (190 mL) at rt. The resulting colourless solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (170 mL). The aqueous solution was extracted with CH_2Cl_2 (4 × 170 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-Boc piperazine (4.34 g, 67%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, J = 5.0 Hz, 4H, NCH_2), 2.80 (t, J = 5.0 Hz, 4H, NCH_2), 1.60 (br s, 1H, NH), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8 (C=O), 79.5 (*C*Me_3), 45.9 (NCH_2), 44.7 (NCH_2), 28.4 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[228]

Lab Book Reference GB7/598

4-Benzyl-piperazine-1-carboxylic acid ester 59[229]



59

N-Boc piperazine (4.67 g, 25.07 mmol) and K_2CO_3 (6.93 g, 50.15 mmol) were added portionwise to a stirred solution of benzyl chloride (3.17 g, 2.88 mL, 25.07 mmol) in EtOH (70 mL) at rt. The resulting white suspension was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressure and the residue was partitioned between H_2O (45 mL) and CH_2Cl_2 (45 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). 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 95:5 toluene-Et_2O as eluent gave *N*-Boc-*N*′-benzyl piperazine **59** (2.14 g, 31%) as a white solid, mp 72-74 °C (lit.,[230] 72-75 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H, Ar), 3.52 (s, 2H, $PhCH_2$), 3.43 (t, J = 5.0 Hz, 4H, $BocNCH_2$), 2.39 (t, J = 5.0 Hz, 4H, NCH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ 154.7 (C=O), 137.8 (*ipso*-Ph), 129.0 (Ph), 128.2 (Ph), 127.1 (Ph), 79.5 (*C*Me_3), 63.0

(Ph*C*H_2), 52.8 (BocNCH_2), 44.1 (NCH_2), 28.4 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[231]

Lab Book Reference GB6/515

ReactIR monitoring of the lithiation of *N*-Boc piperidine 44 by *s*-BuLi/TMEDA

(Scheme 2.8)

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 *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 90 min.

For *N*-Boc piperidine **44**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1674 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **120**. After addition of TMEDA, a new peak appeared at 1647 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **55**. After a lithiation time of 90 min, complete lithiation of *N*-Boc piperidine **44** to lithiated intermediate **55** was observed.

Lab Book Reference GB8/668

ReactIR monitoring of the lithiation of *N*-Boc piperidine 44 by *s*-BuLi/(–)-sparteine 3

(Scheme 2.9)

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 *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 3 min (to verify the stability of readout on ReactIR). The,n a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 40 min.

For *N*-Boc piperidine **44**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1676 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **122**. No other peaks were observed.
Lab Book Reference GB9/775

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/TMEDA
(Scheme 2.10)

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 *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, TMEDA (116 mg, 151 μL, 1.3 mmol) was added dropwise. The solutin was stirred at –78 °C for 15 min.

For *N*-Boc pyrrolidine **38**, a peak at 1699 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1681 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **123**. After addition of TMEDA, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of the lithiated intermediate **76**. After a lithiation time of 3 min, complete lithiation of *N*-Boc pyrrolidine **38** to lithiated intermediate **76** was observed.
Lab Book Reference GB8/666

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/(–)-sparteine 3
(Scheme 2.11)

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 *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 20 min.

For *N*-Boc pyrrolidine **38**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to prelithiation complex **124**. A new peak also appeared at 1646 cm^{-1} which was assigned to lithiated intermediate **125**. After a lithiation time of 20 min, complete lithiation of *N*-Boc pyrrolidine **38** to lithiated intermediate **125** was observed.
Lab Book Reference GB9/774

ReactIR monitoring of the lithiation of homopiperidine 56 by *s*-BuLi/TMEDA (Scheme 2.12)

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 homopiperidine **56** (199 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min.

For homopiperidine **56**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1673 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **126**. Upon addition of TMEDA, the peak at 1673 cm^{-1} decreased substantially, and the peak at 1695 cm^{-1} increased. Over the course of 30 min, new peak at 1631 cm^{-1} then emerged, assigned to $\nu_{C=O}$ of lithiated intermediate **127**. After a lithiation time of 30 min, incomplete lithiation of homopiperidine **56** to lithiated intermediate **127** was observed.
Lab Book Reference GB8/757

ReactIR monitoring of the lithiation of homopiperidine 56 by *s*-BuLi/TMEDA (Scheme 2.13)

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 homopiperidine **56** (199 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 40 min.

For homopiperidine **56**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1679 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **128**. A new peak also appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **127**. After a lithiation time of 40 min, incomplete lithiation of homopiperidine **56** to lithiated intermediate **127** was observed.
Lab Book Reference GB8/758

ReactIR monitoring of the lithiation of homopiperidine 56 by *s*-BuLi/(–)-sparteine 3
(Scheme 2.14)

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 homopiperidine **56** (199 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min.

For homopiperidine **56**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a peak appeared at 1679 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **129**. No peak corresponding to lithiated intermediate **130** was observed.
Lab Book Reference GB8/759

ReactIR monitoring of the lithiation of homopiperidine 56 by *s*-BuLi/(+)-sparteine surrogate 6
(Scheme 2.15)

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 homopiperidine **56** (199 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, a solution of (+)-sparteine surrogate **6** (258 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min.

For homopiperidine **56**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1679 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **131**. A new peak also appeared at 1638 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **132**. After a lithiation time of 30 min, incomplete lithiation of homopiperidine **56** to lithiated intermediate **132** was observed.
Lab Book Reference GB8/760

ReactIR monitoring of the lithiation of acetal piperidine 49 by *s*-BuLi/TMEDA (Scheme 2.16)

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 acetal piperidine **49** (243 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 40 min.

For acetal piperidine **49**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1676 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **133**. After addition of TMEDA, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **134**. After a lithiation time of 30 min, complete lithiation of acetal piperidine **49** to lithiated intermediate **134** was observed.
Lab Book Reference GB8/749

ReactIR monitoring of the lithiation of acetal piperidine 49 by *s*-BuLi/TMEDA (Scheme 2.17)

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 acetal piperidine **49** (243 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 3 min to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min.

For acetal piperidine **49**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **135**. A new peak also appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **134**. After a lithiation time of 20 min, complete lithiation of acetal piperidine **49** to lithiated intermediate **134** was observed.
Lab Book Reference GB9/773

ReactIR monitoring of the lithiation of acetal piperidine 49 by *s*-BuLi/(–)-sparteine 3

(Scheme 2.18)

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 acetal piperidine **49** (243 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min to verify the stability of readout on ReactIR). Then, a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 3 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 30 min.

For acetal piperidine **49**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **136**. A new peak also appeared at 1639 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **137**. After a lithiation time of 30 min, incomplete lithiation of acetal piperidine **49** to lithiated intermediate **137** was observed.
Lab Book Reference GB9/768

ReactIR monitoring of the lithiation of acetal piperidine 49 by *s*-BuLi/(+)-sparteine surrogate 6

(Scheme 2.19)

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 acetal piperidine **49** (243 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 3 min (to verify the stability of readout on ReactIR). Then, a solution of (+)-sparteine surrogate **6** (258 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a

1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 20 min.

For acetal piperidine **49**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1672 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **138**. A new peak also appeared at 1639 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **139**. After a lithiation time of 5 min, incomplete lithiation of acetal piperidine **49** to lithiated intermediate **139** was observed. No further lithiation of acetal piperidine **49** was observed.

Lab Book Reference GB9/769

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/TMEDA

(Scheme 2.20)

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 *N*-Boc-*N*′-benzylpiperazine **59** (270 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 20 min.

For *N*-Boc-*N*′-benzylpiperazine **59**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1679 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **140**. After addition of TMEDA, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **141**. After a lithiation time of 5 min, complete lithiation of *N*-Boc-*N*′-benzylpiperazine **59** to lithiated intermediate **141** was observed.

Lab Book Reference GB8/752

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/TMEDA

(Scheme 2.21)

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 *N*-Boc-*N*′-benzylpiperazine **59** (276 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 3 min (to verify the

stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min.

For *N*-Boc-*N*′-benzylpiperazine **59**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a small peak appeared at 1682 cm^{-1} for a single scan which was assigned to $\nu_{C=O}$ of prelithiation complex **142**. A new peak also appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **141**. After a lithiation time of 5 min, complete lithiation of *N*-Boc-*N*′-benzylpiperazine **59** to lithiated intermediate **141** was observed.

Lab Book Reference GB8/753

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/(–)-sparteine 3

(Scheme 2.22)

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 *N*-Boc-*N*′-benzylpiperazine **59** (276 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 80 min.

For *N*-Boc-*N*′-benzylpiperazine **59**, a peak at 1699 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **143**. A new peak also appeared at 1644 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **144**. After a lithiation time of 75 min, complete lithiation of *N*-Boc-*N*′-benzylpiperazine **59** to lithiated intermediate **144** was observed.

Lab Book Reference GB8/754

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/(+)-sparteine surrogate 6

(Scheme 2.23)

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 *N*-Boc-*N*′-benzylpiperazine **59** (276 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5

min (to verify the stability of readout on ReactIR). Then, a solution of (+)-sparteine surrogate **6** (258 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 15 min.

For *N*-Boc-*N*′-benzylpiperazine **59**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **144**. After a lithiation time of 3 min, complete lithiation of *N*-Boc-*N*′-benzylpiperazine **59** to lithiated intermediate **144** was observed. No peak corresponding to prelithiation complex **143** could be observed.

Lab Book Reference GB8/755

ReactIR monitoring of the lithiation of imidazolidine 64 by *s*-BuLi/TMEDA (–78 °C) (Scheme 2.24)

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 *N*-Boc-*N*′-isopropylimidazolidine **64** (214 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min. Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 15 min.

For *N*-Boc-*N*′-isopropylimidazolidine **64**, a peak at 1709 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1683 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **147** and another peak appeared at 1661 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **148**. After addition of TMEDA, a decrease in the peak at 1683 cm^{-1} was observed with a corresponding further increase in the peak at 1661 cm^{-1}. After a lithiation time of 8 min, partial lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** to lithiated intermediate **148** was observed. No further lithiation of *N*-Boc-*N*′-*i*-Pr imidazolidine **64** was observed.

Lab Book Reference GB8/746

ReactIR monitoring of the lithiation of imidazolidine 64 by *s*-BuLi/TMEDA (–30 °C) (Scheme 2.25)

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 *N*-Boc-*N*′-isopropylimidazolidine **64** (214 mg, 1.0 mmol) in Et_2O was added dropwise. The solution was stirred at –30 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol was added dropwise. The solution was stirred at –30 °C for 5 min. Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –30 °C for 15 min.

For *N*-Boc-*N*′-isopropylimidazolidine **64**, a peak at 1709 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **147**. A new peak also appeared at 1663 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **148**. After a lithiation time of 5 min complete lithiation of *N*-Boc-*N*′-isopropylimidazolidine **64** to lithiated intermediate **148** was observed.

Lab Book Reference GB8/747

ReactIR monitoring of the lithiation of *O*-alkyl carbamate 100 by *s*-BuLi/TMEDA (Scheme 2.26)

Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *O*-alkyl carbamate **100** (265 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 20 min.

For *O*-alkyl carbamate **100**, a peak at 1697 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1672 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **149**. After addition of TMEDA, a new broad peak appeared at 1613 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **150**. After a lithiation time of 20 min, complete lithiation of *O*-alkyl carbamate **100** to lithiated intermediate **150** was observed.

Lab Book Reference GB8/683

ReactIR monitoring of the lithiation of *O*-alkyl carbamate 100 by *s*-BuLi/TMEDA (Scheme 2.27)

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 *O*-alkyl carbamate **100** (265 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min.

For *O*-alkyl carbamate **100**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **151**. A new broad peak also appeared at 1610 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **150**. After a lithiation time of 10 min, complete lithiation of *O*-alkyl carbamate **100** to lithiated intermediate **150** was observed.
Lab Book Reference GB9/772

ReactIR monitoring of the lithiation of *O*-alkyl carbamate 100 by *s*-BuLi/(–)-sparteine 3

(Scheme 2.28)

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 *O*-alkyl carbamate **100** (265 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, a solution of (–)-sparteine **3** (305 mg, 299 μL, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 60 min.

For *O*-alkyl carbamate **100**, a peak at 1696 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **152**. A new broad peak also appeared at 1609 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **153**. After a lithiation time of 60 min, complete lithiation of *O*-alkyl carbamate **100** to lithiated intermediate **153** was observed.
Lab Book Reference GB9/766

ReactIR monitoring of the lithiation of *O*-alkyl carbamate 100 by *s*-BuLi/(+)-sparteine surrogate 6

(Scheme 2.29)

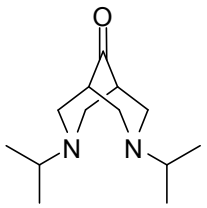
Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *O*-alkyl carbamate **100** (265 mg, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, a solution of (+)-sparteine surrogate **6** (258 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 2 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 5 min.

For *O*-alkyl carbamate **100**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak briefly appeared at 1665 cm^{-1} which was assigned to $\nu_{C=O}$ of prelithiation complex **154**. A new broad peak also appeared at 1609 cm^{-1} which was assigned to $\nu_{C=O}$ of lithiated intermediate **155**. After a lithiation time of 3 min, complete lithiation of *O*-alkyl carbamate **100** to lithiated intermediate **155** was observed.

Lab Book Reference GB9/767

7.4 Experimental for Chapter 3

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one 176[131]

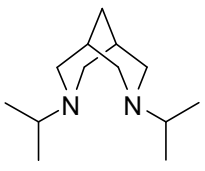


176

i-$PrNH_2$ (12.2 mL, 142.0 mmol) was added dropwise to a stirred solution of *N*-*i*-Pr-4-piperidone (21.1 mL, 142.0 mmol), paraformaldehyde (12.78 g, 426.0 mmol) and AcOH (8.46 mL, 148.0 mmol) in MeOH (200 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% $KOH_{(aq)}$ solution (500 mL) and Et_2O (500 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 500 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave bispidone **176** (21.39 g, 67%) as a colourless oil, bp 128-130 ºC/2.0 mmHg (lit.,[X] bp 110-120 ºC/10^{-5} mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (dd, J = 10.5, 3.0 Hz, 4H, NCH_AH_B), 2.86 (dd, J = 10.5, 7.0 Hz, 4H, NCH_AH_B), 2.85-2.76 (m, 2H, NCH), 2.61-2.54 (m, 2H, COCH), 0.99 (d, J = 6.5 Hz, 12H, Me). Spectroscopic data consistent with those reported in the literature.[132]

Lab Book reference GB2/113

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane 7



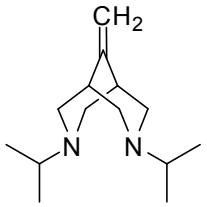
7

Hydrazine monohydrate (6.22 mL, 127.9 mmol) was added dropwise to a stirred mixture of bispidone **176** (5.17 g, 23.0 mmol) and KOH (15.1 g, 269.0 mmol) in diethylene glycol (130 mL) at rt under Ar. The resulting mixture was stirred and heated at 180 °C

for 16 h. After cooling to 60 °C,[1] the mixture was transferred to a separating funnel and H_2O (155 mL) was added. Then, Et_2O (85 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (6 × 85 mL) and the combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 × 100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give di-*i*-Pr bispidine **7** (4.29 g, 88%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68-2.57 (m, 2H, NCH), 2.53 (dd, J = 10.5, 5.5 Hz, 4H, NCH_2), 2.46 (br d, J = 10.5 Hz, 4H, NCH_2), 1.97-1.92 (m, 2H, NCH_2CH), 1.46-1.41 (m, 2H, NCH_2CHCH_2), 0.97 (d, J = 6.5 Hz, 12H, $NCHMe_2$). Spectroscopic data consistent with those reported in the literature.[131] Di-*i*-Pr bispidine **7** was purified by Kügelrohr distillation (bp 110-120 °C, 0.4 mmHg) immediately before use.

Lab Book Reference GB2/109

3,7-Diisopropyl-9-methylene-3,7-diazabicyclo[3.3.1]nonane 156



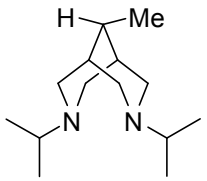
156

KHMDS (65.4 mL of a 0.5 M solution in toluene, 32.7 mmol) was added dropwise to a stirred solution of $MePh_3P^+Br^-$ (11.68 g, 32.7 mmol) in THF (240 mL) at 0 °C under Ar. After stirring at 0 °C for 30 min, a solution of bispidone **176** (7.00 g, 31.2 mmol) in THF (60 mL) was added dropwise. The resulting solution was stirred at 0 °C for 15 min and then stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure and 5 M $HCl_{(aq)}$ solution (250 mL) was added to the residue. The aqueous solution washed with CH_2Cl_2 (2 × 500 mL) and then basified to pH 14 by addition of 5 M $NaOH_{(aq)}$. The aqueous solution was stirred at rt for 1 h and then extracted with Et_2O (8 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kügelrohr distillation gave alkene **156** (4.48 g, 65%) as a colourless oil, bp 120-130 °C/1.2 mmHg; IR (film) 3069, 2931, 1670 (C=C), 1469, 1386, 1358, 1176, 880 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H, $C=CH_2$), 2.78-2.68 (m, 2H, NCH), 2.68-2.60 (m, 8H,

[1] If the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and difficult to work with.

NCH_2), 2.58-2.40 (m, 2H, NCH_2CH), 0.99 (d, J = 6.5 Hz, 12H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.4 (C=CH_2), 104.7 (C=$C$$H_2$), 53.8 ($NCH_2$), 53.4 (NCH), 39.0 ($NCH_2CH$), 18.1 (Me); MS (ESI) *m/z* 223 [$(M + H)^+$, 100], 150 (15), 123 (30); HRMS (ESI) *m/z* calcd for $C_{14}H_{26}N_2$ $(M + H)^+$ 223.2169, found 223.2169 (–0.26 ppm error).
Lab Book Reference GB1/77

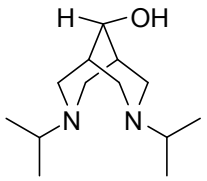
3,7-Diisopropyl-9-methyl-3,7-diazabicyclo[3.3.1]nonane 157



157

A solution of alkene **156** (4.48 g, 20.1 mmol) and $NH_4^+HCO_2^-$ (4.16 g, 66.0 mmol) in EtOH (130 mL) was stirred and heated at reflux under Ar. Then, 20% $Pd(OH)_2/C$ (1.22 g, 1.4 mmol) was added in one portion. The resulting mixture was stirred and heated at reflux for 2 h. After cooling to rt, the resulting mixture was basified to pH 14 by addition of 5 M $NaOH_{(aq)}$ solution. The aqueous solution was stirred at rt for 1 h. Then, the solids were removed by filtration through a minimum amount of Celite® and washed with 5 M $NaOH_{(aq)}$ solution (20 mL). The EtOH was evaporated under reduced pressure and the aqueous residue was extracted with Et_2O (8 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kügelrohr distillation gave methyl bispidine **157** (2.87 g, 65%) as a colourless oil, bp 130-140 °C/0.4 mmHg; IR (film) 2963, 2932, 1381, 1179, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79-2.60 (m, 8H, NCH_2), 2.40-2.34 (m, 2H, NCH), 1.86-1.78 (m, 1H, CHMe), 1.66 (br s, 2H, NCH_2CH), 1.05-0.95 (m, 15H, CHMe + CHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.9 (NCH), 53.6 (NCH), 53.5 (NCH_2), 47.1 (NCH_2), 34.2 (CH), 30.2 (CH), 18.2 (Me), 17.9 (Me), 16.5 (Me); MS (ESI) *m/z* 225 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}N_2$ $(M + H)^+$ 225.2325, found 225.2326 (–0.42 ppm error).
Lab Book Reference GB1/80

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-ol 158

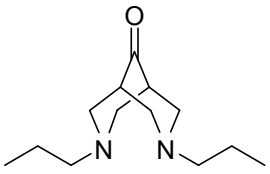


158

A solution of $NaBH_4$ (37 mg, 1.0 mmol) in H_2O (1.5 mL) was added dropwise to a stirred solution of bispidone **176** (200 mg, 0.9 mmol) in EtOH (3.0 mL) at rt under air. The resulting solution was stirred at rt for 16 h. The EtOH was evaporated under reduced pressure and the residue was basified to pH 14 by addition of 5 M $NaOH_{(aq)}$ solution. The solution was stirred at rt for 1 h and then extracted with Et_2O (8 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give bispidol **158** (138 mg, 69%) as a colourless oil, bp 170-180 ºC/5 mmHg; IR (film) 3328 (OH), 2965, 2924, 1469, 1382, 1360, 1221, 1174, 1096, 1069, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (br s, 1H, OH), 3.31 (br s, 1H, C*H*OH), 2.99 (br t, J = 10.5 Hz, 2H), 2.72-2.62 (m, 2H), 2.62-2.42 (m, 4H), 2.28-2.15 (m, 4H), 0.99 (d, J = 6.5 Hz, 6H, Me), 0.94 (d, J = 6.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 73.2 (CHOH), 53.3 (NCH), 52.9 (NCH), 52.4 (NCH_2), 48.5 (NCH_2), 34.6 (NCH_2CH), 18.2 (Me), 18.1 (Me); MS (ESI) *m/z* 227 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{26}N_2O$ $(M + H)^+$ 227.2118, found 227.2124 (–2.85 ppm error).

Lab Book Reference GB1/48

3,7-Dipropyl-3,7-diazabicyclo[3.3.1]nonan-9-one 180



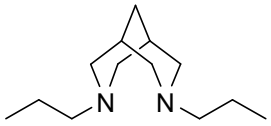
180

n-$PrNH_2$ (5.83 mL, 70.81 mmol) was added dropwise to a stirred solution of *N*-*n*-Pr-4-piperidone (10.7 mL, 10 g, 70.81 mmol), paraformaldehyde (6.38 g, 212.4 mmol) and AcOH (4.22 mL, 73.8 mmol) in MeOH (100 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% $KOH_{(aq)}$ solution (250 mL) and Et_2O (250 mL) were added to the

residue and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 250 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave di-*n*-Pr bispidone **180** (7.01 g, 44%) as a yellow oil, bp 95-100 °C/0.2 mmHg; IR (film) 2958, 1739 (C=O), 1469, 1359, 1208, 1137, 1087, 1036, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (dd, J = 11.0, 2.0 Hz, 4H, NCH_AH_B), 2.79 (dd, J = 11.0, 6.5 Hz, 4H, NCH_AH_B), 2.56 (br s, 2H, COCH), 2.31 (t, J = 7.5 Hz, 4H, NCH_2CH_2), 1.50-1.40 (m, 4H, NCH_2CH_2), 0.89 (t, J = 7.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.1 (C=O), 58.5 (NCH_2), 58.4 (NCH_2), 46.6 (NCH_2CH), 20.3 (CH_2Me), 11.8 (Me); MS (ESI) *m/z* 257 [(M + MeOH + H)$^+$, 100], 225 [(M + H)$^+$, 1]; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}N_2O$ (M + H)$^+$ 225.1961, found 225.1770 (minor peak); *m/z* calcd for $C_{14}H_{24}N_2O$ (M + MeOH + H)$^+$ 257.2224, found 257.2220 (+1.3 ppm error).

Lab Book Reference GB2/148

3,7-Dipropyl-3,7-diazabicyclo[3.3.1]nonane 159



159

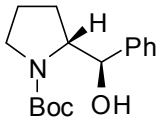
Hydrazine monohydrate (4.72 mL, 86.5 mmol) was added dropwise to a stirred mixture of di-*n*-Pr bispidone **180** (3.5 g, 15.6 mmol) and KOH (9.11 g, 182.0 mmol) in diethylene glycol (90 mL) at rt under Ar. The resulting mixture was stirred and heated at 180 °C for 16 h. After cooling to 60 °C,[2] the mixture was transferred to a separating funnel and H_2O (80 mL) was added. Then, Et_2O (60 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (6 × 60 mL) and the combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 × 90 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give di-*n*-Pr bispidine **159** (2.77 g, 84%) as a colourless oil, bp 100-110 °C/2.0 mmHg; IR (film) 2955, 2932, 1462, 1375, 1290, 1272, 1148, 1106, 1068, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.69 (br d, J = 10.5 Hz, 4H, NCH_AH_B), 2.28 (dd, J = 10.5, 4.5 Hz, 4H, NCH_AH_B), 2.19 (t, J = 7.5 Hz, 4H, NCH_2CH_2), 1.91 (br s, 2H, NCH_2CH), 1.52-1.41 (m, 6H, NCH_2CH_2 + CH_2CHCH_2), 0.87 (t, J = 7.5 Hz, 6H, Me);

[2] If the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and difficult to work with.

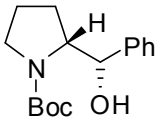
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 61.0 (NCH_2), 57.9 (NCH_2), 29.9 (bridge CH_2), 29.2 (NCH_2CH), 20.1 (NCH_2CH_2), 11.9 (Me); MS (ESI) *m/z* 211 [$(M + H)^+$, 100], 199 (12); HRMS (ESI) *m/z* calcd for $C_{13}H_{26}N_2$ $(M + H)^+$ 211.2169, found 211.2162 (+2.97 ppm error).

Lab Book Reference GB2/150

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-182 and (1*S*,2*R*)-182



(1*R*,2*R*)-**182**



(1*S*,2*R*)-**182**

Using general procedure A, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol), *N*-Boc pyrrolidine **38** (342 mg, 350 μL, 2.0 mmol) and (–)-sparteine **3** (609 mg, 595 μL, 2.6 mmol) for 1 h and then benzaldehyde (424 mg, 406 μL, 4.0 mmol) gave the crude product which contained a 75:25 mixture of (1*R*,2*R*)-**182** and (1*S*,2*R*)-**182** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**182** (343 mg, 62%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –3.1 (*c* 1.0 in $CHCl_3$) (lit.,[130] $[\alpha]_D$ –1.9 (*c* 1.0 in $CHCl_3$) for (1*R*,2*R*)-**182** of 97:3 er); R_F (98:2 CH_2Cl_2-acetone) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H, Ph), 5.93 (br s, 1H, OH), 4.53 (br d, J = 8.0 Hz, 1H, CHO), 4.10 (td, J = 8.0, 3.5 Hz, 1H, NCH), 3.51-3.42 (m, 1H, NCH_2), 3.41-3.33 (m, 1H, NCH_2), 1.79-1.15 (m, 2H, CH_2), 1.14-1.45 (m, 2H, CH_2), 1.53 (s, 9H, CMe_3); CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**182** 24.12 min, (1*S*,2*S*)-**182** 28.85 min and (1*S*,2*R*)-**182** (100 mg, 18%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +75.4 (*c* 1.00 in $CHCl_3$) (lit.,[130] $[\alpha]_D$ +95.3 (*c* 1.00 in $CHCl_3$) for (1*S*,2*R*)-**182** of 97:3 er); R_F (98:2 CH_2Cl_2-acetone) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.41-7.23 (m, 5H, Ph), 5.52 (br s, 0.75H, OH), 5.15 (br s, 0.25H, OH), 4.87 (br s, 0.75H, CHO), 4.31 (br s, 0.75H, NCH), 4.00 (br s, 0.25H, CHO), 3.56 (br s, 0.25H, NCH), 3.30 (br s, 1H, NCH_2), 2.82 (br s, 0.75H, NCH_2), 2.51 (br s, 0.25H, NCH_2), 2.01-1.86 (m, 1H, CH_2), 1.85-1.72 (m, 1H, CH_2), 1.68 (s, 2.25H, CMe_3), 1.66-1.46 (m, 1H, CH_2), 1.52 (s, 6.75H, CMe_3), 1.21-1.13 (m, 1H, CH_2); CSP-HPLC: Chiralcel OD (98:2 hexane-*i*-PrOH,

0.5 mLmin^{-1}) (1*S*,2*R*)-**182** 19.61 min, (1*R*,2*S*)-**182** 24.00 min. Spectroscopic data consistent with those reported in the literature.[130]

Lab Book Reference GB1/84

(Table 3.1, Entry 1)

Using general procedure B, *s*-BuLi (0.87 mL of a 1.3 M solution in hexanes, 1.13 mmol, 1.2 eq.), (–)-sparteine **3** (44 mg, 0.19 mmol, 0.2 eq.), di-*i*-Pr bispidine **7** (198 mg, 0.94 mmol, 1.0 eq.) and *N*-Boc pyrrolidine **38** (161 mg, 165 μL, 0.94 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (198 mg, 190 μL, 1.88 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 (1*R*,2*R*)-**182** (119 mg, 55%, 85:15 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –2.4 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (73 mg, 29%, 85:15 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +59.4 (*c* 1.0 in $CHCl_3$).

Lab Book Reference GB4/309

(Table 3.2, Entry 2)

Using general procedure B, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.50 mmol, 1.2 eq.), (–)-sparteine **3** (58 mg, 0.25 mmol, 0.2 eq.), di-*i*-Pr bispidine **7** (315 mg, 1.50 mmol, 1.2 eq.) and *N*-Boc pyrrolidine **38** (215 mg, 220 μL, 1.25 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (261 mg, 250 μL, 2.50 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 (1*R*,2*R*)-**182** (180 mg, 54%, 84:16 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –2.6 (*c* 1.0 in $CHCl_3$) and (1*S*, 2*R*)-**182** (103 mg, 31%, 82:18 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +56.3 (*c* 1.0 in $CHCl_3$).

Lab Book Reference GB4/310

(Table 3.1, Entry 3)

Using general procedure B, *s*-BuLi (1.98 mL of a 1.3 M solution in hexanes, 2.58 mmol, 1.3 equiv.), (–)-sparteine **3** (93 mg, 0.40 mmol, 0.2 equiv.), di-*i*-Pr bispidine **7** (500 mg, 2.38 mmol, 1.2 equiv.) and *N*-Boc pyrrolidine **38** (350 μL, 1.98 mmol, 1.0 equiv.) in Et_2O (8 mL) and then benzaldehyde (405 μL, 3.97 mmol, 2.0 equiv.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**182** (298 mg, 57%, 82:18 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$

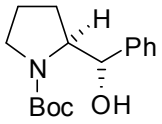
–2.1 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (173 mg mg, 33%, 82:18 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +49.9 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB7/317

(Table 3.1, Entry 4)
Using general procedure B, *s*-BuLi (1.06 mL of a 1.3 M solution in hexanes, 1.38 mmol, 1.0 eq.), (–)-sparteine **3** (81 mg, 0.34 mmol, 0.25 eq.), di-*i*-Pr bispidine **7** (290 mg, 1.38 mmol, 1.0 eq.) and *N*-Boc pyrrolidine **38** (234 mg, 240 µL, 1.38 mmol, 1.0 eq.) in Et_2O (8 mL) then benzaldehyde (293 mg, 280 µL, 2.76 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 (1*R*,2*R*)-**182** (214 mg, 58%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –2.9 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (106 mg, 29%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +52.4 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/333

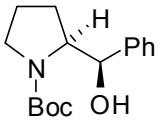
(Table 3.1, Entry 5)
Using general procedure B, *s*-BuLi (1.65 mL of a 1.3 M solution in hexanes, 2.14 mmol, 1.6 eq.), (–)-sparteine **3** (94 mg, 0.40 mmol, 0.3 eq.), di-*i*-Pr bispidine **7** (366 mg, 1.74 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (230 mg, 235 µL, 1.34 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (282 mg, 270 µL, 2.68 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 (1*R*,2*R*)-**182** (221 mg, 62%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –1.24 (*c* 1.0 in $CHCl_3$), and (1*S*,2*R*)-**182** (116 mg, 33%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +93.0 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/318

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*S*)-182 and (1*R*,2*S*)-182

(Table 3.2, Entry 1)



(1*S*,2*S*)-**182**



(1*R*,2*S*)-**182**

Using general procedure B, *s*-BuLi (1.13 mL of a 1.3 M solution in hexanes, 1.47 mmol, 1.0 eq.), (+)-sparteine surrogate **6** (64 mg, 0.37 mmol, 0.25 eq.), di-*i*-Pr bispidine **7** (309 mg, 1.47 mmol, 1.0 eq.) and *N*-Boc pyrrolidine **38** (254 mg, 260 μL, 1.47 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (313 mg, 300 μL, 2.94 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 (1*S*,2*S*)-**182** (220 mg, 56%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +2.8 (*c* 1.0 in $CHCl_3$) and (1*R*,2*S*)-**182** (96 mg, 25%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –87.2 (*c* 1.0 in $CHCl_3$).

Lab Book Reference GB4/323

(Table 3.2, Entry 2)

Using general procedure B, *s*-BuLi (2.64 mL of a 1.3 M solution in hexanes, 3.43 mmol, 1.6 eq.), (+)-sparteine surrogate **6** (112 mg, 0.64 mmol, 0.3 eq.), di-*i*-Pr bispidine **7** (585 mg, 2.78 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (366 mg, 375 μL, 2.14 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (455 mg, 435 μL, 4.28 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 (1*S*,2*S*)-**182** (370 mg, 65%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +0.04 (*c* 1.0 in $CHCl_3$) and (1*R*,2*S*)-**182** (166 mg, 29%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –106.3 (*c* 1.0 in $CHCl_3$).

Lab Book Reference GB4/324

(Table 3.2, Entry 3)

Using general procedure B, *s*-BuLi (0.96 mL of a 1.3 M solution in hexanes, 1.25 mmol, 1.6 eq.), cyclohexane diamine (*R*,*R*)-**8** (58 mg, 0.23 mmol, 0.3 eq.), di-*i*-Pr bispidine **7** (214 mg, 1.02 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (134 mg, 137 μL, 0.78 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (167 mg, 160 μL, 1.57 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 (1*R*,2*R*)-**182** (131 mg, 63%, 84:16 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +2.2 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (57 mg, 27%, 85:15 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –79.5 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/334

(Table 3.3, Entry 1)
Using general procedure B, *s*-BuLi (1.66 mL of a 1.3 M solution in hexanes, 2.16 mmol, 1.6 eq.), (–)-sparteine **3** (95 mg, 0.41 mmol, 0.3 eq.), alkene bispidine **156** (391 mg, 1.76 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (234 mg, 240 μL, 1.35 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (287 mg, 275 μL, 2.70 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 (1*R*,2*R*)-**182** (220 mg, 61%, 92:8 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –2.7 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (107 mg, 30%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +81.8 (*c* 1.0 $CHCl_3$).
Lab Book Reference GB4/349

(Table 3.3, Entry 2)
Using general procedure B, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.50 mmol, 1.6 eq.), (–)-sparteine **3** (66 mg, 0.28 mmol, 0.3 eq.), methyl bispidine **157** (274 mg, 1.22 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (161 mg, 165 μL, 0.94 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (198 mg, 190 μL, 1.88 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 (1*R*,2*R*)-**182** (149 mg, 60%, 79:21 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –1.9 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (81 mg, 32%, 78:22 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +72.4 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB5/388

(Table 3.3, Entry 3)
Using general procedure B, *s*-BuLi (1.27 mL of a 1.3 M solution in hexanes, 1.63 mmol, 2.9 eq.), (–)-sparteine **3** (40 mg, 0.17 mmol, 0.3 eq.), bispidol **158** (167 mg, 0.74 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (98 mg, 100 μL, 0.57 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (199 mg, 190 μL, 1.88 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 (1*R*,2*R*)-**182** (82 mg, 54%, 83:17 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –1.34 (*c* 0.55 in $CHCl_3$) and (1*S*,2*R*)-**182** (47 mg, 31%, 77:23 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +89.6 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/348

(Table 3.3, Entry 4)
Using general procedure B, *s*-BuLi (1.22 mL of a 1.3 M solution in hexanes, 1.59 mmol, 1.6 eq.), (–)-sparteine **3** (70 mg, 0.30 mmol, 0.3 eq.), di-*n*-Pr bispidine **159** (271 mg, 1.29 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 0.99 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (209 mg, 200 μL, 1.99 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 (1*R*,2*R*)-**182** (160 mg, 61%, 55:45 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –0.2 (*c* 1.0 in $CHCl_3$) and (1*S*,2*R*)-**182** (90 mg, 34%, 55:45 er by CPS-HPLC) as a colourless oil, $[\alpha]_D$ +2.4 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/343

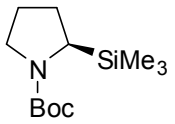
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and *N*-*i*-Pr (+)-sparteine surrogate **160** (289 mg, 1.3 mmol) in Et_2O (7 mL) for 3 h and then benzaldehyde (212 mg, 203 μL, 2.0 mmol) gave the crude product which contained a 75:25 mixture of (1*S*,2*S*)-**182** and (1*R*,2*S*)-**182** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*S*,2*S*)-**182** (140 mg, 50%, 90:10 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +2.5 (*c* 1.0 in $CHCl_3$) and (1*R*,2*S*)-**182** (70 mg, 25%, 89:11 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –69.8 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB9/777

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R,2*R**)-182 and (1*S**,2*R**)-182**

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and di-*i*-Pr bispidine **7** (273 mg, 1.3 mmol) in Et_2O (7 mL) for 3 h and then benzaldehyde (212 mg, 203 μL, 2.0 mmol) gave the crude product which contained a 75:25 mixture of (1*S**,2*S**)-**182** and (1*R**,2*S**)-**182**

by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R**,2*R**)-**182** (170 mg, 61%) as a colourless oil and (1*S**,2*R**)-**182** (86 mg, 31%) as a colourless oil.
Lab Book Reference GB9/779

2-Trimethylsilylpyrrolidine-1-carboxylic acid (*R*)-39



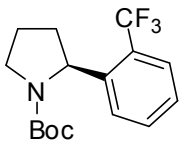
(*R*)-**39**

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and *N*-*i*-Pr (+)-sparteine surrogate **160** (289 mg, 1.3 mmol) in Et_2O (7 mL) for 3 h and then Me_3SiCl (217 mg, 254 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine (*R*)-**39** (198 mg, 81%, 91:9 er by CSP-GC) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.4; $[\alpha]_D$ –65.1 (*c* 1.0 in $CHCl_3$) (lit.[52] $[\alpha]_D$ +69.4 (*c* 2.22 in $CHCl_3$) for (*S*)-**39** of 97:3 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (br s, 1H, NCH), 3.22 (br s, 1H, NCH_2), 3.17-3.00 (m, 1H, NCH_2), 1.96 (br s, 1H, CH), 1.85-1.63 (m, 3H, CH), 1.43 (s, 9H, CMe_3), 0.02 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.5 (C=O), 79.2 (*C*Me_3), 78.3 (*C*Me_3), 47.6 (NCH), 47.5 (NCH), 46.9 (NCH_2), 32.8 (CH_2), 28.4 (C*Me*$_3$), 27.9 (C*Me*$_3$), 17.3 (CH_2), 1.8 ($SiMe_3$), 1.2 ($SiMe_3$); CSP-GC: β-cyclodextrin PM (100 °C) (*S*)-**39** 13.09 min, (*R*)-**39** 13.27 min. Spectroscopic data consistent with those reported in the literature.[52]
Lab Book Reference GB9/778

2-Trimethylsilylpyrrolidine-1-carboxylic acid *rac*-39

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol), *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and di-*i*-Pr bispidine **7** (273 mg, 1.3 mmol) in Et_2O (7 mL) for 3 h and then Me_3SiCl (217 mg, 254 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave pyrrolidine *rac*-**39** (213 mg, 86%) as a colourless oil.
Lab Book Reference GB9/780

(*S*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-183

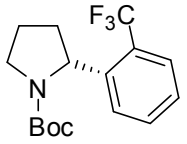


(*S*)-**183**

Using general procedure C, *N*-Boc pyrrolidine **38** (493 mg, 505 μL, 2.88 mmol, 1.0 eq.), *s*-BuLi (2.21 mL of a 1.3 M solution in hexanes, 2.88 mmol, 1.0 eq.), (+)-sparteine surrogate **6** (139 mg, 0.72 mmol, 0.25 eq.) and di-*i*-Pr bispidine **7** (606 mg, 2.88 mmol, 1.0 eq.) in Et_2O (7.0 mL) and then $ZnCl_2$ (1.73 mL of a 1.0 M solution in Et_2O, 1.73 mmol, 0.6 eq.), $Pd(OAc)_2$ (31 mg, 0.14 mmol, 5 mol%), *t*-Bu_3PHBF_4 (32 mg, 0.18 mmol, 6.25 mol%) and *o*-bromobenzotrifluoride (434 mg, 263 μL, 2.02 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-acetone as eluent gave aryl pyrrolidine (*S*)-**183** (481 mg, 75%, 91:9 er by CSP-HPLC) as a white solid, mp 82-83 °C; $[\alpha]_D$ –42.2 (*c* 1.4 in $CHCl_3$); R_F (99:1 CH_2Cl_2-acetone) 0.8; IR ($CHCl_3$) 3013, 2980, 1685 (C=O), 1313, 1216, 1162, 1126, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (80:20 mixture of rotamers) δ 7.68-7.58 (m, 1H, Ar), 7.57-7.43 (m, 1H, Ar), 7.38-7.26 (m, 2H, Ar), 5.38-5.30 (m, 0.2H, NCH), 5.19-5.11 (m, 0.8H, NCH), 3.80-3.64 (m, 2H, NCH), 2.48-2.39 (m, 1H, CH), 2.05-1.84 (m, 2H, CH), 1.83-1.72 (m, 1H, CH), 1.47 (s, 1.8H, CMe_3), 1.12 (s, 7.2H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.3 (C=O), 154.1 (C=O), 144.7 (*ipso*-Ar), 132.1 (Ar), 131.9 (Ar), 127.6 (q, J = 3.0 Hz, Ar), 126.6 (Ar) 126.5 (q, J = 24.0 Hz, CF_3), 126.4 (Ar), 126.0 (Ar), 125.4 (q, J = 6.0 Hz, Ar), 123.0 (*ipso*-Ar), 79.4 (CMe_3), 77.2 (CMe_3), 57.6 (NCH), 47.4 (NCH_2), 35.9 (CH_2), 28.4 (CMe_3), 27.9 (CMe_3), 23.0 (CH_2); MS (ESI) *m/z* 338 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_2F_3$ $(M + Na)^+$ 338.1338, found 338.1334 (+1.2 ppm error); CSP-HPLC: Chiralpak AD (99:1 hexane-*i*-PrOH, 0.7 $mLmin^{-1}$) (*R*)-**183** 9.29 min, (*S*)-**183** 11.31 min. Lab book Reference GB2/155:2

(*R*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-183

(Table 3.4, Entry 2)



(*R*)-**183**

Using general procedure C, *N*-Boc pyrrolidine **38** (280 mg, 1.64 mmol, 1.0 eq.), *s*-BuLi (1.26 mL of a 1.3 M solution in hexanes, 1.64 mmol, 1.0 eq.), (–)-sparteine **3** (96 mg, 0.41 mmol, 0.25 eq.) and di-*i*-Pr bispidine **7** (345 mg, 1.64 mmol, 1.0 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (0.98 mL of a 1.0 M solution in Et_2O, 0.98 mmol, 0.6 eq.), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 5 mol%), *t*-Bu_3PHBF_4 (18 mg, 0.10 mmol, 6.25 mol%) and *o*-bromobenzotrifluoride (159 μL, 1.15 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-acetone as eluent gave aryl pyrrolidine (*R*)-**183** (278 mg, 76%, 80:20 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +40.7 (*c* 1.3 in $CHCl_3$).

Lab Book Reference GB3/246:2

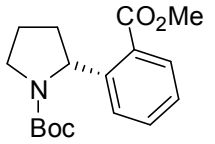
(Table 3.5, Entry 2)

Using general procedure C, *N*-Boc pyrrolidine **38** (216 mg, 1.27 mmol, 1.0 eq.), *s*-BuLi (1.56 mL of a 1.3 M solution in hexanes, 2.03 mmol, 1.6 eq.), (–)-sparteine **3** (89 mg, 0.38 mmol, 0.3 eq.) and di-*i*-Pr bispidine **7** (347 mg, 1.65 mmol, 1.3 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (0.76 mL of a 1.0 M solution in Et_2O, 0.76 mmol, 0.6 eq.), $Pd(OAc)_2$ (14 mg, 0.06 mmol, 5 mol%), *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 0.625 mol%) and *o*-bromobenzotrifluoride (123 μL, 0.89 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-acetone as eluent gave aryl pyrrolidine (*R*)-**183** (249 mg, 88%, 80:20 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +37.5 (*c* 1.0 in $CHCl_3$).

Lab Book Reference GB4/336:2

(*R*)-2-(2-Methoxycarbonylphenyl) pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-184

(Table 3.5, Entry 3)



(*R*)-**184**

Using general procedure C, *N*-Boc pyrrolidine **38** (214 mg, 1.25 mmol, 1.0 eq.), *s*-BuLi (1.54 mL of a 1.3 M solution in hexanes, 2.00 mmol, 1.6 eq.), (–)-sparteine **3** (88 mg, 0.37 mmol, 0.3 eq.) and di-*i*-Pr bispidine **7** (342 mg, 1.62 mmol, 1.3 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (750 μL of a 1.0 M solution in Et_2O, 0.75 mmol, 0.6 eq.), $Pd(OAc)_2$ (14 mg, 0.06 mmol, 5 mol%), *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 6.25 mol%) and methyl 2-bromobenzoate (123 μL, 0.87 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave aryl pyrrolidine (*R*)-**184** (189 mg, 71%, 89:11 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +16.4 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.3; IR (film) 2975, 2876, 1721 (C=O, CO_2Me), 1697 (C=O, Boc), 1479, 1450, 1434, 1394, 1365, 1256, 1164, 1116, 1076, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.94 (d, J = 7.5 Hz, 0.3H, Ar), 7.87 (d, J = 7.5 Hz, 0.7H, Ar), 7.45 (td, J = 7.5, 1.0 Hz, 1H, Ar), 7.33-7.17 (m, 2H, Ar), 5.68 (br d, J = 7.5 Hz, 0.3H, NCH), 5.49 (dd, J = 8.0, 4.5 Hz, 0.7H, NCH), 3.88 (s, 2.1H, OMe), 3.85 (s, 0.9H, OMe), 3.68-3.58 (m, 1.4H, NCH_2), 3.56-3.45 (m, 0.6H, NCH_2), 2.59-2.33 (m, 1H, CH_2), 1.93-1.69 (m, 3H, CH_2), 1.43 (s, 2.7H, CMe_3), 1.10 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 167.6 (C=O, CO_2Me), 154.3 (C=O, Boc), 147.3 (*ipso*-$C_6H_4CO_2Me$), 132.0 (Ar), 130.2 (Ar), 127.9 (*ipso*-C_6H_4CH), 126.1 (Ar), 125.8 (Ar), 79.0 (CMe_3), 58.7 (OMe), 51.9 (NCH), 47.6 (NCH_2), 47.3 (NCH_2), 35.5 (CH_2), 34.6 (CH_2), 28.5 (CMe_3), 28.0 (CMe_3), 23.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_4$ $(M + Na)^+$ 328.1519, found 328.1521 (+1.1 ppm error); CSP-HPLC: Chiralcel OD (95:5 hexane-*i*-PrOH, 1.0 $mLmin^{-1}$) (*R*)-**184** 5.47 min, (*S*)-**184** 6.58 min.

Lab Book Reference GB4/338:2

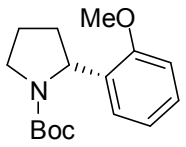
(Table 3.4, Entry 3)

Using general procedure C, *N*-Boc pyrrolidine **38** (344 mg, 2.01 mmol, 1.0 eq.), *s*-BuLi (1.55 mL of a 1.3 M solution in hexanes, 2.01 mmol, 1.0 eq.), (–)-sparteine **3** (118 mg, 0.50 mmol, 0.25 eq.) and di-*i*-Pr bispidine **7** (423 mg, 2.01 mmol, 1.0 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (1.21 mL of a 1.0 M solution in Et_2O, 1.21 mmol, 0.6 eq.), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 5 mol%), *t*-Bu_3PHBF_4 (22 mg, 0.126 mmol, 6.25 mol%) and methyl 2-bromobenzoate (198 μL, 1.41 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave aryl pyrrolidine (*R*)-**184** (309 mg, 50%, 81:19 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +14.9 (*c* 1.4 in $CHCl_3$).

Lab Book Reference GB3/253:2

(*R*)-2-(2-Methoxyphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-181

(Table 3.5, Entry 1)



(*R*)-**181**

Using general procedure C, *N*-Boc pyrrolidine **38** (243 mg, 1.42 mmol, 1.0 eq.), *s*-BuLi (1.75 mL of a 1.3 M solution in hexanes, 2.27 mmol, 1.6 eq.), (–)-sparteine **3** (100 mg, 0.43 mmol, 0.3 eq.) and di-*i*-Pr bispidine **7** (388 mg, 1.85 mmol, 1.3 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (852 μL of a 1.0 M solution in Et_2O, 0.85 mmol, 0.6 eq.), $Pd(OAc)_2$ (16 mg, 0.07 mmol, 5 mol%), *t*-Bu_3PHBF_4 (16 mg, 0.09 mmol, 6.25 mol%) and *o*-bromoanisole (124 μL, 0.99 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave aryl pyrrolidine (*R*)-**181** (253 mg, 92%, 89:11 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +59.8 (*c* 1.0 in acetone) (lit.,[89] $[\alpha]_D$ +109.0 (*c* 1.7 in acetone) for (*R*)-**181** of 96:4 er). R_F (98:2 CH_2Cl_2-acetone) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.26-7.13 (m, 1H, Ar), 7.06 (d, J = 7.5 Hz, 0.7H, Ar), 7.01 (d, J = 7.5 Hz, 0.3H, Ar), 6.89 (t J = 7.5 Hz, 1H, Ar), 6.85 (br d, J = 8.0 Hz, 1H, Ar), 5.25 (br d, J = 7.5 Hz, 0.3H, NCH), 5.18-5.01 (m, 0.7H, NCH), 3.83 (s, 3H, OMe), 3.69-3.40 (m, 2H, NCH_2), 2.38-2.12 (m, 1H, CH_2), 1.94-1.71 (m, 3H, CH_2), 1.47 (s, 2.7H, CMe_3), 1.19 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz,

$CDCl_3$) (rotamers) δ 156.1 (C=O), 154.6 (C=O), 132.9 (*ipso*-Ar), 127.5 (*ipso*-Ar), 127.3 (Ar), 125.9 (Ar), 120.1 (Ar), 110.3 (Ar), 110.1 (Ar), 79.0 (CMe_3), 78.8 (CMe_3), 56.1 (OMe), 55.3 (NCH), 55.2 (NCH), 47.2 (NCH_2), 46.8 (NCH_2), 33.9 (CH_2), 32.8 (CH_2), 28.5 (CMe_3), 28.1 (CMe_3), 23.1 (CH_2). CSP-HPLC: Chiralpak AD (99:1 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (*R*)-**181** 22.8 min, (*S*)-**181** 19.6 min. Spectroscopic data consistent with those reported in the literature.[89]

Lab Book Reference GB4/337:2

(Table 3.4, Entry 1)

Using general procedure C, *N*-Boc pyrrolidine **38** (348 mg, 2.03 mmol, 1.0 eq.), *s*-BuLi (1.56 mL of a 1.3 M solution in hexanes, 2.03 mmol, 1.0 eq.), (–)-sparteine **3** (119 mg, 0.51 mmol, 0.25 eq.) and di-*i*-Pr bispidine **7** (427 mg, 2.03 mmol, 1.0 eq.) in Et_2O (7 mL) and then $ZnCl_2$ (1.22 mL of a 1.0 M solution in Et_2O, 1.22 mmol, 0.6 eq.), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 5 mol%), *t*-Bu_3PHBF_4 (23 mg, 0.127 mmol, 6.25 mol%) and *o*-bromoanisole (177 μL, 1.42 mmol, 0.7 eq.) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave aryl pyrrolidine (*R*)-**181** (196 mg, 50%, 80:20 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +23.6 (*c* 1.0 in acetone).

Lab Book Reference GB3/247:2

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine XX by *s*-BuLi/*N*-*i*-Pr-(+)-sparteine surrogate 160

(Scheme 3.19)

Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt underAr. After cooling to –78 °C, a solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 4 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 4 min (to verify the stability of readout on ReactIR). Then, a solution of *N*-*i*-Pr (+)-sparteine surrogate **160** (289 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 40 min.

For *N*-Boc pyrrolidine **38**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *s*-BuLi, this peak decreased and a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in prelithiation complex **123**. Upon addition of *N*-*i*-Pr (+)-sparteine surrogate **160**, the peak at 1679 cm^{-1} decreased substantially, and the

peak at 1702 cm^{-1} increased. Over the course of 40 min, a new peak at 1646 cm^{-1} then emerged, assigned to $\nu_{C=O}$ in lithiated intermediate **185**.

Lab Book Reference GB8/727

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/*N*-*i*-Pr-(+)-sparteine surrogate 160

(Scheme 3.20)

N-*i*-Pr (+)-sparteine surrogate **160** (289 mg, 1.3 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and Et_2O (12 mL) were added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, the solution was stirred for 5 min and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 1 h.

For *N*-Boc pyrrolidine **38**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *N*-Boc pyrrolidine **38**, a large peak at 1702 cm^{-1} and a smaller peak at 1680 cm^{-1} which was assigned to $\nu_{C=O}$ in prelithiation complex **186** were observed. Over the course of 1 h, there was a slow increase in a peak at 1645 cm^{-1} which was assigned to $\nu_{C=O}$ in lithiated intermediate **185**, with a corresponding decrease in the peak at 1702 cm^{-1}.

Lab Book Reference GB8/726

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine XX by *s*-BuLi/di-*N*-*i*-Pr bispidine 7

(Scheme 3.22)

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 *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, a solution of di-*i*-Pr bispidine **7** (273 mg, 1.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 40 min.

For *N*-Boc pyrrolidine **38**, a peak at 1702 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *s*-BuLi, this peak decreased and a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in prelithiation complex **123**. Upon addition of di-*i*-

Pr bispidine **7**, the peak at 1679 cm^{-1} decreased substantially, and the peak at 1702 cm^{-1} increased. Over the course of 40 min, a new peak at 1645 cm^{-1} then emerged, assigned to $\nu_{C=O}$ in lithiated intermediate **187**.

Lab Book Reference GB8/729

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/di-*N*-*i*-Pr bispidine 7

(Scheme 3.23)

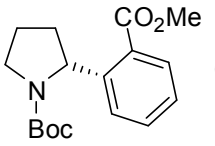
Di-*i*-Pr bispidine **7** (273 mg, 1.3 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and Et_2O (12 mL) were added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, the solution was stirred for 5 min and a solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred at –78 °C for 40 min.

For *N*-Boc pyrrolidine **38**, a peak at 1701 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *N*-Boc pyrrolidine **38**, a large peak at 1701 cm^{-1} and a smaller peak at 1682 cm^{-1} which was assigned to $\nu_{C=O}$ in prelithiation complex **188** were observed. Over the course of 40 min, there was a slow increase in a peak at 1648 cm^{-1} which was assigned to $\nu_{C=O}$ in lithiated intermediate **187**, with a corresponding decrease in the peak at 1701 cm^{-1}.

Lab Book Reference GB8/728

7.5 Experimental for Chapter 4

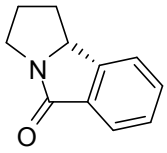
(*R*)-2-(2-Methoxycarbonylphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-184



(*R*)-**184**

Using general procedure D, *s*-BuLi (7.7 mL of a 1.3 M solution in hexanes, 10.0 mmol), *N*-Boc pyrrolidine **38** (1.71 g, 1.75 mL, 10.0 mmol) and (–)-sparteine (2.34 g, 2.30 mL, 10.0 mmol) in Et_2O (35 mL) and then $ZnCl_2$ (6.0 mL of a 1.0 M solution in Et_2O, 6.0 mmol), $Pd(OAc)_2$ (112 mg, 0.5 mmol, 5 mol%), *t*-Bu_3PHBF_4 (112 mg, 0.625 mmol, 6.25 mol%) and methyl 2-bromobenzoate (1.83 g, 1.19 mL, 8.5 mmol) at rt gave the crude product. Purifiaction by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave aryl pyrrolidine (*R*)-**184** (1.37 g, 53%, 95:5 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +18.7 (*c* 1.0 in $CHCl_3$).
Lab Book Reference GB4/321

(*R*)-1,2,3,9b-Tetrahydropyrrolo[2,1-*a*]isoindol-5-one (*R*)-200



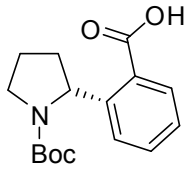
(*R*)-**200**

TFA (187 mg, 122 μL, 1.64 mmol) was added dropwise to a stirred solution of aryl pyrrolidine (*R*)-**184** (100 mg, 0.33 mmol, 95:5 er) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 3.5 h. The solvent was evaporated under reduced pressure and excess TFA was removed by azeotroping with toluene (3 × 10 mL). The residue was dissolved in MeOH (10 mL) and then K_2CO_3 (227 mg, 1.64 mmol) was added. The resulting solution was stirred at rt under air for 16 h. The solvent was evaporated under reduced pressure. H_2O (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated and 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. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave isoindolone (*R*)-**200** (39 mg, 68%) as a white solid, mp 72-

74 °C; R_F (1:1 petrol-EtOAc) 0.4; $[\alpha]_D$ +11.3 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 3006, 2980, 2895, 1684 (C=O), 1617, 1469, 1389, 1334 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 1H, Ar), 7.52 (td, *J* = 7.5, 1.0 Hz, 1H, Ar), 7.48-7.41 (m, 2H, Ar), 4.68 (dd, *J* = 10.5, 5.5 Hz, 1H, NCH), 3.78-3.66 (m, 1H, NCH_2), 3.43 (ddd, *J* = 11.5, 8.5, 3.5 Hz, 1H, NCH_2), 2.44-2.26 (m, 3H, CH), 1.33-1.18 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O), 146.4 (*ipso*-Ar), 133.6 (*ipso*-Ar), 131.5 (Ar), 128.3 (Ar), 123.9 (Ar), 122.6 (Ar), 64.6 (NCH), 41.9 (NCH_2), 29.7 (CH_2), 29.2 (CH_2); MS (ESI) *m/z* 196 [$(M + Na)^+$, 58], 174 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NO$ $(M + H)^+$ 174.0913, found 173.0919 (–3.4 ppm error).

Lab Book Reference GB3/214

(*R*)-2-(2-Carbonylphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-201



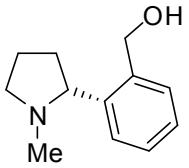
(*R*)-**201**

NaOH (23 mL of a 0.2 M solution in H_2O, 4.52 mmol) was added dropwise to a stirred solution of aryl pyrrolidine (*R*)-**184** (690 mg, 2.26 mmol, 95:5 er) in MeOH (23 mL) at rt under air. The resulting solution was stirred at rt for 16 h. The MeOH was evaporated under reduced pressure. Then, 5 M $HCl_{(aq)}$ was added dropwise until pH 3 and the aqueous solution was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give acid (*R*)-**201** (500 mg, 76%) as a white solid, mp 61-62 °C; $[\alpha]_D$ +24.8 (*c* 0.9 in $CHCl_3$); IR ($CHCl_3$) 3010 (OH), 2979, 1687 (C=O), 1405, 1367, 1263, 1216, 1164, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 8.15-7.81 (m, 1H, Ar), 7.51 (br s, 1H, Ar), 7.38-7.26 (m, 2H, Ar), 5.63 (br s, 1H, NCH), 3.67 (br s, 2H, NCH_2), 2.52 (br s, 1H, CH), 1.98-1.78 (m, 3H, CH), 1.45 (br s, 4.5 H, CMe_3), 1.16 (br s, 4.5 H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 171.0 (C=O, CO_2H), 154.6 (C=O, Boc), 148.3 (*ipso*-Ar), 143.7 (*ipso*-Ar), 132.9 (Ar), 132.2 (Ar), 131.1 (Ar), 126.8 (Ar), 126.5 (Ar), 125.7 (Ar), 80.4 (CMe_3), 79.4 (CMe_3), 58.7 (NCH), 58.6 (NCH), 47.9 (NCH_2), 47.4 (NCH_2), 35.5 (CH_2), 35.2 (CH_2), 28.5 (CMe_3), 28.1 (CMe_3), 23.7 (CH_2), 23.2 (CH_2); MS (ESI) *m/z* 314

[(M + Na)$^+$, 64], 292 [(M + H)$^+$, 13], 236 (100), 192 (59), 174 (37); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_4$ (M + Na)$^+$ 314.1363, found 314.1362 (+0.4 ppm error).

Lab Book Reference GB3/250

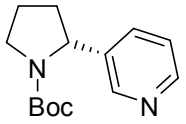
[2-((*R*)-1-Methylpyrrolidin-2-yl)phenyl]methanol (*R*)-199



(*R*)-**199**

A solution of aryl pyrrolidine (*R*)-**184** (1.17 g, 3.83 mmol, 95:5 er) in THF (25 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.45 g, 38.31 mmol) in THF (35 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 1 h then stirred and heated at reflux for 16 h. The solution was allowed to cool to rt and then 1 M $NaOH_{(aq)}$ (5 mL) was added dropwise. The solids were removed by filtration through Celite® and washed with 9:1 CH_2Cl_2-MeOH. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-MeOH as eluent gave amino alcohol (*R*)-**199** (529 mg, 72%) as a yellow oil, R_F (9:1 CH_2Cl_2-MeOH) 0.4; $[\alpha]_D$ +31.1 (*c* 1.0 in $CHCl_3$); IR (film) 3365 (OH), 2946, 2873, 2784, 1451, 1203, 1184, 1024, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 4H, Ar), 5.04 (d, J = 12.5 Hz, 1H, OCH_2), 4.38 (d, J = 12.5 Hz, 1H, OCH_2), 3.35-3.27 (m, 2H, NCH + NCH_2), 2.41-2.31 (m, 1H, NCH_2), 2.23 (s, 3H, Me), 2.31-2.04 (m, 3H, CH), 2.03-1.92 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.4 (*ipso*-Ar), 140.0 (*ipso*-Ar), 130.9 (Ar), 130.8 (Ar), 128.0 (Ar), 127.6 (Ar), 73.3 (NCH), 64.7 (OCH_2), 56.8 (NCH_2), 40.4 (Me), 31.5 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 192 [(M + H)$^+$, 100], 174 (4); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ (M + H)$^+$ 192.1383, found 192.1389 (–3.2 ppm error).
Lab Book Reference GB4/332

(*R*)-2-Pyridin-3-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-84[89]

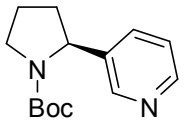


(*R*)-**84**

s-BuLi (13.48 mL of a 1.3 M solution in hexanes, 17.52 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (3.0 g, 3.07 mL, 17.52 mmol) and (–)-sparteine **3** (4.11 g, 4.02 mL, 17/52 mmol) in Et_2O (60 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, $ZnCl_2$ (10.51 mL of a 1.0 M solution in Et_2O, 10.51 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min. Then, 3-bromopyridine (2.36 g, 1.44 mL, 14.91 mmol) in TBME (45 mL) was added. A mixture of *t*-Bu_3PHBF_4 (197 mg, 1.0 mmol, 6.25 mol%) and $Pd(OAc)_2$ (198 mg, 0.88 mmol, 5 mol%) was added in one portion. The reaction flask was transferred to a pre-heated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (3.3 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (175 mL). The filtrate was washed with H_2O (175 mL) and brine (175 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 petrol-EtOAc as eluent gave pyridyl pyrrolidine (*R*)-**84** (1.45 g, 40%, 96:4 er by chiral shift NMR spectroscopy of a derivative) as a colourless oil, R_F (6:4 petrol-EtOAc) 0.2; $[\alpha]_D$ +78.1 (*c* 1.0 in CH_2Cl_2) (lit.,[89] $[\alpha]_D$ +83.6 (*c* 1.55 in CH_2Cl_2) for (*R*)-**84** of 96:4 er); ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.45-8.43 (m, 2H, Ar), 7.50-7.43 (m, 1H, Ar), 7.25-7.16 (m, 1H, Ar), 4.93 (br s, 0.4H, NCH), 4.75 (br s, 0.6H, NCH), 3.64-3.46 (m, 2H, NCH), 2.40-2.25 (m, 1H, CH), 1.95-1.77 (m, 3H, CH), 1.42 (s, 3.6H, CMe_3), 1.17 (s, 5.4H, CMe_3). Spectroscopic data consistent with those reported in the literature.[89]

Lab Book Reference GB3/200

(*S*)-2-Pyridin-3-ylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-84

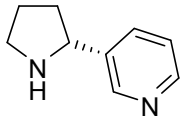


(*S*)-**84**

s-BuLi (1.71 mL of a 1.3 M solution in hexanes, 2.22 mmol, 1.0 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate **6** (97 mg, 0.56 mmol, 0.25 eq.) and di-*i*-Pr bispidine **7** (467 mg, 2.22 mmol, 1.0 eq.) in Et_2O (6 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *N*-Boc pyrrolidine **38** (380 mg, 389 μL, 2.22 mmol, 1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 4 h. Then, $ZnCl_2$ (1.33 mL of a 1.0 M solution in Et_2O, 1.33 mmol, 0.6 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min. Then, 3-bromopyridine (246 mg, 153 μL, 1.56 mmol, 0.7 eq.) in TBME (5 mL) was added. A mixture of *t*-Bu_3PHBF_4 (25 mg, 0.13 mmol, 6.25 mol%) and $Pd(OAc)_2$ (25 mg, 0.11 mmol, 5 mol%) was added in one portion. The reaction flask was transferred to a pre-heated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (2 × 10 mL). The filtrate was washed with H_2O (20 mL) and brine (20 mL) dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 petrol-EtOAc as eluent gave pyridyl pyrrolidine (*S*)-**84** (179 mg, 46%, 92:8 er by chiral shift NMR spectroscopy of a derivative) as a colourless oil, $[\alpha]_D$ +80.0 (*c* 1.0 in CH_2Cl_2) (lit.,[89] $[\alpha]_D$ –83.6 (*c* 1.55 in CH_2Cl_2) for (*R*)-**84** of 94:6 er).

Lab Book Reference GB4/286:3

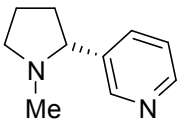
(*R*)-Nornicotine (*R*)-210



(*R*)-**210**

Using general procedure F, pyridyl pyrrolidine (*R*)-**84** (750 mg, 3.02 mmol) and TFA (6.89 g, 4.49 mL, 60.4 mmol) in CH_2Cl_2 (40 mL) for 16 h gave nornicotine (*R*)-**210** (339 mg, 76%) as a colourless oil, $[\alpha]_D$ +34.2 (*c* 1.2 in MeOH) (lit.,[232] $[\alpha]_D$ –35.2 (*c* 1.0 in MeOH) for (*S*)-**210** of 92:8 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.0 Hz, 1H, Ar), 8.42 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 7.66 (dt, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.19 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 4.10 (t, *J* = 7.5 Hz, 1H, NCH), 3.20-3.11 (m, 1H, NCH_2), 3.08-2.96 (m, 1H, NCH_2), 2.28 (br s, 1H, NH), 2.23-2.14 (m, 1H, CH), 1.96-1.77 (m, 2H, CH), 1.68-1.56 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.2 (Ar), 147.8 (Ar), 139.9 (*ipso*-Ar), 133.6 (Ar), 122.9 (Ar), 59.6 (NCH), 46.6 (NCH_2), 34.0 (CH_2), 25.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[232]
Lab Book Reference GB3/210

(*R*)-Nicotine (*R*)-97



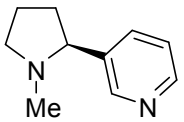
(*R*)-**97**

Using general procedure G, nornicotine (*R*)-**210** (169 mg, 1.14 mmol), paraformaldehyde (171 mg, 5.70 mmol) and formic acid (262 mg, 215 μL, 5.70 mmol) in H_2O (15 mL) gave (*R*)-nicotine (*R*)-**97** (169 mg, 91%, 96:4 er by chiral shift NMR spectroscopy in the presence of 2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a colourless oil, $[\alpha]_D$ +129.6 (*c* 0.85 in EtOH) (lit.,[232] $[\alpha]_D$ –145.0 (*c* 1.0 in EtOH) for (*S*)-nicotine of 99.5:0.5 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H, Ar), 8.47 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 7.70-7.65 (m, 1H, Ar), 7.24 (dd, *J* = 8.0, 5.0 Hz, Ar), 3.22 (t, *J* = 7.5 Hz, 1H, NCH), 3.06 (t, *J* = 8.5 Hz, 1H, NCH), 2.34-2.25 (m, 1H, NCH), 2.24-2.07 (m, 4H, NMe + CH), 2.01-1.88 (m, 1H, CH), 1.86-1.65 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.4 (Ar), 148.5 (Ar), 138.6 (*ipso*-Ar), 134.7 (Ar), 123.4 (Ar), 68.7 (NCH), 56.9 (NCH_2), 40.2 (NMe), 35.1 (CH_2), 22.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[232]

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.079 M solution of nicotine was prepared by dissolving nicotine (*R*)-**97** (9 mg, 0.055 mmol) in $CDCl_3$ (0.7 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (50 mg, 0.22 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (NMe, major), 1.90 (NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that nicotine (*R*)-**97** was present in 96:4 er.

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.078 M solution of nicotine was prepared by dissolving nicotine (*R*)-**97** (8.9 mg, 0.055 mmol) in $CDCl_3$ (0.7 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (49 mg, 0.22 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (NMe, minor), 1.90 (NMe, major). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that nicotine (*R*)-**97** was present in 95:5 er.
Lab Book Reference GB3/211 (synthesis) and GB3/215 (chiral shift)

(*S*)-Nicotine (*S*)-97



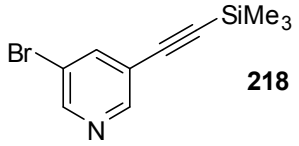
(*S*)-**97**

Using general procedure F, pyridyl pyrrolidine (*S*)-**84** (110 mg, 0.44 mmol) and TFA (1.01 g, 658 μL, 8.86 mmol) in CH_2Cl_2 (6 mL) for 16 h gave (*S*)-nornicotine (*S*)-**210**. Then, using general procedure G, the crude product, paraformaldehyde (80 mg, 2.66 mmol) and formic acid (123 mg, 80 μL, 2.66 mmol) in H_2O (7 mL) gave (*S*)-nicotine (*S*)-**97** (68 mg, 96%, 92:8 er by chiral shift NMR spectroscopy in the presence of 2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a colourless oil, $[\alpha]_D$ –81.0 (*c* 1.0 in EtOH) (lit.,[232] $[\alpha]_D$ –145.0 (*c* 1.0 in EtOH) for (*S*)-nicotine of 99.5:0.5 er). Spectroscopic data consistent with those reported in the literature.[232]

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.052 M solution of nicotine was prepared by dissolving nicotine (*S*)-**97** (5 mg, 0.031 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (34 mg, 0.12 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (NMe, major), 1.90 (NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that nicotine (*S*)-**97** was present in 92:8 er.

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.026 M solution of nicotine was prepared by dissolving nicotine (*S*)-**97** (3 mg, 0.018 mmol) in $CDCl_3$ (0.7 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (20 mg, 0.072 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (NMe, minor), 1.90 (NMe, major). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that nicotine (*S*)-**97** was present in 92:8 er.
Lab Book Reference GB4/287 + GB4/288:1 (synthesis) and GB4/288:2 (chiral shift)

3-Bromo-5-trimethylsilylethynylpyridine 218[161]

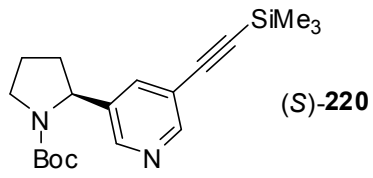


218

Trimethylsilylacetylene (622 μL, 4.40 mmol) was added dropwise to a stirred solution of 3,5-dibromopyridine (947 mg, 4.00 mmol), CuI (76 mg, 0.40 mmol) and $Pd(PPh_3)_2Cl_2$ (281 mg, 0.40 mmol) in Et_3N (1.4 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, H_2O (6 mL) was added and the resulting solution was extacted with Et_2O (3 × 6 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-CH_2Cl_2 as eluent gave bromopyridine **218** (666 mg, 72%) as a brown oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 2H, Ar), 7.90 (s, 1H, Ar), 0.27 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (Ar), 150.3 (Ar), 141.5 (Ar), 122.0 (*ipso*-Ar), 120.2 (*ipso*-Ar), 100.3 (C≡C), 99.7 (C≡C), –0.7 ($SiMe_3$). Spectroscopic data consistent with those reported in the literature.[161]

Lab Book Reference GB4/354:2

(*S*)-2-(5-Trimethylsilylethynylpyridin-3-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-220

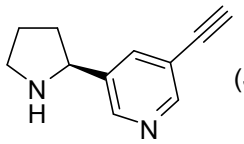


(*S*)-**220**

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) and (+)-sparteine surrogate **6** (213 mg, 1.3 mmol) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred for 30 min. Then, bromopyridine **218** (178 mg, 0.7 mmol) in TBME (5 mL) was added. A mixture of *t*-Bu_3PHBF_4 (11 mg, 0.06 mmol, 6.25 mol%) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%) was added in one portion. The reaction flask was transfered to a pre-heated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (20 mL). The filtrate was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 93:7 CH_2Cl_2-MeOH as eluent gave pyridyl pyrrolidine (*S*)-**220** (75 mg, 44%, 92:8 er by chiral shift NMR spectroscopy of a derivative, (*S*)-**98**) as a yellow oil, R_F (93:7 CH_2Cl_2-MeOH) 0.4; $[\alpha]_D$ –57.3 (*c* 1.0 in $CHCl_3$); IR (film) 2973, 2880, 2159, 1697 (C=O), 1448, 1392, 1366, 1250, 1164, 1115, 846, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 8.56 (br s, 1H, Ar), 8.40 (br s, 1H, Ar), 7.54 (s, 1H, Ar), 4.91 (br s, 0.3H, NCH), 4.75 (br s, 0.7H, NCH), 3.62 (br s, 2H, NCH), 2.34 (br s, 1H, CH), 1.98-1.69 (m, 3H, CH), 1.45 (br s, 2.7H, CMe_3), 1.21 (br s, 6.3H, CMe_3), 0.25 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.1 (C=O), 150.1 (Ar), 146.6 (Ar), 139.4 (*ipso*-Ar) 137.0 (*ipso*-Ar), 135.7 (Ar), 101.3 (C≡C), 98.1 (C≡C), 79.7 (*C*Me_3), 58.7 (NCH), 58.5 (NCH), 47.0 (NCH_2), 35.6 (CH_2), 34.3 (CH_2), 28.3 (C*Me*$_3$), 28.0 (C*Me*$_3$), 23.2 (CH_2), –

0.3 ($SiMe_3$); MS (ESI) *m/z* 345 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}N_2O_2Si$ $(M + H)^+$ 345.1993, found 345.1995 (–0.7 ppm error).
Lab Book Reference GB6/500:2

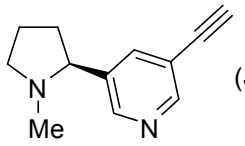
(*S*)-3-Ethynyl-5-pyrrolidin-2-ylpyridine (*S*)-221



(*S*)-**221**

TFA (466 mg, 304 μL, 4.09 mmol) was added dropwise to a stirred solution of pyridyl pyrrolidine (*S*)-**220** (50 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. Then, the solvent and excess TFA were evaporated under reduced pressure. H_2O (5 mL) was added to the residue and 5 M $NaOH_{(aq)}$ was added dropwise until pH 14. CsF (310 mg, 2.04 mmol) was added and the resulting solution was stirred at rt under air for 1 h. Then, 5 M $HCl_{(aq)}$ was added until pH 1 and the resulting solution was extracted with CH_2Cl_2 (3 × 6 mL). The aqueous layer was adjusted to pH 14 by addition of 5 M $NaOH_{(aq)}$ and extracted with Et_2O (8 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give pyridyl pyrrolidine (*S*)-**221** (26 mg, 76%) as a yellow oil, $[\alpha]_D$ –100.8 (*c* 0.45 in $CHCl_3$); IR ($CHCl_3$) 3292 (NH), 2964, 2871, 1444, 1416, 892, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 2.0 Hz, 1H, Ar), 8.54 (d, J = 2.0 Hz, 1H, Ar), 7.82 (t, J = 2.0 Hz, Ar), 4.16 (t, J = 7.5 Hz, 1H, NCH), 3.19 (s, 1H, C≡CH), 3.22-3.14 (m, 1H, NCH), 3.09-3.02 (m, 1H, NCH), 2.27-2.17 (m, 1H, CH), 2.12 (br s, 1H, NH), 2.00-1.80 (m, 2H, CH), 1.70-1.60 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (Ar), 148.1 (Ar), 140.1 (*ipso*-Ar), 137.2 (Ar), 118.8 (*ipso*-Ar), 80.6 (≡CH), 80.2 (≡C), 59.4 (NCH), 46.9 (NCH_2), 34.4 (CH_2), 25.5 (CH_2); MS (ESI) *m/z* 173 [$(M + H)^+$, 100], 156 (13); HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2$ $(M + H)^+$ 173.1073, found 173.1077 (–1.9 ppm error).
Lab Book Reference GB6/509:1

(*S*)-(+)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine, SIB1508Y (*S*)-98



(*S*)-**98**

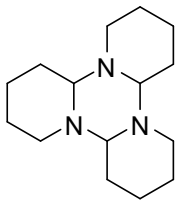
Using general procedure G, (*S*)-pyridyl pyrrolidine (*S*)-**221** (26 mg, 0.15 mmol), paraformaldehyde (22 mg, 0.75 mmol) and formic acid (34 mg, 22 μL, 0.75 mmol) in H_2O (3 mL) gave SIB1508Y (*S*)-**98** (19 mg, 68%, 92:8 er by chiral shift NMR spectroscopy in the presence of 1-(9-anthryl)-2,2,2-trifluroethanol) as a colourless oil, $[\alpha]_D$ –78.7 (*c* 0.7 in EtOH) (lit.,[159] $[\alpha]_D$ –162.0 (*c* 0.8 in EtOH) for SIB1508Y derived from natural (*S*)-nicotine); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.0 Hz, 1H, Ar), 8.49 (d, J = 2.0 Hz, 1H, Ar), 7.81 (t, J = 2.0 Hz, 1H, Ar), 3.24 (ddd, J = 9.5, 7.5, 2.0 Hz, 1H, NCH), 3.20 (s, 1H, C≡CH), 3.10 (t, J = 8.0 Hz, 1H, NCH), 2.32 (q, J = 9.5 Hz, 1H, NCH), 2.27-2.18 (m, 1H, CH), 2.17 (s, 3H, NMe), 2.04-1.90 (m, 1H, CH), 1.89-1.76 (m, 1H, CH), 1.75-1.63 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.5 (Ar), 149.0 (Ar), 138.5 (*ipso*-Ar), 138.0 (Ar), 119.1 (*ipso*-Ar), 80.5 (≡C), 80.3 (≡CH), 68.4 (NCH), 56.9 (NCH_2), 40.4 (NMe), 35.2 (CH_2), 22.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[159]

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.036 M solution of SIB1508Y was prepared by dissolving SIB1508Y (*S*)-**98** (4 mg, 0.021 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (24 mg, 0.087 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (NMe, major), 1.99 (NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that SIB1508Y (*S*)-**98** was present in 92:8 er.

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.031 M solution of SIB1508Y was prepared by dissolving SIB1508Y (*S*)-**98** (4 mg, 0.021 mmol) in $CDCl_3$ (0.7 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (24 mg, 0.087 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (NMe,

minor), 1.99 (NMe, major). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that SIB1508Y (*S*)-**98** was present in 92:8 er.
Lab Book Reference GB6/512:1 (synthesis) and GB6/512:2 (chiral shift)

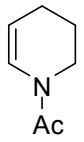
Dodecahydro-4a,8a,12a-triazatriphenylene 229[163]



229

Piperidine (5.0 g, 5.9 mL, 58.7 mmol) was added dropwise to a stirred solution of *N*-chlorosuccinimide (8.34 g, 62.5 mmol) in Et_2O (60 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h and the solids were removed by filtration. The filtrate washed with water (2 × 35 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue. A solution of NaOMe in MeOH [freshly prepared from Na (1.53 g, 66.7 mmol) and MeOH (35 mL)] was added to the oily residue at rt under Ar. The resulting solution was stirred and heated at reflux for 45 min. After cooling to rt, H_2O was added until all the solids had dissolved. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 125 mL). The combined organic layers were evaporated under reduced pressure until a sticky residue remained. Et_2O (100 mL) was added to the residue and the solution was dried ($MgSO_4$) and evaporated under reduced pressure to give tricyclic product **229** (2.72 g, 56%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dt, J = 11.0, 5.0 Hz, 3H, NCH), 2.76 (br d, J = 5.5 Hz, 3H, NCH), 2.04-1.91 (m, 3H, NCH), 1.76-1.58 (m, 9H, CH_2), 1.57-1.46 (m, 6H, CH_2), 1.31-1.18 (m, 3H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 81.8 (NCHN), 46.0 (NCH_2), 28.7 (CH_2), 25.3 (CH_2), 21.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[163]
Lab Book Reference GB3/234

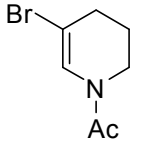
1-(3,4-Dihydro-2*H*-pyridin-1-yl)ethanone 228



228

A solution of dodecahydro-4a,8a,12a-triazatriphenylene **229** (2.72 g, 10.91 mmol) in acetic anhydride (48 mL) was stirred and heated at 50 °C under Ar for 16 h. After cooling to rt, EtOAc (55 mL) was added and the solution was washed with 1 M $NaOH_{(aq)}$ (3 × 30 mL) and H_2O (2 × 30 mL) and evaporated under reduced pressure. Saturated $Na_2CO_{3(aq)}$ (40 mL) was added to the residue and the resulting aqueous solution was extracted with EtOAc (10 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give enamide **228** (2.66 g, 65%) as a brown oil, ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.07 (dt, J = 8.5, 2.0 Hz, 0.3H, NCH=), 6.47 (dt, J = 8.5, 2.0 Hz, 0.7H, NCH=), 4.96 (dt, J = 8.5, 4.0 Hz, 0.3H, NCH=C*H*), 4.86 (dt, J = 8.5, 4.0 Hz, 0.7H, NCH=C*H*), 3.58 (t, J = 6.0 Hz, 1.4H, NCH_2), 3.48 (t, J = 6.0 Hz, 0.6H, NCH_2), 2.05 (s, 2.1H, Me), 2.04 (s, 0.9H, Me), 2.01-1.94 (m, 2H, CH_2), 1.81-1.67 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.0 (C=O), 168.5 (C=O), 125.8 (NCH=), 123.8 (NCH=), 108.7 (NCH=*C*H), 108.4 (NCH=*C*H), 44.0 (NCH_2), 39.8 (NCH_2), 21.6 (CH_2), 21.3 (Me), 21.2 (CH_2), 21.0 (CH_2), 20.9 (Me), 20.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[233]
Lab Book Reference GB3/236

1-(4-Bromo-3,4-dihydro-2*H*-pyridin-1-yl)ethanone 227



227

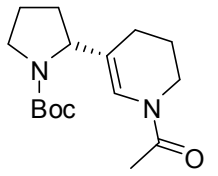
Br_2 (356 mg, 115 μL, 2.23 mmol) was added dropwise to a stirred solution of enamide **228** (250 mg, 2.00 mmol) in CH_2Cl_2 (8 mL) at –78 °C under Ar until an orange colour persisted. Then, *i*-Pr_2NEt (283 mg, 381 μL, 2.19 mmol) was added and the resulting solution was allowed to warm to rt and stirred for 45 min. Saturated $Na_2S_2O_{3(aq)}$ (8 mL) was added and the two layers were separated. The aqueous layer was extracted with

CH_2Cl_2 (3 × 18 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 7:3 petrol-EtOAc as eluent gave vinyl bromide **227** (534 mg, 91%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.3; IR (film) 2931, 1640 (C=O), 1392, 1349, 1296, 1257, 986, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.55 (t, J = 1.5 Hz, 0.3H, CH=), 6.91 (t, J = 1.5 Hz, 0.7H, CH=), 3.69-3.63 (m, 1.4H, NCH_2), 3.58-3.53 (m, 0.6H, NCH_2), 2.51-2.42 (m, 2H, CH), 2.15 (s, 2.1H, Me), 2.13 (s, 0.9H, Me), 2.03-1.06 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.4 (C=O), 167.8 (C=O), 126.7 (CH=), 124.9 (CH=), 108.2 (CBr), 42.8 (NCH_2), 38.5 (NCH_2), 31.2 (CH_2), 31.0 (CH_2), 21.6 (Me), 21.3 (Me); MS (ESI) *m/z* 204 [$(M + H)^+$, 11], 148 (33), 126 (100); HRMS (ESI) *m/z* calcd for $C_7H_{10}NO^{79}Br$ $(M + H)^+$ 204.0019, found 204.0019 (–0.4 ppm error).

Lab Book Reference GB9/830

(*R*)-2-(1-Acetyl-1,4,5,6-tetrahydropyridin-3-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)-226

(Table 4.1, Entry 5)



(*R*)-**226**

Using general procedure E, *N*-Boc pyrrolidine **38** (395 mg, 405 μL, 2.31 mmol), *s*-BuLi (2.30 mL of a 1.3 M solution in hexanes, 3.00 mmol) and (–)-sparteine **3** (703 mg, 690 μL, 3.00 mmol) in TBME (8 mL) and then $ZnCl_2$ (1.39 mL of a 1.0 M solution in Et_2O, 1.39 mmol), Pd_2dba_3 (52 mg, 0.06 mmol, 2.5 mol%), *t*-Bu_3PHBF_4 (26 mg, 0.14 mmol, 6.25 mol%) and vinyl bromide **227** (330 mg, 1.62 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-petrol as eluent gave *N*-Boc maackiamine (*R*)-**226** (266 mg, 56%, 95:5 er by CSP-HPLC) as a colourless oil, R_F (8:2 EtOAc-petrol) 0.3; $[\alpha]_D$ +40.9 (*c* 1.0 in $CHCl_3$); IR(film) 2972, 2930, 1692 (C=O), 1649 (C=O), 1394, 1366, 1331, 1258, 1165, 1113, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.13-7.02 (m, 0.3H, AcNCH), 6.39 (s, 0.7H, AcNCH), 4.32-4.05 (m, 1H, NCH), 3.69-3.44 (m, 4H, NCH), 2.12 (s, 3H, Me), 1.99-1.93

(m, 4H, CH_2), 1.90-1.68 (m, 4H, CH_2), 1.41 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.8 (C=O), 167.3 (C=O), 154.3 (br, N*C*H=C), 121.0 (NCH=*C*), 79.0 (*C*Me_3), 61.0 (NCH), 46.8 (NCH_2), 44.1 (NCH_2), 40.1 (NCH_2), 31.7 (CH_2), 30.7 (CH_2), 28.3 (C*Me*$_3$), 23.4 (CH_2), 21.9 (NCO*Me*), 21.7 (CH_2), 21.3 (NCO*Me*), 21.1 (CH_2); MS (ESI) *m/z* 317 [$(M + Na)^+$, 100], 295 [$(M + H)^+$, 60], 239 (18); HRMS (ESI) *m/z* calcd for $C_{16}H_{26}N_2O_3$ $(M + Na)^+$ 328.1519, found 328.1521 (–0.1 ppm error); CSP-HPLC: Chiralpak AD (90:10 hexane-*i*-PrOH, 1.0 $mLmin^{-1}$) (*R*)-**226** 7.60 min, (*S*)-**226** 9.80 min.

Lab Book Reference GB4/307

(Table 4.1, Entry 1)

Using general procedure E, *N*-Boc pyrrolidine **38** (219 mg, 225 μL, 1.28 mmol), *s*-BuLi (1.01 mL of a 1.3 M solution in hexanes, 1.28 mmol) and (–)-sparteine **3** (300 mg, 295 μL, 1.28 mmol) in Et_2O (8 mL) and then $ZnCl_2$ (0.77 mL of a 1.0 M solution in Et_2O, 0.77 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol, 5 mol%), *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 6.25 mol%) and vinyl bromide **227** (222 mg, 1.09 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-petrol as eluent gave *N*-Boc maackiamine (*R*)-**226** (108 mg, 29%, 94:6 er by CSP-HPLC) as a colourless oil.

Lab Book Reference GB3/242

(Table 4.1, Entry 2)

Using general procedure E, *N*-Boc pyrrolidine **38** (190 mg, 195 μL, 1.11 mmol), *s*-BuLi (1.11 mL of a 1.3 M solution in hexanes, 1.44 mmol) and (–)-sparteine **3** (337 mg, 330 μL, 1.44 mmol) in TBME (8 mL) and then $ZnCl_2$ (0.64 mL of a 1.0 M solution in Et_2O, 0.64 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (12 mg, 0.07 mmol, 6.26 mol%) and vinyl bromide **227** (158 mg, 0.74 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-petrol as eluent gave *N*-Boc maackiamine (*R*)-**226** (80 mg, 37%, 80:20 er by CSP-HPLC) as a colourless oil.

Lab Book Reference GB4/292

(Table 4.1, Entry 3)

s-BuLi (1.11 mL of a 1.3 M solution in hexanes, 1.44 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (190 mg, 195 μL, 1.11 mmol) and (–)-sparteine **3** (337 mg, 330 μL, 1.44 mmol) in TBME (8 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, $ZnCl_2$ (0.64 mL of a 1.0 M solution in Et_2O, 0.64 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, vinyl bromide **227** (158 mg, 0.74 mmol) in TBME (1 mL) was added. A mixture of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5 mol%) and *t*-Bu_3PHBF_4 (12 mg, 0.07 mmol, 6.25 mol%) was added in one portion. The reaction flask was transferred to a pre-heated oil bath and the resulting mixture was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite®, and washed with Et_2O (20 mL). The filtrate was washed with 10% $NH_4Cl_{(aq)}$ (2 × 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-petrol as eluent gave *N*-Boc maackiamine (*R*)-**226** (94 mg, 43%, 93:7 er by CSP-HPLC) as a colourless oil.

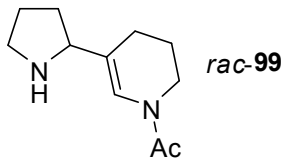
Lab book Reference GB4/293

(Table 4.1, Entry 4)

Using general procedure E, *N*-Boc pyrrolidine **38** (508 mg, 520 μL, 2.97 mmol), *s*-BuLi (2.98 mL of a 1.3 M solution in hexanes, 3.87 mmol) and (–)-sparteine **3** (907 mg, 890 μL, 3.87 mmol) in TBME (8 mL) and then $ZnCl_2$ (1.78 mL of a 1.0 M solution in Et_2O, 1.78 mmol), Pd_2dba_3 (68 mg, 0.07 mmol, 2.5 mol%), *t*-Bu_3PHBF_4 (33 mg, 0.17 mmol, 6.25 mol%) and vinyl bromide **227** (425 mg, 2.08 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-petrol as eluent gave *N*-Boc maackiamine (*R*)-**226** (248 mg, 40%, 92:8 er by CSP-HPLC) as a colourless oil.

Lab book Reference GB4/304

1-(5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone, *rac*-Maackiamine *rac*-99



rac-**99**

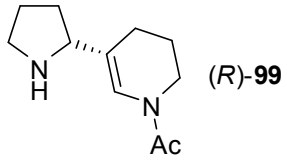
Using general procedure F, (*R*)-*N*-Boc maackiamine (*R*)-**226** (77 mg, 0.26 mmol, 95:5 er) and TFA (149 mg, 97 μL, 1.31 mmol) in CH_2Cl_2 (5 mL) for 4 h gave *rac*-maackiamine *rac*-**99** (448 mg, 96%, 50:50 er by chiral shift NMR spectroscopy in the presence of 1-(9-anthryl)-2,2,2-trifluroethanol) as a brown oil, R_F (7:7:2 EtOAc-hexane-Et_2NH) 0.3; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.21 (s, 0.3H, AcNCH=), 6.62 (s, 0.7H, AcNCH=), 3.71-3.45 (m, 3H, NCH), 3.09-3.02 (m, 1H, NCH), 2.97-2.87 (m, 1H, NCH), 2.17-2.01 (m, 3H, CH + NH), 2.16 (s, 2.1H, Me), 2.15 (s, 0.9H, Me), 1.94-1.71 (m, 5H, CH), 1.63-1.47 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.6 (C=O), 168.2 (C=O), 122.1 (NCH=*C*), 121.7 (NCH=*C*), 121.5 (N*C*H=C), 119.9 (N*C*H=C), 62.4 (NCH), 62.3 (NCH), 46.4 (NCH_2), 46.3 (NCH_2), 44.2 (NCH_2), 40.1 (NCH_2), 30.1 (CH_2), 29.5 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 21.7 (Me), 21.5 (CH_2), 21.2 (Me), 21.0 (CH_2). Spectroscopic data consistent with those reported in the literature.[138]

Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.043 M solution of *rac*-maackiamine was prepared by dissolving maackiamine *rac*-**XX** (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl) ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (AcNCH=), 6.12 (AcNCH=). In a similar fashion, a 0.043 M solution of *rac*-maackiamine was prepared by dissolving maackiamine *rac*-**99** (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (AcNCH=), 6.12 (AcNCH=). Integration of the major and minor AcNCH signals of each rotamer in each of the ^1H NMR spectra indicated that the sample of maackiamine **99** was racemic.

Lab Book Reference: GB3/239:1 (synthesis), GB4/294 (chiral shift)

$BF_3.OEt_2$ (85 mg, 74 μL, 0.6 mmol) was added dropwise to a stirred solution of (*R*)-*N*-Boc maackiamine (*R*)-**226** (60 mg, 0.2 mmol, 80:20 er) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 1.3 h and 0.5 M $NaOH_{(aq)}$ (2.4 mL) was added. The layers were separated and the aqueous was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give *rac*-maackiamine *rac*-**99** (23 mg, 53%, 50:50 er by chiral shift NMR spectroscopy in the presence of 2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a brown oil.
Lab Book Reference GB4/294

1-((*R*)-5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone, Maackiamine (*R*)-99



(*R*)-**99**

t-$BuMe_2SiOTf$ (197 mg, 170 μL, 0.8 mmol) was added dropwise to a stirred solution of *N*-Boc maackiamine (*R*)-**226** (200 mg, 0.68 mmol, 95:5 er) and pyridine (79 mg, 80 μL, 1.0 mmol) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h and then the solvent was evaporated under reduced pressure. The residue was dried thoroughly under high vacuum. The residue was dissolved in saturated $NH_4Cl_{(aq)}$ (10 mL) and the aqueous solution was extracted with Et_2O (5 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. THF (7.5 mL) was added to the residue and the resulting solution was added dropwise to a stirred suspension of CsF (152 mg, 1.0 mmol) in THF (7.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h and the solvent was evaporated under reduced pressure. 1 M $NaOH_{(aq)}$ (15 mL) was added to the residue and the resulting aqueous solution was extracted with Et_2O (5 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by preparative TLC on silica with 7:7:2 EtOAc-hexane-Et_2NH as eluent gave (*R*)-maackiamine (*R*)-**99** (71 mg, 54%, 95:5 er by chiral shift NMR spectroscopy in the presence of (*R*)-1-(9-anthryl)-2,2,2-trifluroethanol)) as a colourless oil, R_F (7:7:2 EtOAc-hexane-Et_2NH) 0.3; $[\alpha]_D$ +12.8 (*c* 1.0 in EtOH) (lit.,[138] $[\alpha]_D$ +110 (*c* 0.01 in EtOH) for

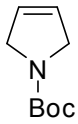
natural maackiamine). Spectroscopic data consistent with those reported in the literature.[138]

Enantiomer ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: a 0.043 M solution of maackiamine was prepared by dissolving maackiamine (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (AcNCH=, major), 6.19 (AcNCH=, minor). Integration of the major and minor AcNCH singals of each rotamer in the ^{1}H NMR spectra indicated that maackiamine (*R*)-**99** was present in 95:5 er.

Lab Book Reference: GB4/316

7.6 Experimental for Chapter 5

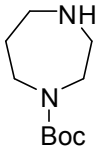
2,5-Dihydropyrrole-1-carboxylic acid *tert*-butyl ester 261



261

Di-*t*-butyl dicarbonate (3.42 g, 15.67 mmol) was added portionwise to a stirred solution of 3-pyrroline (1.0 g, 1.1 mL, 14.47 mmol) in CH_2Cl_2 (30 mL) at 0 °C under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by Kügelrohr short path distillation gave *N*-Boc-3-pyrroline **261** (2.45 g, 100%) as a colourless oil, bp 65-75 °C/1.5 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.69 (m, 2H, HC=CH), 4.18-4.03 (m, 4H, NCH_2), 1.46 (s, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[234]
Lab Book Reference GB6/560

[1,4]-Diazepane-1-carboxylic acid *tert*-butyl ester

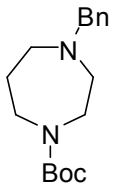


Di-*t*-butyl dicarbonate (16.4 g, 78.15 mmol) was added portionwise to a stirred solution of homopiperazine (15.0 g, 149.88 mmol) in CH_2Cl_2 (300 mL) at 0 °C. The resulting colourless solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure and H_2O (300 mL) and CH_2Cl_2 (300 mL) were added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-Boc homopiperazine (8.12 g, 52%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48-3.28 (m, 4H, NCH_2), 2.91-2.70 (m, 4H, NCH_2), 1.82-1.63 (m, 2H, CH_2), 1.53 (br s, 1H, NH), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.5 (C=O), 155.3 (C=O), 79.0 (CMe_3), 78.9 (CMe_3), 50.0 (NCH_2), 49.6 (NCH_2), 49.5 (NCH_2), 49.4 (NCH_2), 48.3 (NCH_2),

48.0 (NCH_2), 45.9 (NCH_2), 45.2 (NCH_2), 30.5 (CH_2), 30.4 (CH_2), 28.3 (CMe_3). Spectroscopic data consistent with those reported in the literature.[235]

Lab Book Reference GB7/651

4-Benzyl-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester 272

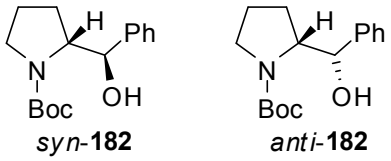


272

N-Boc homopiperazine (1.0 g, 4.99 mmol) and K_2CO_3 (1.38 g, 9.98 mmol) were added portionwise to a stirred solution of benzyl chloride (6.32 g, 5.74 mL, 4.99 mmol) in EtOH (15 mL) at rt. The resulting white suspension was stirred and heated at reflux for 16 h. After cooling to rt, the solvent was evaporated under reduced pressue and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). 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-Et_2O as eluent gave *N*-Boc-*N*′-benzyl homopiperazine **272** (1.05 g, 72%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.1; bp 212-214 °C/3.0 mmHg; IR (film) 2975, 2935, 2814, 1692 (C=O), 1478, 1455, 1413, 1365, 1247, 1174, 1121, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 4H, Ph), 7.28-7.17 (m, 1H, *p*-Ph), 3.62 (s, 2H, $PhCH_2$), 3.55-3.40 (m, 4H, NCH_2), 2.71-2.56 (m, 4H, NCH_2), 1.91-1.73 (m, 2H, CH_2), 1.50-1.46 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.6 (C=O), 155.5 (C=O), 139.2 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 128.1 (Ph), 126.9 (Ph), 126.8 (Ph), 79.1 (CMe_3), 79.1 (CMe_3), 62.2 ($PhCH_2$), 56.1 (NCH_2), 55.7 (NCH_2), 54.8 (NCH_2), 54.6 (NCH_2), 46.7 (NCH_2), 46.2 (NCH_2), 46.0 (NCH_2), 45.2 (NCH_2), 28.4 (CMe_3), 28.3 (CMe_3), 27.9 (CH_2), 27.8 (CH_2); MS (ESI) *m/z* 291 [$(M + H)^+$, 100], 235 (22); HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_2$ $(M + H)^+$ 291.2067, found 291.2075 (–2.9 ppm error).

Lab Book reference GB6/518

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-182 and *anti*-182



syn-**182** *anti*-**182**

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 **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) and (–)-sparteine (305 mg, 299 μL, 1.3 mmol, 1.3 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 10 min and allowed to warm to rt. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers separated. The aqueous layer was extracted with Et_2O (3 × 10 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 pyrrolidine *syn*-**182** (171 mg, 62%, 50:50 er by CSP-HPLC) as a colourless oil and pyrrolidine *anti*-**182** (96 mg, 35%, 50:50 er by CSP-HPLC) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 97%.

Lab Book Reference GB8/676

Table 5.1, Entry 1:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) at –78 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (16 mg, 6%) as a colourless oil and pyrrolidine *anti*-**182** (6 mg, 2%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 8%.

Lab Book Reference: GB5/413

Table 5.1, Entry 2:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (151 mg, 57%) as a colourless oil, and pyrrolidine *anti*-**182** (85 mg, 32%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 89%.

Lab Book Reference GB5/381

Table 5.1, Entry 3:

Using general procedure XX, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in 2-methyl THF (7 mL) at –78 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (145 mg, 55%) as a colourless oil, and pyrrolidine *anti*-**182** (98 mg, 37%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 92%.

Lab Book Reference GB5/417

Table 5.1, Entry 4:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) at –40 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (48 mg, 18%) as a colourless oil, and pyrrolidine *anti*-**182** (22 mg, 8%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 26%.

Lab Book Reference GB5/415

Table 5.1, Entry 5:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (118 mg, 43%) as a colourless oil, and pyrrolidine *anti*-**182** (58 mg, 21%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 64%.
Lab Book Reference GB5/447

Table 5.1, Entry 6:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in 2-methyl THF (7 mL) at –40 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (150 mg, 57%) as a colourless oil, and pyrrolidine *anti*-**182** (98 mg, 37%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 94%.
Lab Book Reference GB5/418
.

Table 5.1, Entry 7:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) at –30 °C for 1 h and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB5/433

Table 5.1, Entry 8:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 1 h and benzaldehyde (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 pyrrolidine *syn*-**182** (66 mg, 25%) as a colourless oil, and pyrrolidine *anti*-**182** (33 mg, 12%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 37%.
Lab Book Reference GB5/432

Table 5.1, Entry 9:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in 2-methyl THF (7 mL) at –30 °C for 1 h and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB5/437

Table 5.1, Entry 10:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 10 min and benzaldehyde (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 pyrrolidine *syn*-**182** (162 mg, 58%) as a colourless oil, and pyrrolidine *anti*-**182** (86 mg, 31%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 89%.

Lab Book Reference GB5/441

Table 5.1, Entry 11:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 5 min and benzaldehyde (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 pyrrolidine *syn*-**182** (155 mg, 56%) as a colourless oil, and pyrrolidine *anti*-**182** (77 mg, 28%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 84%.

Lab Book Reference GB5/440

Table 5.1, Entry 12:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in 2-methyl THF (7 mL) at –30 °C for 5 min and benzaldehyde (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 pyrrolidine *syn*-**182** (126 mg, 49%) as a

colourless oil, and pyrrolidine *anti*-**182** (67 mg, 24%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 73%.
Lab Book Reference GB8/691

Table 5.1, Entry 13:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –20 °C for 30 min and benzaldehyde (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 pyrrolidine *syn*-**182** (18 mg, 7%) as a colourless oil, and pyrrolidine *anti*-**182** (7 mg, 3%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 10%.
Lab Book Reference GB5/375

Table 5.1, Entry 14:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –20 °C for 5 min and benzaldehyde (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 pyrrolidine *syn*-**182** (122 mg, 44%) as a colourless oil, and pyrrolidine *anti*-**182** (61 mg, 22%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 66%.
Lab Book Reference GB5/452

Table 5.1, Entry 15:
Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –20 °C for 2 min and benzaldehyde (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 pyrrolidine *syn*-**182** (104 mg, 37%) as a colourless oil, and pyrrolidine *anti*-**182** (56 mg, 20%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 57%.
Lab Book Reference GB5/450

Table 5.1, Entry 16:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –10 °C for 5 min and benzaldehyde (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 pyrrolidine *syn*-**182** (54 mg, 19%) as a colourless oil, and pyrrolidine *anti*-**182** (28 mg, 10%) as a colourless oil. The total yield of *syn*-**182** and *anti*-**182** is 29%.

Lab Book Reference GB5/453

Table 5.1, Entry 17:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –10 °C for 1 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

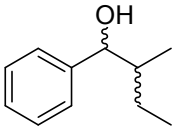
Lab Book Reference GB5/451

Table 5.1, Entry 18:

Using general procedure H, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at 0 °C for 30 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB5/368

Methyl-1-phenylbutan-1-ol 249



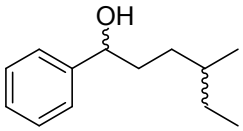
249

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.0 eq.) was added dropwise to Et_2O (7 mL) at –78 °C under Ar and the resulting solution was stirred at –78 °C for 1 h. Then, benzaldehyde (138 mg, 132 μL, 1.3 mmol, 1.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min. The solution was allowed

to warm to rt and saturated $NH_4Cl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-EtOAc as eluent gave a 50:50 mixture of diastereomeric alcohols **249** (140 mg, 66%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.16 (m, 5H, Ph), 4.46 (d, J = 6.0 Hz, 0.5H, CHO), 4.37 (d, J = 6.0 Hz, 0.5H, CHO), 2.07 (br s, 1H, OH), 1.82-1.59 (m, 1.5H), 1.45-1.27 (m, 1H), 1.26-0.96 (m, 1H), 0.94-0.79 (m, 4H), 0.77-0.58 (m, 1.5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.8 (*ipso*-Ph), 143.5 (*ipso*-Ph), 128.1 (Ph), 127.3 (Ph), 127.1 (Ph), 126.6 (Ph), 126.3 (Ph), 78.7 (CHO), 78.0 (CHO), 41.8 (CH), 41.5 (CH), 25.8 (CH_2), 24.8 (CH_2), 15.0 (Me), 13.9 (Me), 11.6 (Me), 11.3 (Me). Spectroscopic data consistent with those reported in the literature.[236]

Lab Book Reference GB5/424

4-Methyl-1-phenylhexan-1-ol 250



250

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.0 eq.) was added dropwise to THF (7 mL) at 0 °C under Ar and the resulting solution was stirred at 0 °C for 30 min. Then, benzaldehyde (138 mg, 132 μL, 1.3 mmol, 1.0 eq.) was added and the resulting solution was stirred at 0 °C for 30 min. The solution was allowed to warm to rt and saturated $NH_4Cl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-EtOAc as eluent gave a 50:50 mixture of diastereomeric alcohols **250** (72 mg, 29%, 58% based on *s*-BuLi) as a yellow oil, R_F (9:1 petrol-EtOAc) 0.5; IR (film) 3379 (OH), 2959, 2932, 2873, 1454, 908, 734, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 4H, Ph), 7.17-7.23 (m, 1H, Ph), 4.59-4.52 (m, 1H, CHO), 1.88 (br s, 1H, OH), 1.79-1.54 (m, 2H), 1.52-1.32 (m, 0.5H), 1.32-1.16 (m, 3H), 1.11-0.93 (m,

1.5H), 0.81-0.73 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9 (*ipso*-Ph), 144.8 (*ipso*-Ph), 128.4 (Ph), 127.4 (Ph), 127.4 (Ph), 125.9 (Ph), 125.8 (Ph), 75.1 (CHO), 75.0 (CHO), 36.6 (CH_2), 36.5 (CH_2), 34.3 (CH), 34.3 (CH), 32.5 (CH_2), 32.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 19.1 (Me), 19.0 (Me), 11.3 (Me), 11.3 (Me); MS (ESI) *m/z* 192 [M^+, 17], 174 [$(M - H_2O)^+$, 31], 117 (21), 107 (100), 79 (24); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O$ M^+ 192.1514, found 192.1512 (–1.0 ppm error).
Lab Book Reference GB5/427

Attempted Lithiation-trapping of *N*-Boc pyrrolidine 38 with *n*-BuLi and LDA

Table 5.2, Entry 1:
Using general procedure I, *n*-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at 0 °C for 60 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB5/410

Table 5.2, Entry 2:
Using general procedure I, *n*-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at rt for 60 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB5/411

Table 5.2, Entry 3:
Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C for 60 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB6/494

Table 5.2, Entry 4:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 30 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/495

Table 5.2, Entry 5:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –20 °C for 30 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/498

Table 5.2, Entry 6:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at 0 °C for 60 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/492

Table 5.2, Entry 7:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at 0 °C for 180 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/493

Table 5.2, Entry 8:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at rt for 30 min and benzaldehyde (212 mg, 203 μL, 2.0 mmol, 2.0 eq.) gave none of *syn*-**182** and *anti*-**182** by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/497

Table 5.2, Entry 9:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at 0 °C for 30 min and benzyl bromide (342 mg, 238 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

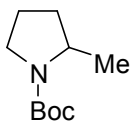
Lab Book Reference GB6/502

Table 5.2, Entry 10:

Using general procedure I, LDA (650 μL of a 2.0 M solution in THF/*n*-heptane/ethyl benzene, 1.3 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at rt for 30 min and benzyl bromide (342 mg, 238 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/501

***N*-Boc-2-methylpyrrolidine 251**



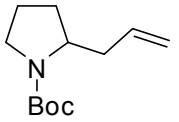
251

Using general procedure K, *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and Me_2SO_4 (252 mg, 189 μL, 2.0 mmol, 2.0 eq.) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 24:1 petrol-EtOAc as

eluent gave methyl pyrrolidine **251** (129 mg, 70%) as a colourless oil, R_F (24:1 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (br s, 1H, NCH), 3.32 (br s, 2H, NCH_2), 2.02-1.89 (m, 1H, CH_2), 1.89-1.80 (m, 1H, CH_2), 1.80-1.68 (m, 1H, CH_2), 1.61-1.47 (m, 1H, CH_2), 1.43 (s, 9H, CMe_3), 1.12 (d, J = 5.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.5 (C=O), 79.8 (CMe$_3$), 78.7 (CMe$_3$), 54.2 (NCH), 53.9 (NCH), 52.8 (Me), 46.1 (NCH_2), 33.1 (CH_2), 32.4 (CH_2), 28.4 (CMe_3), 23.4 (CH_2), 22.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book Reference GB6/476

2-Allylpyrrolidine-1-carboxylic acid *tert*-butyl ester 252



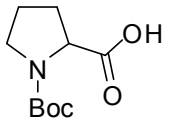
252

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 **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, a solution of LiCl (42 mg, 1.0 mmol) and CuCN (45 mg, 0.5 mmol) in THF (1 mL) was added dropwise and the resulting solution was stirred at –30 °C for 30 min. Allyl bromide (218 mg, 156 μL, 1.8 mmol) was added dropwise and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.5 mL), saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the resulting biphasic mixture was stirred at rt for 10 min. The solids were removed by filtration through Celite® and washed with Et_2O (2 × 5 mL). The two layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 10 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 9:1 petrol-EtOAc as eluent gave allyl pyrrolidine **252** (137 mg, 65%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.4; ^{1}H NMR δ 5.82-5.64 (m, 1H, CH=CH$_2$), 5.13-4.93 (m, 2H, CH=CH_2), 3.79 (br s, 1H, NCH), 3.52-3.18 (m, 2H, NCH_2), 2.69-2.34 (m, 1H, CH_2CH=CH$_2$), 2.20-2.03 (m, 1H, CH_2CH=CH$_2$), 1.97-1.65 (m, 4H, CH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.4 (C=O), 135.1 (CH=CH$_2$),

116.9 (CH=*C*H_2), 79.0 (*C*Me_3), 78.8 (*C*Me_3), 56.7 (NCH), 46.6 (NCH_2), 46.2 (NCH_2), 38.9 (CH_2), 38.1 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 28.4 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.5 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[237]

Lab Book Reference GB6/463

_N_-Boc Proline 253

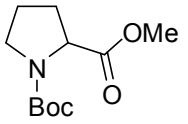


253

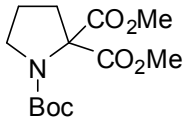
s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. The solution was then stirred at –30 °C under a CO_2 atmosphere for 10 min and then allowed to warm to rt. 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) 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 9:1 CH_2Cl_2-MeOH as eluent gave *N*-Boc proline **253** (106 mg, 49%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.33 (br s, 0.5H, NCH), 4.24 (br s, 0.5H, NCH), 3.62-3.14 (m, 2H, NCH_2), 2.38-2.17 (m, 1H, CH_2), 2.13-1.68 (m, 3H, CH_2), 1.47 (s, 4.5 H, CMe_3), 1.42 (s, 4.5 H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.9 (C=O, Boc), 153.9 (C=O, CO_2H), 80.9 (*C*Me_3), 80.1 (*C*Me_3), 59.4 (NCH), 46.9 (NCH_2), 46.3 (NCH_2), 30.8 (CH_2), 28.9 (CH_2), 28.4 (C*Me*$_3$), 28.2 (C*Me*$_3$), 24.3 (CH_2), 23.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[52]

Lab Book Reference GB6/466

Methyl (±)-*N*-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylate 254 and pyrrolidine-1,2,2-tricarboxylic acid 1-*tert*-butyl ester 2,2-dimethyl ester 257



254

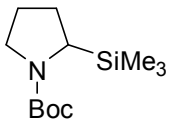


257

Using general procedure K, *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and methyl chloroformate (188 mg, 154 μL, 2.0 mmol, 2.0 eq.) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave methyl ester **254** (116 mg, 51%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz) (60:40 mixture of rotamers) δ 4.31 (dd, J = 8.5, 3.5 Hz, 0.4H, NCH), 4.21 (dd, J = 8.0, 4.0 Hz, 0.6H, NCH), 3.72 (s, 1.2H, OMe), 3.71 (s, 2.8H, OMe), 3.60-3.30 (m, 2H, NCH_2), 2.30-2.10 (m, 1H, CH_2), 2.02-1.74 (m, 3H, CH_2), 1.45 (s, 3.6H, CMe_3), 1.40 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.7 (C=O, CO_2Me), 173.5 (C=O, CO_2Me), 153.8 (C=O, Boc), 153.5 (C=O, Boc), 79.8 (*C*Me_3), 79.8 (*C*Me_3), 59.0 (NCH), 58.6 (NCH), 52.1 (OMe), 51.9 (OMe), 46.5 (NCH_2), 46.2 (NCH_2), 30.8 (CH_2), 29.9 (CH_2), 28.3 (C*Me*$_3$), 28.2 (C*Me*$_3$), 24.3 (CH_2), 23.6 (CH_2) and disubstituted pyrrolidine **257** (51 mg, 18%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.4; IR (film) 2977, 1752 (C=O, CO_2Me), 1703 (C=O, Boc), 1391, 1369, 1262, 1162, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 3.77 (s, 6H, OMe), 3.58 (t, J = 7.0 Hz, 1.3H, NCH_2), 3.51 (t, J = 7.0 Hz, 0.7H, NCH_2), 2.52-2.42 (m, 2H, CH_2), 1.90-1.81 (m, 2H, CH_2), 1.45 (s, 3.15H, CMe_3), 1.38 (s, 5.85H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 169.9 (C=O, CO_2Me), 169.7 (C=O, CO_2Me), 153.8 (C=O, Boc), 153.3 (C=O, Boc), 80.6 (*C*Me_3), 80.2 (*C*Me_3), 71.9 (N*C*CH_2), 71.8 (N*C*CH_2), 52.9 (OMe), 52.7 (OMe), 47.3 (NCH_2), 46.2 (NCH_2), 38.2 (CH_2), 36.7 (CH_2), 28.2 (C*Me*$_3$), 28.0 (C*Me*$_3$), 23.7 (CH_2), 22.9 (CH_2); MS (ESI) *m/z* 310 [(M + Na)$^+$, 26], 288 [(M + H)$^+$, 8], 232 (29), 188 (100); HRMS (ESI) *m/z* calcd for $C_{13}H_{21}NO_6$ (M + Na)$^+$ 310.1261, found 310.1263 (–0.5 ppm error). Spectroscopic data of **254** consistent with those reported in the literature.[238]

Lab Book Reference GB6/468

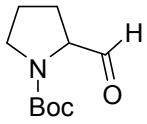
2-Trimethylsilyl pyrrolidine-1-carboxylic acid *tert*-butyl ester 39



39

Using general procedure K, *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and trimethylsilyl chloride (218 mg, 256 μL, 2.0 mmol, 2.0 eq.) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave silyl pyrrolidine **39** (172 mg, 71%) as a colourless oil.
Lab Book Reference GB5/460

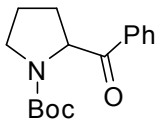
_N_-Boc Pyrrolidine-2-carboxaldehyde 255



255

Using general procedure K, *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-Et_2O as eluent gave aldehyde **255** (134 mg, 67%) as a colourless oil, R_F (1:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 9.52 (d, J = 1.5 Hz, 0.4H, CHO), 9.42 (d, J = 3.0 Hz, 0.6H, CHO), 4.16 (br t, J = 6.0 Hz, 0.4H, NCH), 4.02 (ddd, J = 10.5, 6.0, 3.0 Hz, 0.6H, NCH), 3.69-3.14 (m, 2H, NCH_2), 2.26-1.74 (m, 4H, CH_2), 1.44 (s, 3.6H, CMe_3), 1.39 (s, 5.4 H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 200.6 (C=O, CHO), 200.4 (C=O, CHO), 162.7 (C=O, Boc), 81.5 (CMe_3), 80.7 (CMe_3), 65.0 (NCH), 64.8 (NCH), 46.8 (NCH_2), 45.9 (NCH_2), 33.4 (CH_2), 32.7 (CH_2), 28.4 (CMe_3), 28.3 (CMe_3), 27.9 (CH_2), 23.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[119]
Lab Book Reference GB6/464

2-Benzoylpyrrolidine-1-carboxylic acid *tert*-butyl ester 256

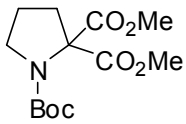


256

Following general procedure K, *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and a solution of *N,N*-dimethylbenzamide (298 mg, 2.0 mmol, 2.0 eq.) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave benzoyl pyrrolidine **256** (211 mg, 77%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2979, 1696 (C=O), 1404, 1367, 1164, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.05-7.91 (m, 2H, *o*-Ph), 7.60-7.51 (m, 1H, *p*-Ph), 7.50-7.41 (m, 2H, *m*-Ph), 5.32 (dd, J = 10.0, 3.5 Hz, 0.4H, NCH), 5.18 (dd, J = 10.0, 3.0 Hz, 0.6H, NCH), 3.77-3.58 (m, 1H, NCH_2), 3.56-3.43 (m, 1H, NCH_2), 2.23-2.18 (m, 1H, CH_2), 2.00-1.82 (m, 3H, CH_2), 1.4 (s, 5.4H, CMe_3), 1.24 (s, 3.6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 198.9 (PhC=O), 198.3 (PhC=O), 154.4 (C=O, Boc), 153.8 (C=O, Boc), 135.1 (*ipso*-Ph), 134.9 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.1 (Ph), 79.7 (CMe_3), 79.6 (CMe_3), 61.3 (NCH), 61.0 (NCH), 46.7 (NCH_2), 46.5 (NCH_2), 30.8 (CH_2), 29.7 (CH_2), 28.4 (CMe_3), 28.1 (CMe_3), 24.1 (CH_2), 23.5 (CH_2); MS (ESI) *m/z* 298 [$(M + Na)^+$, 12], 276 [$(M + H)^+$, 8], 220 (23), 176 [$(M + H - Boc)^+$, 100], 158 (13); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3$ $(M + H)^+$ 276.1594, found 276. 1604 (–3.6 ppm error).

Lab Book Reference GB5/459:2

Pyrrolidine-1,2,2-tricarboxylic acid 1-*tert*-butyl ester 2,2-dimethyl ester 257

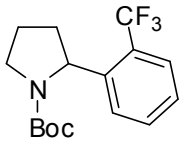


257

s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol, 2.6 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, methyl chloroformate (283 mg, 231 μL, 3.0 mmol, 3.0 eq.) was added. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm

to rt. 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) 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 9:1 petrol-EtOAc as eluent gave disubstituted pyrrolidine **257** (219 mg, 76%) as a colourless oil.
Lab Book Referecnce GB4/360

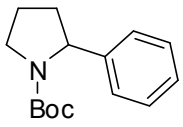
2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 183



183

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 **38** (171 mg, 175 μL, 1.0 mmol) in THF at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, $ZnCl_2$ (0.6 mL of a 1.0M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –30 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, 2-bromobenzotrifluoride (160 mg, 97 μL, 0.7 mmol) was added. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol) and *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol) was added in one portion. The resulting solution was stirred at rt for 16 h. 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the solution stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and H_2O (20 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-acetone as eluent gave aryl pyrrolidine **183** (161 mg, 73%) as a colourless oil.
Lab Book Reference GB7/602

***N*-Boc-2-Phenyl pyrrolidine 77**

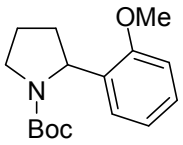


77

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) and bromobenzene (110 mg, 74 μL, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave phenyl pyrrolidine **77** (137 mg, 79%) as a white solid, R_F (CH_2Cl_2) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.35-7.25 (m, 2H, Ph), 7.25-7.08 (m, 3H, Ph), 4.97 (br s, 0.25H, NCH), 4.76 (br s, 0.75H, NCH), 3.87-3.34 (m, 2H, NCH_2), 2.32 (br s, 1H, CH_2), 2.04-1.74 (m, 3H, CH_2), 1.46 (br s, 2.25H, CMe_3), 1.18 (br s, 6.75H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.6 (C=O), 145.1 (*ipso*-Ph), 128.1 (Ph), 126.4 (Ph), 125.5 (Ph), 125.1 (Ph), 80.1 (CMe_3), 79.1 (CMe_3), 61.3 (NCH), 47.2 (NCH_2), 47.1 (NCH_2), 36.0 (CH_2), 35.9 (CH_2), 28.4 (CMe_3), 28.1 (CMe_3), 23.4 (CH_2), 23.2 (CH_2). Spectroscopic data consistent with those reported in the literature.[83]

Lab Book Reference GB7/609

_N_-Boc-2-(2-Methoxyphenyl)pyrrolidine 181

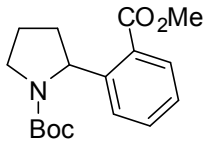


181

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) and 2-bromoanisole (131 mg, 86 μL, 0.7 mmol) gave the crude product. Pruification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave aryl pyrrolidine **181** (155 mg, 80%) as a brown solid.

Lab Book Reference GB6/711

2-(2-Methoxycarbonylphenyl) pyrrolidine-1-carboxylic acid *tert*-butyl ester 184

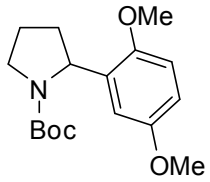


184

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) and methyl 2-bromobenzoate (150 mg, 98 μL, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave aryl pyrrolidine **184** (147 mg, 69%) as a yellow oil.

Lab Book Reference GB7/610

2-(2,5-Dimethoxyphenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 258



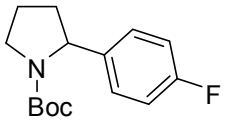
258

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.625 mmol, 6.25 mol%) and 1-bromo-2,5-dimethoxybenzene (152 mg, 105 μL, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with 6:1 petrol-EtOAc as eluent gave aryl pyrrolidine **258** (160 mg, 74%) as a colourless oil, R_F (6:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 3006, 2978, 1681 (C=O), 1495, 1403, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 6.82-6.50 (m, 3H, Ar), 5.20 (br d, J = 7.5 Hz, 0.4H, NCH), 5.05 (dd, J = 8.0, 4.0 Hz, 0.6H, NCH), 3.78 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.69-3.31 (m, 2H, NCH_2), 2.39-2.10 (m, 1H, CH_2), 1.94-1.67 (m, 3H, CH_2), 1.46 (s, 3.6H, CMe_3), 1.21 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.5 (C=O), 154.2 (C=O), 153.5 (*ipso*-C_6H_3OMe), 153.3 (*ipso*-C_6H_3OMe), 151.2 (*ipso*-C_6H_3OMe), 150.4 (*ipso*-C_6H_3OMe), 134.3 (*ipso*-Ar), 133.3 (*ipso*-Ar), 112.5 (Ar), 112.2 (Ar), 111.4 (Ar), 111.3 (Ar), 111.2 (Ar), 110.8 (Ar), 79.1 (*C*Me_3), 78.9 (*C*Me_3), 56.4, 56.2, 56.0, 55.7, 55.6, 55.5, 47.2 (NCH_2), 46.8 (NCH_2), 33.9 (CH_2), 32.8 (CH_2), 28.5 (C*Me*$_3$), 28.1 (C*Me*$_3$), 23.2 (CH_2), 23.0 (CH_2); MS (ESI) *m/z* 330 [$(M + Na)^+$, 100], 308 [$(M + H)^+$, 43], 252 (59), 208 (8); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_4$ $(M + Na)^+$ 330.1676, found 330.1680 (–

1.2 ppm error); *m/z* calcd for $C_{17}H_{25}NO_4$ $(M + H)^+$ 308.1859, found 308.1859 (–0.7 ppm error).

Lab Book Reference GB7/615

_N_-Boc-2-(4-Fluorophenyl)pyrrolidine 259

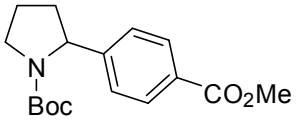


259

Using general procedure L, Pd(OAc) (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%), and 1-bromo-4-fluorobenzene (122 mg, 77 μL, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave aryl pyrrolidine **259** (158 mg, 85%) as a colourless oil, R_F (8:2 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.13 (br dd, J = 8.0, 6.0 Hz, 2H, Ar), 6.98 (t, J = 8.0 Hz, 2H, Ar), 4.92 (br s, 0.25H, NCH), 4.74 (br s, 0.75H, NCH), 3.80-3.40 (m, 2H, NCH_2), 2.48-2.17 (m, 1H, CH_2), 2.00-1.69 (m, 3H, CH_2), 1.46 (s, 2.25H, CMe_3), 1.20 (s, 6.75H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 161.6 (d, J = 244.0 Hz, *ipso*-C_6H_4F), 154.5 (C=O), 126.8 (d, J = 24.0 Hz, Ar), 126.5 (*ipso*-C_6H_4), 114.9 (d, J = 20.0 Hz, Ar), 79.3 (CMe_3), 60.7 (NCH), 53.4 (NCH_2), 47.0 (NCH_2), 36.1 (CH_2), 34.9 (CH_2), 28.4 (CMe_3), 28.1 (CMe_3), 23.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[83]

Lab Book Reference GB7/613

_N_-Boc-2-(4-carboxymethylphenyl)pyrrolidine 260



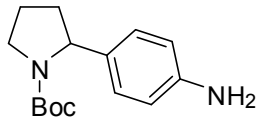
260

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) and methyl 4-bromobenzoate (150 mg, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave aryl pyrrolidine **260** (121 mg, 57%) as a colourless oil,

R_F (3:1 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.97 (d, J = 8.5 Hz, 2H, *o*-$C_6H_4CO_2Me$), 7.23 (d, J = 8.5 Hz, 2H, *m*-$C_6H_4CO_2Me$), 4.96 (br s, 0.3H, NCH), 4.79 (br s, 0.7H, NCH), 3.90 (s, 3H, OMe), 3.71-3.51 (m, 2H, NCH_2), 2.46-2.21 (m, 1H, CH_2), 1.99-1.79 (m, 3H, CH_2), 1.45 (s, 2.7H, CMe_3), 1.16 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 166.9 (C=O, CO_2Me), 154.4 (C=O, Boc), 150.6 (*ipso*-$C_6H_4CO_2Me$), 129.7 (Ar), 129.6 (Ar), 128.4 (*ipso*-Ar), 125.4 (Ar), 79.4 (CMe_3), 61.1 (OMe), 52.0 (NCH), 47.1 (NCH_2), 35.9 (CH_2), 34.7 (CH_2), 28.4 (CMe_3), 28.1 (CMe_3), 23.5 (CH_2), 23.2 (CH_2). Spectroscopic data consistent with those reported in the literature.[83]

Lab Book Reference GB7/614

_N_-Boc-2-(4-Aminophenyl)pyrrolidine 81



81

Using general procedure L, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) and 4-bromoaniline (120 mg, 0.7 mmol) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave aryl pyrrolidine **81** (117 mg, 64%) as an orange oil, R_F (1:1 petrol-EtOAc) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 6.94 (d, J = 7.0 Hz, 2H, *m*-$C_6H_4NH_2$), 6.61 (d, J = 7.0 Hz, 2H, *o*-$C_6H_4NH_4$), 4.85 (br s, 0.25H, NCH), 4.67 (br s, 0.75H, NCH), 3.84-3.32 (m, 4H, NH_2 + NCH_2), 2.39-2.10 (m, 1H, CH_2), 2.02-1.66 (m, 3H, CH_2), 1.44 (s, 2.25H, CMe_3), 1.21 (s, 6.75H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.6 (C=O), 144.7 (*ipso*-$C_6H_4NH_2$), 135.3 (*ipso*-Ar), 135.1 (*ipso*-Ar), 126.5 (Ar), 114.9 (Ar), 79.0 (CMe_3), 60.7 (NCH), 47.1 (NCH_2), 46.9 (NCH_2), 35.9 (CH_2), 28.2 (CMe_3), 23.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[83]

Lab Book Reference GB7/616

Attempted Diamine-Free Lithiation-Trapping of _N_-Boc Piperidine 44

Table 5.3, Entry 1:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C for 180 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/505

Table 5.3, Entry 2:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C for 360 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/552

Table 5.3, Entry 3:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 180 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/559

Table 5.3, Entry 4:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 60 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/558

Table 5.3, Entry 5:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 60 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/506

Table 5.3, Entry 6:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 60 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/504

Table 5.3, Entry 7:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 5 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/503

Table 5.3, Entry 8:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 5 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB6/554

Attempted Diamine-Free Lithiation-Trapping of *N*-Boc Homopiperidine 56

Table 5.4, Entry 1:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –78 °C for 360 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.

Lab Book Reference GB7/634

Table 5.4, Entry 2:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at

–78 °C for 360 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/633

Table 5.4, Entry 3:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 180 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/645

Table 5.4, Entry 4:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 180 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/644

Table 5.4, Entry 5:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 60 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/643

Table 5.4, Entry 6:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 60 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/642

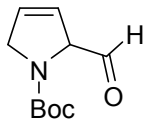
Table 5.4, Entry 7:

Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –40 °C for 30 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB6/508

Table 5.4, Entry 8:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 5 min and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/631

Table 5.4, Entry 9:
Using general procedure J, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and *N*-Boc homopiperidine **56** (199 mg, 1.0 mmol, 1.0 eq.) in THF (7 mL) at –30 °C for 5 min and DMF (146 mg, 155 μL, 2.0 mmol, 2.0 eq.) gave no trapped product by ^{1}H NMR spectroscopy of the crude product.
Lab Book Reference GB7/632

2-Formyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester 264



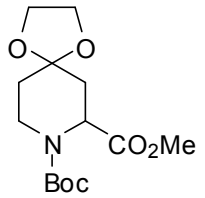
264

Using general procedure K, *N*-Boc pyrroline **261** (169 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and DMF (146 mg, 155 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave aldehyde **264** (39 mg, 20%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.6; IR ($CHCl_3$) 3009, 2980, 2933, 2872, 1735 (C=O, CHO), 1692 (C=O, Boc), 1400, 1369, 1256, 1173, 1128 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 9.43 (d, J = 3.0 Hz, 0.3H, CHO), 9.34 (d, J = 3.0 Hz, 0.7H, CHO), 6.11-6.05 (m, 0.7H, CH=CH), 6.03-5.98 (m,

0.3H, CH=CH), 5.67-5.60 (m, 0.3H, CH=CH), 5.59-5.53 (m, 0.7H, CH=CH), 4.94-4.86 (m, 0.3H, NCH), 4.83-4.74 (m, 0.7H, NCH), 4.32-4.27 (m, 1.4H, NCH_2), 4.25-4.20 (m, 0.6H, NCH_2), 1.49 (s, 2.7H, CMe_3), 1.44 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 198.4 (C=O, CHO), 198.0 (C=O, CHO), 154.4 (C=O, Boc), 153.5 (C=O, Boc), 130.7 (CH=CH), 130.2 (CH=CH), 122.9 (CH=CH), 122.6 (CH=CH), 81.0 (CMe_3), 80.6 (CMe_3), 72.7 (NCH), 72.5 (NCH), 53.8 (NCH_2), 53.7 (NCH_2), 28.3 (CMe_3), 28.2 (CMe_3); MS (ESI) *m/z* 220 [$(M + Na)^+$, 100], 158 (25), 142 (16), 112 (12), 98 (17); HRMS (ESI) *m/z* calcd for $C_{10}H_{15}NO_3$ $(M + Na)^+$ 220.0944, found 220.0944 (+0.3 ppm error).

Lab Book Reference GB7/565

1,4-Dioxa-8-azaspiro[4.5]decane-7,8-dicarboxylic acid 8-*tert* butyl ester 7-methyl ester 265

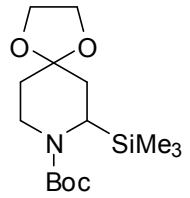


265

Using general procedure K, acetal piperidine **49** (243 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and methyl chloroformate (189 mg, 155 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave acetal piperidine **265** (84 mg, 24%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.1; IR ($CHCl_3$) 3010, 2979, 1745 (C=O, CO_2Me), 1691 (C=O, Boc), 1260, 1141, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.96 (br s, 0.5H, NCH), 4.77 (br s, 0.5H, NCH), 4.25-4.04 (m, 1H, NCH_2), 4.01-3.83 (m, 5H, NCH_2 + OCH_2CH_2O), 3.72 (s, 3H, OMe), 3.41-3.12 (m, 1H, CH_2), 2.43-2.27 (m, 1H, CH_2), 1.86-1.70 (m, 1H, CH_2), 1.69-1.54 (m, 1H, CH_2), 1.47 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 171.9 (C=O, CO_2Me), 171.6 (C=O, CO_2Me), 155.5 (C=O, Boc), 155.1 (C=O, Boc), 106.2 (OCO), 80.3 (CMe_3), 64.5 (OCH_2), 64.1 (OCH_2), 54.1 (OMe), 53.1 (OMe), 51.9 (NCH), 51.8 (NCH), 39.9 (NCH_2), 39.2 (NCH_2), 34.6 (CH_2), 34.5 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 28.3 (CMe_3), 28.2 (CMe_3); MS (ESI) *m/z* 324 [$(M + Na)^+$, 53], 302 [$(M + H)^+$, 55], 278 (25), 260 (21), 246 (84),

228 (13), 202 (100); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_6$ $(M + Na)^+$ 324.1418, found 324.1427 (–2.8 ppm error).
Lab Book Reference GB7/579

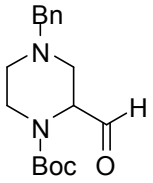
7-Trimethylsilanyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylic acid *tert*-butyl ester 50



50

Using general procedure K, acetal piperidine **49** (243 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and Me_3SiCl (217 mg, 254 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 6:1 petrol-EtOAc as eluent gave acetal piperidine **50** (46 mg, 14%) as a colourless oil, R_F (6:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3009, 2957, 1675 (C=O), 1419, 1247, 1170, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 4H, OCH_2), 3.71 (br s, 1H, NCH), 3.28 (br s, 1H, NCH_2), 2.95 (br s, 1H, NCH_2), 1.83-1.55 (m, 4H, CH), 1.44 (s, 9H, CMe_3), 0.08 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 107.5 (OCO), 79.2 (*C*Me_3), 64.4 (OCH_2), 64.2 (OCH_2), 44.4 (CH_2), 35.4 (CH_2), 28.4 (C*Me*$_3$), –0.9 ($SiMe_3$); MS (ESI) *m/z* 338 [$(M + Na)^+$, 70], 316 [$(M + H)^+$, 100], 260 (86), 244 (85), 216 (46); HRMS (ESI) *m/z* calcd for $C_{15}H_{29}NO_4Si$ $(M + Na)^+$ 316.1939, found 316.1947 (–2.6 ppm error).
Lab Book Reference GB7/581

4-Benzyl-2-formylpiperazine-1-carboxylic acid *tert*-butyl ester 266

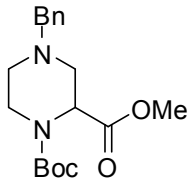


266

Using general procedure K, piperazine **59** (276 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and DMF (146 mg, 155 μL, 2.0 mmol)

gave the crude product. Purification by flash column chromatography on silic with 3:1 petrol-EtOAc as eluent gave aldehyde **266** (217 mg, 71%) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.9; IR ($CHCl_3$) 2978, 2818, 1736 (C=O, CHO), 1691 (C=O, Boc), 1392, 1967, 1298, 1170, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 9.52 (s, 0.5H, CHO), 9.49 (s, 0.5H, CHO), 7.35-7.22 (m, 5H, Ph), 4.58 (br s, 0.5H, NCH), 4.39 (br s, 0.5H, NCH), 3.90 (d, J = 12.5 Hz, 0.5H, NCH_2), 3.78 (d, J = 12.5 Hz, 0.5H, NCH_2), 3.57 (br d, J = 13.5 Hz, 1H, NCH_2Ph), 3.44 (br d, J = 13.5 Hz, 1H, NCH_2Ph), 3.30 (d, J = 12.0 Hz, 1H, NCH_2), 3.16 (t, J = 12.0 Hz, 0.5H, NCH_2), 3.06 (t, J = 12.0 Hz, 0.5H, NCH_2), 2.77 (d, J = 10.0 Hz, 0.5H, NCH_2), 2.71 (d, J = 10.0 Hz, 0.5H, NCH_2), 2.35-2.22 (m, 1H, NCH_2), 2.12 (t, J = 12.0 Hz, 0.5H, NCH_2), 2.11 (t, J = 12.0 Hz, 0.5H, NCH_2), 1.48 (s, 4.5H, CMe_3), 1.43 (s, 4.5, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 199.8 (C=O, CHO), 199.5 (C= O, CHO), 155.7 (C=O, Boc), 155.2 (C=O, Boc), 137.4 (*ipso*-Ph), 128.6 (Ph), 128.3 (Ph), 127.2 (Ph), 80.4 (CMe_3), 62.5 (NCH_2Ph), 61.5 (NCH), 60.4 (NCH), 52.1 (NCH_2), 51.1 (NCH_2), 50.8 (NCH_2), 42.0 (NCH_2), 40.9 (NCH_2), 28.3 (CMe_3), 28.1 (CMe_3); MS (ESI) *m/z* 337 (100), 323 (25), 305 [$(M + H)^+$, 12], 249 (15); HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N_2O_3$ $(M + H)^+$ 305.1860, found 305.1861(–0.6 ppm error).
Lab Book Reference GB6/530

4-Benzylpiperazine-1,2-dicarbxylic acid-1-*tert*-butl ester-2-methyl ester 267



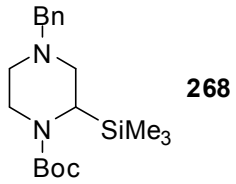
267

Using general procedure K, piperazine **59** (276 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and methyl chloroformate (189 mg, 155 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 7:1 petrol-Et_2O as eluent gave piperazine **267** (276 mg, 83%) as a colourless oil, R_F (7:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.39-7.18 (m, 5H, Ph), 4.72 (br s, 0.5H, NCH), 4.55 (br s, 0.5H, NCH), 3.87 (br d, J = 14.5 Hz, 0.5H, NCH_2), 3.77 (br d, J = 15.0 Hz, 0.5H, NCH_2), 3.74 (s, 1.5H, OMe), 3.71 (s, 1.5H, OMe), 3.59 (d, J = 14.0 Hz, 0.5H,

NCH_2Ph), 3.56 (d, J = 14.0 Hz, 0.5H, NCH_2Ph), 3.48 (d, J = 14.0 Hz, 0.5H, NCH_2Ph), 3.42 (d, J = 14.0 Hz, 0.5H, NCH_2Ph), 3.37-3.10 (m, 2H, NCH_2), 2.80 (br d, J = 11.0 Hz, 0.5H, NCH_2), 2.75 (br d, J = 11.0 Hz, 0.5H, NCH_2), 2.19 (td, J = 11.5, 4.0 Hz, 1H, NCH_2), 2.10 (br t, J = 12.0 Hz, 1H, NCH_2), 1.48 (s, 4.5H, CMe_3), 1.43 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 171.2 (C=O, CO_2Me), 170.9 (C=O, CO_2Me), 155.7 (C=O, Boc), 155.2 (C=O, Boc), 137.6 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.1 (Ph), 80.1 (CMe_3), 62.2 (NCH_2Ph), 55.4 (OMe), 54.3 (OMe), 53.4 (NCH_2), 52.4 (NCH_2), 52.2 (NCH_2), 51.8 (NCH), 41.9 (NCH_2), 40.9 (NCH_2), 28.2 (CMe_3), 28.1 (CMe_3). Spectroscopic data consistent with those reported in the literature.[109]

Lab Book Reference GB7/588

4-Benzyl-2-trimethylsilanylpiperazine-1-carboxylic acid *tert*-butyl ester 268

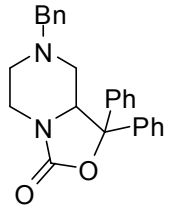


268

Using general procedure K, piperazine **59** (276 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and Me_3SiCl (217 mg, 260 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave silyl piperazine **268** (273 mg, 78%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2956, 2804, 1679 (C=O), 1454, 1416, 1365, 1294, 1248, 1171, 1110, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 4H, Ph), 7.24 -7.17 (m, 1H, *p*-Ph), 4.18 -3.67 (m, 1H, NCH), 3.66 -3.45 (m, 1H, NCH_2), 3.41-3.34 (m, 2H, NCH_2Ph), 3.04-2.16 (m, 4H, NCH_2), 1.90 (t, J = 11.5 Hz, 0.5H, NCH_2), 1.88 (t, J = 11.5 Hz, 0.5H, NCH_2), 1.42 (s, 9H, CMe_3), 0.05 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 138.3 (*ipso*-Ph), 129.2 (Ph), 128.1 (Ph), 127.1 (Ph), 79.2 (CMe_3), 63.4 (CH_2Ph), 54.2 (NCH_2), 53.1 (NCH_2), 41.5 (NCH_2), 28.4 (CMe_3), 27.9 (NCH), –0.9 ($SiMe_3$); MS (ESI) *m/z* 349 [$(M + H)^+$, 100], 293 (8); HRMS (ESI) *m/z* calcd for $C_{19}H_{32}N_2O_2Si$ $(M + H)^+$ 349.2306, found 349.2313 (–1.9 ppm error).

Lab Book Reference GB7/587

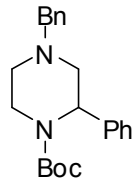
7-Benzyl-1,1-diphenylhexahydro-oxazolo[3,4-*α*]pyrazin-3-one 269



269

Using general procedure K, piperazine **59** (276 mg, 1.0 mmol) in THF (7 mL), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and a solution of benzophenone (364 mg, 2.0 mmol) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 85:15 petrol-EtOAc as eluent gave pyrazinone **269** (302 mg, 79%) as a colourless oil, R_F (85:15 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3066, 3031, 2815, 1757 (C=O), 1450, 1412, 1248, 996, 909, 733, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.52 (m, 2H, Ph), 7.46-7.21 (m, 13H, Ph), 4.60 (dd, J = 11.5, 3.5 Hz, 1H, NCH), 3.85 (dd, J = 13.0, 3.0 Hz, 1H, NCH_2), 3.55 (d, J = 13.0 Hz, 1H, NCH_2Ph), 3.35 (d, J = 13.0 Hz, 1H, NCH_2Ph), 3.14 (td, J = 13.0, 4.0 Hz, 1H, NCH_2), 2.73 (br d, J = 11.5 Hz, 1H, NCH_2), 2.61 (br d, J = 11.5 Hz, 1H, NCH_2), 1.98 (td, J = 11.5, 4.0 Hz, 1H, NCH_2), 1.63 (t, J = 11.5 Hz, 1H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 142.2 (*ipso*-Ph), 138.5 (*ipso*-Ph), 137.1 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 128.0 (Ph), 127.7 (Ph), 127.1 (Ph), 125.7 (Ph), 125.6 (Ph), 85.0 (CPh_2), 62.7 (NCH_2Ph), 61.0 (NCH), 55.6 (NCH_2), 50.6 (NCH_2), 41.5 (NCH_2); MS (ESI) *m/z* 385 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}N_2O_2$ $(M + H)^+$ 385.1911, found 385.1919 (–2.2 ppm error). Lab Book Reference GB7/589

4-Benzyl-2-phenylpiperazine-1-carboxylic acid *tert*-butyl ester 270



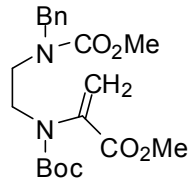
270

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 piperazine **59** (276 mg, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –30 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, a solution of bromobenzene (110 mg, 74 μL, 0.7 mmol) in *t*-butyl methyl ether (5 mL) was added. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%) and *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) in one portion. The reaction flask was transferred to a pre-heated oil bath and the resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the solution stirred at rt for 1 h. The solids were removed by filtration through Celite® and washed with Et_2O (20 mL). The filtrate was washed with saturated brine (20 mL) and H_2O (20 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-EtOAc as eluent gave phenyl piperazine **270** (136 mg, 55%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3009, 2979, 2808, 1682 (C=O), 1453, 1421, 1367, 1168, 1123, 909, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.52-7.45 (m, 1H, Ph), 7.42-7.16 (m, 9H, Ph), 5.21 (br s, 0.5H, NCH), 3.96 (br s, 0.5H, NCH), 3.89 (br d, J = 13.0 Hz, 1H, NCH_2), 3.77 (d, J = 13.0 Hz, 0.5H, NCH_2), 3.54 (d, J = 13.0 Hz, 0.5H, NCH_2), 3.42 (d, J = 13.0 Hz, 0.5H, NCH_2), 3.28-3.19 (m, 1H, NCH_2), 3.06-2.54 (m, 3H, NCH_2), 2.38 (dd, J = 12.0, 4.5 Hz, 0.5H, NCH_2), 2.14 (td, J = 12.0, 3.0 Hz, 0.5H, NCH_2), 2.05 (td, J = 12.0, 3.0 Hz, 0.5H, NCH_2), 1.45 (s, 4.5H, CMe_3), 1.43 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.9 (C=O), 154.4 (C=O), 141.0 (*ipso*-Ph), 140.4 (*ipso*-Ph), 138.6 (*ipso*-Ph), 137.8 (*ipso*-Ph), 129.1 (Ph), 128.7 (Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 127.1 (Ph), 126.8 (Ph), 126.7 (Ph), 79.8 (CMe_3), 79.7 (CMe_3), 67.1 (NCH), 63.1 (NCH_2), 58.9 (NCH_2), 54.9 (NCH_2),

53.3 (NCH_2), 51.5 (NCH_2), 39.8 (NCH_2), 28.4 (CMe_3), 28.4 (CMe_3); MS (ESI) *m/z* 353 [$(M + H)^+$, 100], 297 (6); HRMS (ESI) *m/z* calcd for $C_{22}H_{28}N_2O_2$ $(M + H)^+$ 353.2224, found 353.2224 (–0.1 ppm error).

Lab Book Reference GB7/649

2-[2-(Benzylmethoxycarbonylamino)ethyl]-*tert*-butoxycarbonylamino acrylic acid methyl ester 271



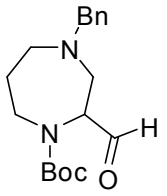
271

s-BuLi (2.57 mL of a 1.3 M solution in hexanes, 3.34 mmol) was added dropwise to a stirred solution of piperazine **59** (355 mg, 1.28 mmol) in THF (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, methyl chloroformate (366 mg, 300 μL, 3.85 mmol) was added dropwise. The resulting solution was stirred at –78 °C for 1 h. Then, the resulting solution was allowed to warm to rt and saturated $NH_4Cl_{(aq)}$ (10 mL) was added. The two layers were separated and 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. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alkene **271** (177 mg, 45%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.1; IR ($CHCl_3$) 2978, 1703 (C=O, CO_2Me + Boc), 1476, 1439, 1393, 1367, 1246, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.36-7.17 (m, 5H, Ph), 5.88 (br s, 0.5H, CH_2=), 5.84 (br s, 0.5H, CH_2=), 5.53 (br s, 0.5H, CH_2=), 5.31 (br s, 0.5H, CH_2=), 4.51 (s, 2H, CH_2Ph), 3.78-3.66 (m, 8H, 2 × OMe + NCH_2), 3.65-3.48 (m, 1H, NCH_2), 3.47-3.35 (m, 1H, NCH_2), 1.40 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_6$) (rotamers) δ 165.2 (C=O), 157.0 (C=O), 156.8 (C=O), 153.6 (C=O), 140.4 (*C*=CH_2), 140.0 (*C*=CH_2), 137.6 (*ipso*-Ph), 128.5 (Ph), 127.9 (Ph), 127.2 (Ph), 127.1 (Ph), 117.2 (CH_2=), 116.7 (CH_2=), 81.2 (*C*Me_3), 81.1 (*C*Me_3), 52.7 (OMe), 52.2 (OMe), 51.0 (*C*H_2Ph), 50.7 (*C*H_2Ph), 47.9 (NCH_2), 47.2 (NCH_2), 45.3 (NCH_2), 44.3 (NCH_2), 28.1 (CMe_3), 28.0 (CMe_3); MS (ESI) *m/z* 393 [$(M + H)^+$, 53], 337 (17), 293

(100); HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_2O_6$ $(M + H)^+$ 393.2020, found 393.2022 (–0.6 ppm error).

Lab Book Reference GB5/400

4-Benzyl-2-formyl[1,4]diazepane-1-carboxylic acid *tert*-butyl ester 273

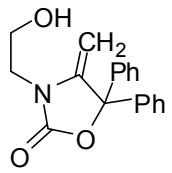


273

Using general procedure K, homopiperazine **272** (290 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and DMF (146 mg, 155 μL, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc as eluent gave aldehyde **273** (131 mg, 41%) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2972, 2929, 2817, 1730 (C=O, CHO), 1691 (C=O, Boc), 1453, 1392, 1365, 1300, 1252, 1155, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 9.51 (s, 0.4H, CHO), 9.46 (s, 0.6H, CHO), 7.36-7.22 (m, 5H, Ph), 4.53 (dd, J = 8.0, 3.5 Hz, 0.4H, NCH), 4.20 (dd, J = 8.0, 3.5 Hz, 0.6H, NCH), 4.12 (dd, J = 14.5, 8.0 Hz, 0.4H, NCH_2), 3.90 (ddd, J = 14.5, 8.0, 2.5 Hz, 0.6H, NCH_2), 3.68-3.54 (m, 2.4H, NCH_2), 3.44 (ddd, J = 15.0, 9.0, 2.5 Hz, 0.6H, NCH_2), 3.19-3.07 (m, 1H, NCH_2), 2.98 (dd, J = 14.5, 4.0 Hz, 0.4H, NCH_2), 2.91 (dd, J = 14.5, 3.0 Hz, 0.6H, NCH_2), 2.79-2.63 (m, 1H, NCH_2), 2.59-2.50 (m, 0.4H, NCH_2), 2.45 (ddd, J = 12.0, 8.5, 3.0 Hz, 0.6H, NCH_2), 1.86-1.64 (m, 2H, CH_2), 1.49 (s, 3.6H, CMe_3), 1.41 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 201.5 (CHO), 200.9 (CHO), 155.8 (C=O, Boc), 154.9 (C=O, Boc), 138.6 (*ipso*-Ph), 138.3 (*ipso*-Ph), 128.8 (Ph), 128.7 (Ph), 128.3 (Ph), 128.3 (Ph), 127.3 (Ph), 127.2 (Ph), 80.8 (CMe_3), 80.4 (CMe_3), 65.5 (NCH), 64.8 (NCH), 62.5 (NCH_2), 61.7 (NCH_2), 56.4 (NCH_2), 55.9 (NCH_2), 53.6 (NCH_2), 53.5 (NCH_2), 44.7 (NCH_2), 43.9 (NCH_2), 29.3 (CH_2), 28.9 (CH_2), 28.4 (CMe_3), 28.2 (CMe_3); MS (ESI) *m/z* 351 [$(M + MeOH + H)^+$, 12], 337 [$(M + H_2O + H)^+$, 100], 319 [$(M + H)^+$, 72], 263 (62); HRMS (ESI) *m/z* calcd for $C_{18}H_{26}N_2O_3$ $(M + H)^+$ 319.2016, found 319.2006 (+3.4 ppm error).

Lab Book Reference GB6/531

3-(2-Hydroxyethyl)-4-methylene-5,5-diphenyloxazolidin-2-one 275

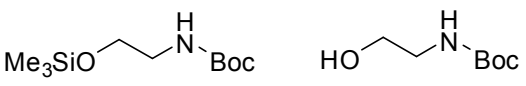


275

s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) was added dropwise to a stirred solution of *N*-Boc-4-morpholine **274** (187 mg, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 5 min. Then, a solution of benzophenone (546 mg, 3.0 mmol) in THF (1 mL) was added. The resulting solution was stirred at –30 °C for 10 min. Then, the resulting mixture was allowed to warm to rt and 1 M $NaOH_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 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 1:1 petrol-EtOAc as eluent gave oxazolidinone **275** (190 mg, 64%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.4; IR (film) 3456 (OH), 3062, 2938, 1766 (C=O), 1681, 1655, 1448, 1401, 1336, 1231, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.28 (m, 10H, Ph), 4.65 (d, J = 3.0 Hz, 1H, CH_2=), 4.21 (d, J = 3.0 Hz, 1H, CH_2=), 3.83 (t, J = 5.5 Hz, 2H, CH_2O), 3.69 (t, J = 5.5 Hz, 2H, CH_2N); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 147.1 (*C*=CH_2), 140.3 (*ipso*-Ph), 128.6 (Ph), 128.3 (Ph), 127.0 (Ph), 89.2 (*C*Ph_2), 86.7 (CH_2=), 58.9 (CH_2O), 44.1 (CH_2N); MS (ESI) *m/z* 318 [$(M + Na)^+$, 67], 296 [$(M + H)^+$, 100], 252 (42); HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_3$ $(M + Na)^+$ 318.1101, found 318.1094 (+2.2 ppm error).

Lab Book Reference GB7/564

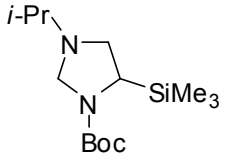
Attempted *s*-BuLi/(–)-sparteine-mediated lithiation-trapping of *N*-Boc morpholine 274



279 **280**

s-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol) was added dropwise to a stirred solution of *N*-Boc-4-morpholine **274** (187 mg, 1.0 mmol) and (–)-sparteine **3** (609 mg, 597 μL, 2.6 mmol) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 60 min. Then, Me_3SiCl (326 mg, 381 μL, 3.0 mmol) was added and the resulting solution was stirred at –78 °C for 10 min. Then, the mixture was allowed to warm to rt and saturated $NH_4.Cl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 ×10 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 9:1 and then 2:1 petrol-Et_2O and then 100% EtOAc gave *O*-trimethylsilyl-*N*-Boc ethanolamine **279** (177 mg, 76%) as a colourless oil, R_F (2:1 petrol-Et_2O) 0.9; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.03-3.94 (m, 1H, OCH_2), 3.94-3.85 (m, 1H, OCH_2), 3.57-3.49 (m, 1H, NCH_2), 3.40-3.28 (m, 1H, NCH_2), 1.44 (br s, 9H, CMe_3), 0.09 (br s, 9H, $SiMe_3$) and *N*-Boc ethanolamine **280** (12 mg, 7%) as a colourless oil, R_F (EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.99 (br s, 1H, OH), 3.71 (t, J = 5.0 Hz, 2H, OCH_2), 3.30 (t, J = 5.0 Hz, 1H, NCH_2), 3.29 (t, J = 5.0 Hz, 1H, NCH_2), 2.42 (br s, 1H, NH), 1.45 (s, 9H, CMe_3). Spectroscopic data of **279**[239] and **280**[231] consistent with those reported in the literature.

3-Isopropyl-5-trimethylsilylimidazolidine-1-carboxylic acid *tert*-butyl ester 281



281

Using general procedure M, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and Me_3SiCl (217 mg, 253 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 5:1 petrol-EtOAc as eluent gave silyl imidazolidine **281** (210 mg, 73%) as a colourless oil, R_F (5:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.36 (d, J = 6.0 Hz, 0.4H, NCH_2N), 4.28 (d, J = 6.0 Hz, 0.6H, NCH_2N), 3.63 (d, J = 6.0 Hz, 0.4H, NCH_2N),

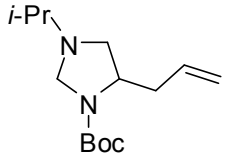
3.56 (d, J = 6.0 Hz, 0.6H, NCH_2N), 3.31-3.18 (m, 1H, NCHCH_2), 3.15-2.95 (m, 1H, NCHCH_2), 2.55 (br t, J = 7.5 Hz, 0.4H, NCHSi), 2.39 (br t, J = 7.5 Hz, 0.6H, NCHSi), 2.33 (septet, J = 6.5 Hz, 1H, NCHMe$_2$), 1.44 (s, 3.6H, CMe_3), 1.42 (s, 5.4H, CMe_3), 1.07 (d, J = 6.5 Hz, 6H, CHMe_2), 0.05 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.4 (C=O), 79.7 (CMe$_3$), 78.9 (CMe$_3$), 67.6 (NCH_2N), 53.4 (NCHCH$_2$), 53.0 (NCHMe$_2$), 28.4 (NCHSi), 28.2 (NCHSi), 21.6 (CMe_3), 21.5 (CMe_3), –2.4 ($SiMe_3$), –3.6 ($SiMe_3$). Spectroscopic data consistent with those reported in the literature.[75]

Lab Book Reference GB7/573

Using general procedure K, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and Me_3SiCl (271 mg, 253 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 5:1 petrol-EtOAc as eluent gave silyl imidazolidine **281** (181 mg, 63%) as a colourless oil.

Lab Book Reference GB7/562

5-Allyl-3-Isopropylimidazoidine-1-carboxylic acid *tert*-butyl ester 282



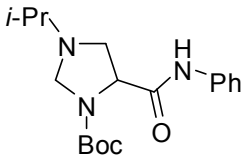
282

Using general procedure M, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and allyl bromide (242 mg, 173 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave imidazolidine **282** as a colourless oil, R_F (1:1 petrol-EtOAc) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 5.94-5.42 (m, 1H, CH=CH_2), 5.24-4.78 (m, 2H, CH=CH_2), 4.22 (d, J = 6.0 Hz, 0.55H, NCH_2H), 4.03 (d, J = 6.0 Hz, 0.45H, NCH_2N), 3.93-3.68 (m, 2H, NCH_2H + NCHCH_2), 2.94 (t, J = 8.0 Hz, 0.55H, NCHCH_2), 2.87 (t, J = 8.0 Hz, 0.45H, NCHCH_2), 2.74-2.42 (m, 2H, NCHCH_2 + CH_2=CHCH_2), 2.34 (septet, 1H, J = 6.5 Hz, NCHMe$_2$), 2.30-2.61 (m, 1H, CH_2=CHCH_2), 1.43 (s, 9H,

CMe_3), 1.05 (d, J = 6.5 Hz, 3.3H, NCHMe_2), 1.04 (d, J = 6.5 Hz, 2.7H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.4 (C=O), 153.3 (C=O), 134.6 (CH=CH_2), 134.4 (CH=CH_2), 117.3 (CH=CH_2), 79.6 (CMe$_3$), 67.2 (NCH_2N), 55.9 (NCH_2), 55.7 (NCHCH_2), 55.0 (NCH_2), 53.1 (NCHMe$_2$), 38.0 (CH_2=CHCH_2), 37.3 (CH2=CHCH2), 28.3 (CMe_3), 21.4 (NCHMe_2). Spectroscopic data consistent with those reported in the literature.[75]

Lab Book Reference GB7/618

3-Isopropyl-5-phenylcarbamoylimidazolidine-1-carboxylic acid *tert*-butyl ester 283

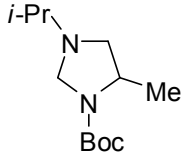


283

Using general procedure M, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and phenylisocycanate (238 mg, 217 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave imidazolidine **283** (245 mg, 74%) as a white solid, R_F (1:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers), δ 9.25 (br s, 0.5H, NH), 8.27 (br s, 0.5H, NH), 7.51 (d, J = 8.0 Hz, 2H, Ph), 7.31 (br s, 2H, Ph), 7.09 (br s, 1H, Ph), 4.64-4.23 (m, 1.5H, NCH + NCH_2N), 4.23-4.08 (m, 0.5H, NCH_2N), 4.08-3.93 (m, 1H, NCH_2N), 3.65-3.39 (m, 0.5H, NCH_2), 3.32-3.09 (m, 1H, NCH_2), 3.09-2.73 (m, 1H, NCH_2), 2.50 (septet, J = 6.5 Hz, 1H, NCHMe$_2$), 1.45 (br s, 9H, CMe_3), 1.12 (d, J = 6.5 Hz, 6H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 169.6 (C=O, amide), 153.4 (C=O, Boc), 137.5 (*ipso*-Ph), 128.8 (Ph), 124.0 (Ph), 119.6 (Ph), 81.4 (CMe$_3$), 67.2 (NCH_2N), 67.1 (NCH_2N), 61.2 (NCH_2), 55.1 (NCH), 52.5 (NCHMe$_2$), 28.2 (CMe_3), 21.3 (NCHMe_2). Spectroscopic data consistent with those reported in the literature.[75]

Lab book Reference GB7/603

3-Isopropyl-5-methylimidazolidine-1-carboxylic acid *tert*-butyl ester 284

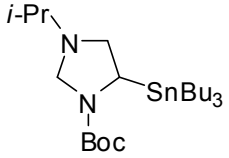


284

Using general procedure M, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and iodomethane (284 mg, 125 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 5:1 petrol-EtOAc as eluent gave imidazolidine **284** (151 mg, 66%) as a colourless oil, R_F (5:1 petrol-EtOAc) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 4.23 (d, J = 6.0 Hz, 0.55H, NCH_2N), 4.04 (d, J = 6.0Hz, 0.45H, NCH_2N), 3.97-3.66 (m, 2H, NC*H*Me + NCH_2N), 3.05 (t, J = 8.0 Hz, 0.55H, NCHCH_2), 2.97 (t, J = 8.0 Hz, 0.45H, NCHCH_2), 2.41-2.21 (NCHCH_2 + NC*H*Me_2), 1.41 (s, 9H, CMe_3), 1.24 (d, J = 6.0 Hz, 1.35H, Me), 1.19 (d, J = 6.0Hz, 1.65H, Me), 1.05 (d, J = 6.0 Hz, 3.3H, NCHMe_2), 1.04 (d, J = 6.0 Hz, 2.7H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.8 (C=O), 79.4 (*C*Me_3), 67.1 (NCH_2N), 59.0 (NCH*C*H_2), 58.1 (NCH*C*H_2), 53.2 (N*C*HMe), 52.2 (N*C*HMe_2), 28.4 (C*Me*$_3$), 21.4 (NCH*Me*$_2$), 21.3 (NCH*Me*$_2$), 19.7 (Me), 19.2 (Me). Spectroscopic data consistent with those reported in the literature.[75]

Lab Book Reference GB7/604

1-Isopropyl-5-tributylstannylimidazolidine-1-carboxylic acid *tert*-butyl ester 285



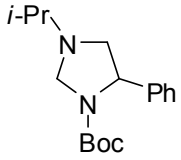
285

Using general procedure M, *N*-Boc-*N*′-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol), *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) and tributylstannyl

chloride (651 mg, 542 μL, 2.0 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave imidazolidine **285** (287 mg, 57%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 4.22 (d, J = 6.0 Hz, 0.7H, NCH_2N), 4.12 (d, J = 6.0 Hz, 0.3H, NCH_2N), 3.86 (d, J = 6.0 Hz, 0.3H, NCH_2N), 3.60 (d, J = 6.0 Hz, 0.7H, NCH_2N), 3.67-3.55 (m, 0.3H, NCHSn), 3.43 (dd, J = 10.0, 6.5 Hz, 0.7H, NCHSn), 3.18 (dd, J = 9.5, 6.5 Hz, 0.7H, NCHCH_2), 3.03 (dd, J = 9.0, 7.0 Hz, 0.3H, NCHCH_2), 2.79 (dd, J = 9.0, 6.0 Hz, 0.3H, NCHCH_2), 2.52 (t, J = 9.5 Hz, 0.7H, NCHCH_2), 2.39 (septet, J = 6.0 Hz, 1H, NCHMe$_2$), 1.62-1.38 (m, 6H, $SnCH_2$), 1.42 (s, 9H, CMe_3), 1.37-1.22 (m, 6H, $SnCH_2CH_2$), 1.11 (d, J = 6.0 Hz, 1.8H, NCHMe_2), 1.09 (d, J = 4.0 Hz, 4.2H, NCHMe_2), 1.00-0.75 (m, 15H, $SnCH_2CH_2CH_2$ + $SnCH_2CH_2CH_2Me$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 152.9 (C=O), 152.8 (C=O), 79.7 (CMe$_3$), 78.9 (CMe$_3$), 66.8 (NCH_2N), 66.7 (NCH_2N), 55.7 (NCHCH_2), 55.2 (NCHCH_2), 53.3 (NCHMe$_2$), 53.0 (NCHMe$_2$), 45.9 (NCHSn), 45.0 (NCHSn), 29.0 ($SnCH_2$), 28.4 (CMe_3), 27.9 (CMe_3), 27.7 ($SnCH_2$), 27.4 ($SnCH_2CH_2$), 26.7 ($SnCH_2CH_2$), 21.6 (NCHMe_2), 20.4 (NCHMe_2), 13.6 (CH_2Me), 13.5 (CH_2Me), 9.9 (CH$_2$Me), 9.4 (CH$_2$Me). Spectroscopic data consistent with those reported in the literature.[75]

Lab Book Reference GB7/620

3-Isopropyl-5-phenylimidazolidine-1-carboxylic acid *tert*-butyl ester 286



286

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-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 10 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) was added and the resulting solution was stirred at –30 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (110 mg, 74 μL, 0.7 mmol) in TBME (5 mL) was added. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%) and *t*-

Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) was added in one portion. The reaction flask was transferred to a pre-heated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (20 mL). The filtrate was washed with saturated brine (20 mL) and H_2O (20 mL), 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 phenyl imidazolidine **286** (87 mg, 43%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 3015, 2978, 1690 (C=O), 1410, 1217, 1165, 908, 777, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.39-7.21 (m, 5H, Ph), 4.89 (br t, J = 7.0 Hz, 0.25 H, NCHPh), 4.77 (t, J = 8.0 Hz, 0.75H, NCHPh), 4.53 (d, J = 6.0 Hz, 0.75H, NCH_2N), 4.32 (d, J = 5.0 Hz, 0.25H, NCH_2N), 4.17-4.06 (m, 1H, NCH_2N), 3.39 (t, J = 8.0 Hz, 0.75H, NCHCH_2), 3.29 (t, J = 7.0 Hz, 0.25H, NCHCH_2), 2.68-2.57 (m, 1H, NCHCH_2), 2.46 (septet, J = 6.5 Hz, 1H, NCHMe$_2$), 1.44 (s, 2.25H, CMe_3), 1.17 (s, 6.75H, CMe_3), 1.12 (d, J = 6.5 Hz, 1.5H, NCHMe_2), 1.11 (d, J = 6.5 Hz, 4.5H, NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.6 (C=O), 142.8 (*ipso*-Ph), 128.4 (Ph), 128.1 (Ph), 127.0 (Ph), 126.4 (Ph), 126.1 (Ph), 79.6 (CMe$_3$), 68.2 (NCH_2N), 68.0 (NCH_2N), 60.9 (NCHPh), 60.6 (NCHCH_3), 53.1 (NCHMe$_2$), 28.4 (CMe_3), 28.0 (CMe_3), 21.6 (NCHMe_2), 21.5 (NCHMe_2); MS (ESI) *m/z* 291 [$(M + H)^+$, 100], 235 (45); HRMS (ESI) *m/z* calcd for $C_{17}H_{26}N_2O_2$ $(M + H)^+$ 291.2067, found 291.2073 (–1.0 ppm error).
Lab Book Reference GB7/654

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'*-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol) in THF (7 mL) at –30 °C under Ar. The resulting solution was stirred at –30 °C for 10 min. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol) as added and the resulting solution was stirred at –30 °C for 30 min. The solution was allowed to warm to rt and stirred at rt for 30 min. Then, bromobenzene (110 mg, 74 μL, 0.7 mmol) in TBME (5 mL) was added. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%) and *t*-Bu_3PHBF_4 (11 mg, 0.0625 mmol, 6.25 mol%) was added in one portion. The resulting solution was stirred at rt for 16 h. 35% $NH_4OH_{(aq)}$ (0.2 mL) was added and the reaction solution was stirred at rt for 1 h. The solids were removed by filtration

through a pad of Celite® and washed with Et_2O (20 mL). The filtrate was washed with saturated brine (20 mL) and H_2O (20 mL), 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 phenyl imidazolidine **286** (43 mg, 21%) as a colourless oil.

Lab Book Reference GB7/653

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/THF (–30 °C)

(Scheme 5.24)

THF (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 *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –30 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added. The solution was stirred at –30 °C for 20 min.

For *N*-Boc pyrrolidine **38**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *s*-BuLi, a new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **287**. After a lithiation time of 3 min, complete lithiation of *N*-Boc pyrrolidine **38** to lithiated intermediate **287** was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/667

ReactIR monitoring of the lithiation of *N*-Boc pyrrolidine 38 by *s*-BuLi/THF (–78 °C)

(Scheme 5.25)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc pyrrolidine **38** (171 mg, 175 μL, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 15 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added. The solution was stirred at –78 °C 45 min.

For *N*-Boc pyrrolidine **38**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. Upon addition of *s*-BuLi, a new peak at 1660 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **287**. After a lithiation time of 45 min,

lithiation was still incomplete. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/725

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/THF (–30 °C) (Scheme 5.26)

THF (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 *N*-Boc-*N*′-benzyl piperazine **59** (276 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –30 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –30 °C for 10 min.

For *N*-Boc-*N*′-benzyl piperazine **59**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of the lithiated intermediate **288**. After a lithiation time of 3 min, complete lithiation of *N*-Boc-*N*′-benzyl piperazine **59** to lithiated intermediate **288** was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/750

ReactIR monitoring of the lithiation of piperazine 59 by *s*-BuLi/THF (–78 °C) (Scheme 5.27)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N*′-benzyl piperazine **59** (276 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 5 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C. for 45 min.

For *N*-Boc-*N*′-benzyl piperazine **59**, a peak at 1696 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak appeared at 1646 cm^{-1} which was assigned to $\nu_{C=O}$ of the lithiated intermediate **288**. After a lithiation time of 45 min, complete lithiation of *N*-Boc-*N*′-benzyl piperazine **59** to lithiated intermediate **288** was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/751

Attampted ReactIR monitoring of the lithiation of *N*-Boc piperidine 44 by *s*-BuLi/TMEDA in THF

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, TMEDA (151 mg, 196 μL, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 45 min.

For *N*-Boc piperidine **44**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. No other peaks were observed after the addition of *s*-BuLi or TMEDA.

Lab Book Reference GB8/669

Attampted ReactIR monitoring of the lithiation of *N*-Boc piperidine 44 by *s*-BuLi/THF

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to rt, –30 °C, a solution of *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred for 10 min (to verify stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.0 mmol) was added dropwise. The solution was stirred at –30 °C for 25 min.

For *N*-Boc piperidine **44**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. No other peaks were observed after the addition of *s*-BuLi.

Lab Book Reference GB8/670

Attampted ReactIR monitoring of the lithiation of *N*-Boc piperidine 44 by *s*-BuLi/(+)-sparteine surrogate 6 in THF

THF (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 *N*-Boc piperidine **44** (185 mg, 192 μL, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 30 min (to verify stability of readout on ReactIR). Then, a solution of (+)-sparteine surrogate **6** (227 mg, 1.3 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 20 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 20 min.

For *N*-Boc piperidine **44**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. No other peaks were observed after the addition of *s*-BuLi and (+)-sparteine surrogate.

Lab Book Reference GB8/671

ReactIR monitoring of the lithiation of *N*-Boc-*N′*-*iso*-propylimidazolidine 64 by *s*-BuLi/THF (–78 °C)

(Scheme 5.29)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N′*-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.0 mmol) was added dropwise. The solution was stirred at –78 °C for 25 min.

For *N*-Boc-*N′*-*i*-Pr imidazolidine **64**, a peak at 1705 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1663 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **290**. After a lithiation time of 3 min, partial lithiation (~60%) of *N*-Boc-*N′*-*i*-Pr imidazolidine **64** to lithiated intermediate **290** was observed. After a further 20 min incubation, no further lithiation was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/672

ReactIR monitoring of the lithiation of *N*-Boc-*N'*-*iso*-propylimidazolidine 64 by *s*-BuLi/THF (–30 °C)

(Scheme 5.30)

THF (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 *N*-Boc-*N′*-*i*-Pr imidazolidine **64** (214 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –30 °C for 8 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.0 mmol) was added dropwise. The solution was stirred at –30 °C for 10 min.

For *N*-Boc-*N′*-*i*-Pr imidazolidine **64**, a peak at 1705 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1662 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **290**. After a lithiation time of 3 min, partial

lithiation of *N*-Boc-*N*′-*i*-Pr imidazolidine **64** to lithiated intermediate **290** was observed. After a further 7 min incubation, slower complete lithiation of *N*-Boc-*N*′-*i*-Pr imidazolidine **64** was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/673

ReactIR monitoring of the lithiation of *N*-Boc-*N*'-benzylhomopiperazine 272 by *s*-BuLi/THF (–78 °C)

(Scheme 5.31)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-*N*′-benzyl homopiperazine **272** (290 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 1 h.

For *N*-Boc-*N*′-benzyl hompiperazine **272**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1645 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **291**. After a lithiation time of 1 h, partial lithiation (~40%) of *N*-Boc-*N*′-benzyl homopiperazine **272** to lithiated intermediate **291** was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/674

ReactIR monitoring of the lithiation of *N*-Boc-*N*'-benzylhomopiperazine 272 by *s*-BuLi/THF (–30 °C)

(Scheme 5.32)

THF (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 *N*-Boc-*N*′-benzyl homopiperazine **272** (290 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –30 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –30 °C for 1 h.

For *N*-Boc-*N*′-benzyl hompiperazine **272**, a peak at 1695 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1646 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **291**. After a lithiation time of 20 min, partial

lithiation (~60%) of *N*-Boc-*N*′-benzyl homopiperazine **272** to lithiated intermediate **291** was observed. After a further 40 min incubation, no further lithiation was observed. No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/675

ReactIR monitoring of the lithiation of *O*-alkyl carbamate 100 by *s*-BuLi/THF (Scheme 5.32)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *O*-alkyl carbamate **100** (263 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The solution was stirred at –78 °C for 10 min (to verify the stability of readout on ReactIR). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –78 °C for 1 h.

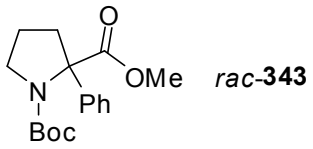
For *O*-alkyl carbamate **100**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new broad peak at 1630 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **292**. After a lithiation time of 1 h, lithiation was still incomplete (~40% completion). No peak corresponding to a prelithiation complex was observed.

Lab Book Reference GB8/684

7.7 Experimental for Chapter 6

***rac*-2-Phenyl pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester *rac*-343**

(Table 6.2, entry 1)



rac-**343**

Using general procedure N, *s*-BuLi (615 μL of a 1.3 M solution in hexanes, 0.80 mmol) and phenyl pyrrolidine *rac*-**77** (153 mg, 0.62 mmol) in THF (4 mL) at –78 °C for 30 min and methyl chloroformate (117 mg, 95 μL, 1.24 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (33 mg, 17%) as a colourless oil, R_F (3:1 petrol-Et_2O) 0.2; IR (film) 2977, 1747 (C=O, CO_2Me), 1697 (C=O, Boc), 1391, 1250, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.40-7.30 (m, 4H, Ph), 7.30-7.21 (m, 1H, Ph), 3.76 (s, 2.25H, OMe), 3.73 (s, 0.75H, OMe), 3.75-3.55 (m, 2H, NCH_2), 2.67-2.52 (m, 1H, CH_2), 2.32-2.22 (m, 1H, CH_2), 1.95-1.84 (m, 1H, CH_2), 1.72-1.60 (m, 1H, CH_2), 1.49 (s, 2.25H, CMe_3), 1.21 (s, 6.75H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.7 (C=O, CO_2Me), 162.0 (C=O, CO_2Me), 154.5 (C=O, Boc), 154.2 (C=O, Boc), 140.6 (*ipso*-Ph), 138.0 (*ipso*-Ph), 128.6 (Ph), 127.8 (Ph), 127.6 (Ph), 127.4 (Ph), 127.3 (Ph), 127.1 (Ph), 80.2 (CMe_3), 78.8 (CMe_3), 71.5 (NC), 71.4 (NC), 52.2 (OMe), 47.5 (NCH_2), 44.5 (NCH_2), 43.2 (CH_2), 41.5 (CH_2), 35.8 (CH_2), 33.1 (CH_2), 28.0 (CMe_3), 27.7 (CMe_3); MS (ESI) *m/z* 328 [$(M + Na)^+$, 100], 250 (55), 206 (27); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_4$ $(M + Na)^+$ 328.1519, found 328.1526 (–2.1 ppm error).
Lab Book Reference GB8/699

(Table 6.2, entry 2)

Using general procedure N, *n*-BuLi (250 μL of a 2.05 M solution in hexanes, 0.50 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at –78 °C for 60 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (41 mg, 33%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (66 mg, 66% recovery) as a colourless oil.

Lab Book Reference GB8/704

(Table 6.2, entry 3)

Using general procedure N, *n*-BuLi (250 μL of a 2.05 M solution in hexanes, 0.50 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at –78 °C for 180 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (48 mg, 39%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (52 mg, 52% recovery) as a colourless oil.

Lab Book Reference GB8/705

(Table 6.2, entry 4)

Using general procedure O, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol), TMEDA (58 mg, 75 μL, 0.5 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at –78 °C for 60 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (38 mg, 31%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (65 mg, 65% recovery) as a colourless oil.

Lab Book Reference GB8/708

(Table 6.2, entry 5)

Using general procedure O, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol), TMEDA (58 mg, 75 μL, 0.5 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at –78 °C for 180 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (40 mg, 33%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (49 mg, 49% recovery) as a colourless oil.

Lab Book Reference GB8/709

(Table 6.2, entry 6)

Using general procedure O, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol), TMEDA (58 mg, 75 μL, 0.5 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in Et_2O (4 mL) at –78 °C for 60 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica

with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (35 mg, 29%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (70 mg, 70% recovery) as a colourless oil.
Lab Book Reference GB8/714

(Table 6.2, entry 7)
Using general procedure O, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol), TMEDA (58 mg, 75 μL, 0.5 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in Et_2O (4 mL) at –78 °C for 180 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (39 mg, 32%) as a colourless oil and recovered phenyl pyrrolidine *rac*-**77** (52 mg, 52% recovery) as a colourless oil.
Lab Book Reference GB8/715

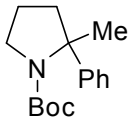
(Table 6.3, entry 3)
Using general procedure N, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at 0 °C for 10 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (88 mg, 72%) as a colourless oil.
Lab Book Reference GB8/713

(Table 6.3, entry 4)
Using general procedure N, *n*-BuLi (200 μL of a 2.5 M solution in hexanes, 0.50 mmol) and phenyl pyrrolidine *rac*-**77** (100 mg, 0.40 mmol) in THF (4 mL) at 0 °C for 5 min and methyl chloroformate (76 mg, 62 μL, 0.80 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (94 mg, 77%) as a colourless oil.
Lab Book Reference GB8/712

(Table 6.3, entry 5)
Using general procedure N, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine *rac*-**77** (50 mg, 0.20 mmol) in THF (4 mL) at rt for 5 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by

flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (25 mg, 41%) as a colourless oil.
Lab Book Reference GB9/785

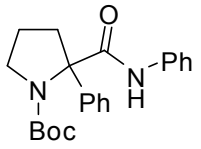
***rac*-2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-334**



rac-**334**

Using general procedure P, *n*-BuLi (232 μL of a 2.5 M solution in hexanes, 0.58 mmol) and phenyl pyrrolidine *rac*-**77** (110 mg, 0.44 mmol) in THF (4 mL) and dimethyl sulfate (112 mg, 84 μL, 0.89 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**334** (158 mg, 98%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 3017, 2975, 1674 (C=O), 1400, 1216, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.32-7.18 (m, 5H, Ph), 3.74-3.66 (m, 2H, NCH_2), 2.11-1.98 (m, 2H, CH_2), 1.90-1.81 (m, 2H, CH_2), 1.74 (s, 0.9H, Me), 1.58 (s, 2.1H, Me), 1.45 (s, 2.7H, CMe_3), 1.11 (s, 6.3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.7 (C=O), 148.8 (*ipso*-Ph), 128.1 (Ph), 126.2 (Ph), 125.3 (Ph), 79.1 (*C*Me_3), 64.8 (NC), 48.6 (NCH_2), 48.4 (NCH_2), 45.6 (CH_2), 28.3 (C*Me*$_3$), 27.8 (C*Me*$_3$), 25.1 (CH_2), 21.8 (CH_2); MS (ESI) *m/z* 284 [$(M + Na)^+$, 100], 206 (65); HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_2$ $(M + Na)^+$ 284.1621, found 284.1617 (+1.5 ppm error).
Lab Book Reference GB8/722

***rac*-2-Phenyl-2-phenylcarbamoylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-347**



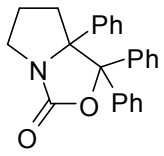
rac-**347**

Using general procedure P, *n*-BuLi (232 μL of a 2.5 M solution in hexanes, 0.58 mmol) and phenyl pyrrolidine *rac*-**77** (110 mg, 0.44 mmol) in THF (4 mL) and phenyl

isocyanate (106 mg, 97 μL, 0.89 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**347** (158 mg, 98%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2976, 1718 (C=O, amide), 1688 (C=O, Boc), 1600, 1555, 1446, 1390, 1368, 1154, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 2H, Ph), 7.34-7.29 (m, 6H, Ph), 7.24-7.28 (m, 2H, Ph), 3.86-3.57 (m, 2H, NCH_2), 3.34-3.15 (br s, 1H, NH), 2.05-1.67 (m, 4H, CH_2), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 170.8 (C=O, amide), 156.5 (C=O, Boc), 153.1 (*ipso*-Ph), 152.2 (*ipso*-Ph), 141.5 (*ipso*-Ph), 139.2 (*ipso*-Ph), 129.0 (Ph), 128.9 (Ph), 128.8 (Ph), 128.5 (Ph), 127.4 (Ph), 125.0 (Ph), 123.9 (Ph), 123.8 (Ph), 123.0 (Ph), 119.9 (Ph), 119.7 (Ph), 118.6 (Ph), 81.1 (CMe_3), 75.0 (NC), 49.9 (NCH_2), 41.4 (CH_2), 28.0 (CMe_3), 27.5 (CMe_3), 23.3 (CH_2); MS (ESI) *m/z* 389 [$(M + Na)^+$, 100], 367 [$(M + H)^+$, 39], 311 (46), 267 (32); HRMS (ESI) *m/z* $C_{22}H_{26}N_2O_3$ $(M + Na)^+$ 389.1836, found 389.1827 (+2.2 ppm error).

Lab Book Reference GB8/721

rac-1,1,7a-Triphenyltetrahydropyrrolo[1,2-*c*]oxazol-3-one _rac_-348

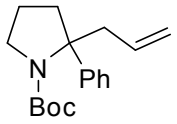


rac-**348**

Using general procedure P, *n*-BuLi (124 μL of a 2.5 M solution in hexanes, 0.31 mmol) and phenyl pyrrolidine *rac*-**77** (60 mg, 0.24 mmol) in THF (4 mL) and benzophenone (88 mg, 0.48 mmol) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave oxazolidone *rac*-**348** (87 mg, 84%) as a white solid, mp 134-135 °C; R_F (9:1 petrol-Et_2O) 0.1; IR ($CHCl_3$) 3018, 1747 (C=O), 1449, 1350, 1216, 1016, 759, 704, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.73 (m, 2H, Ph), 7.48-7.38 (m, 2H, Ph), 7.38-7.30 (m, 1H, Ph), 7.30-7.22 (m, 2H, Ph), 7.20-7.11 (m, 3H, Ph), 7.04-6.92 (m, 5H, Ph), 3.88 (ddd, J = 12.0, 9.0, 7.0 Hz, 1H, NCH_2), 2.90 (ddd, J = 12.0, 10.0, 3.5 Hz, 1H, NCH_2), 2.63 (dd, J = 12.0, 7.0 Hz, 1H, CH_2), 2.00-1.89 (m, 1H, CH_2), 1.69-1.58 (m, 1H, CH_2), 1.56-1.40 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.3 (C=O), 140.9 (*ipso*-Ph), 140.8 (*ipso*-Ph), 136.9 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 128.3 (Ph), 128.0 (Ph), 127.8 (Ph), 127.6 (Ph), 127.4 (Ph), 126.7 (Ph), 126.5 (Ph), 126.3 (Ph), 89.2 ($OCPh_2$), 80.3 (NC), 44.2 (NCH_2), 34.3 (CH_2),

23.1 (CH_2); MS (ESI) *m/z* 378 [$(M + Na)^+$, 84], 356 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}NO_2$ $(M + H)^+$ 356.1645, found 356.1640 (+1.3 ppm error).
Lab Book Reference GB8/741

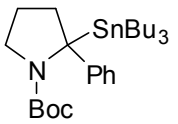
***rac*-2-Allyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-349**



rac-**349**

Using general procedure P, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine *rac*-**77** (50 mg, 0.20 mmol) in THF (4 mL) and allyl bromide (48 mg, 35 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**349** (54 mg, 95%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 3018, 2979, 1675 (C=O), 1395, 1367, 1216, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.33-7.27 (m, 2H, Ph), 7.24-7.16 (m, 3H, Ph), 5.93-5.73 (m, 0.7H, CH=), 5.26-5.12 (m, 1.3H, CH= + CH_2=), 3.91-3.77 (m, 0.7H, CH_2=), 3.75-3.64 (m, 0.3H, CH_2=), 3.55-3.31 (m, 1H, NCH_2), 3.20-3.08 (m, 0.3H, NCH_2), 2.88-2.70 (m, 0.7H, NCH_2), 2.66-2.56 (m, 0.3H, CH_2), 2.39-2.20 (m, 0.7H, CH_2), 1.98-1.82 (m, 0.6H, CH_2), 1.81-1.67 (m, 1.4H, CH_2), 1.60-1.54 (m, 1H, CH_2), 1.46 (s, 2.7H, CMe_3), 1.19 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.7 (C=O), 148.5 (*ipso*-Ph), 148.4 (*ipso*-Ph), 134.4 (CH=), 128.4 (Ph), 128.1 (Ph), 126.4 (Ph), 126.3 (Ph), 125.2 (Ph), 125.1 (Ph), 118.8 (CH_2=), 79.4 ($C$$Me_3$), 78.8 ($C$$Me_3$), 68.1 (NC), 61.2 (NC), 49.1 (NCH_2), 49.0 (NCH_2), 42.2 (CH_2), 41.3 (CH_2), 41.2 (CH_2), 28.3 (CMe_3), 27.9 (CMe_3), 20.8 (CH_2); MS (ESI) *m/z* 310 [$(M + Na)^+$, 79], 288 [$(M + H)^+$, 10], 232 (100); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_2$ $(M + H)^+$ 288.1958, found 288.1955 (+0.9 ppm error).
Lab Book Reference GB9/788

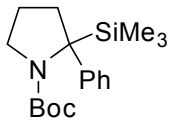
***rac*-2-Phenyl-2-tributylstannanylpyrrolidine-1-carboxylic acid *tert*-butyl ester *rac*-350**



rac-**350**

Using general procedure P, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine *rac*-**77** (50 mg, 0.20 mmol) in THF (4 mL) and tributylstannyl chloride (130 mg, 108 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 99:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**350** (90 mg, 84%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.2; IR ($CHCl_3$) 2956, 2924, 2871, 1678 (C=O), 1402, 1158, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.5, 7.5 Hz, 2H, *m*-Ph), 7.04 (br t, J = 7.5 Hz, 1H, *p*-Ph), 6.98 (dd, J = 8.5, 1.0 Hz, 2H, *o*-Ph), 3.50 (ddd, J = 11.0, 9.0, 1.5 Hz, 1H, NCH_2), 3.33 (td, J = 11.0, 7.0 Hz, 1H, NCH_2), 2.41 (dd, J = 12.5, 5.0 Hz, 1H, CH_2), 2.15 (td, J = 12.0, 6.0 Hz, 1H, CH_2), 1.83-1.68 (m, 1H, CH_2), 1.58-1.48 (m, 1H, CH_2), 1.51 (s, 9H, CMe_3), 1.46-1.34 (m, 6H, CH_2), 1.31-1.18 (m, 6H, CH_2), 0.93-0.73 (m, 15H, CH_2 + Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 148.1 (*ipso*-Ph), 128.3 (Ph), 124.3 (Ph), 123.9 (Ph), 78.9 (*C*Me_3), 62.8 (NC), 46.3 (NCH_2), 38.4 (CH_2), 28.9 (CH_2), 28.3 (C*Me*$_3$), 27.3 (CH_2), 23.5 (CH_2), 13.4 (Me), 11.7 (CH_2); MS (ESI) *m/z* 560 [$(M + Na)^+$, 13], 480 (100), 424 (12); HRMS (ESI) *m/z* calcd for $C_{27}H_{47}NO_2Sn$ $(M + Na)^+$ 560.2526, found 560.2526 (0.0 ppm error).
Lab Book Reference GB9/789

rac-2-Phenyl-2-trimethylsilanylpyrrolidine-1-carboxylic acid _tert_-butyl ester _rac_-351



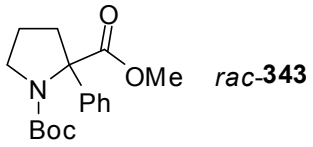
rac-**351**

Using general procedure P, *n*-BuLi (232 μL of a 2.5 M solution in hexanes, 0.58 mmol) and phenyl pyrrolidine *rac*-**77** (110 mg, 0.44 mmol) in THF (4 mL) and Me_3SiCl (97 mg, 113 μL, 0.89 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**351** (158 mg, 65%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.9; IR (film) 2972, 1695 (C=O), 1396, 1246, 1165, 1126, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 7.0 Hz, 2H, *m*-Ph), 7.16-7.08 (m, 3H, Ph), 3.52 (t, J = 9.5 Hz, 1H, NCH_2), 3.32 (ddd, J = 11.0, 9.5, 7.0 Hz, 1H, NCH_2), 2.21 (t, J = 12.0 Hz, 1H, CH_2), 2.02 (ddd, J = 13.0, 12.0, 6.0 Hz, 1H, CH_2), 1.76-1.67 (m, 1H, CH_2), 1.57-1.46 (m, 1H, CH_2), 1.50 (s, 9H, CMe_3), 0.03 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (C=O), 145.3 (*ipso*-Ph), 128.3 (Ph),

125.3 (Ph), 125.0 (Ph), 78.7 (*C*Me_3), 60.9 (NC), 47.6 (NCH_2), 37.9 (CH_2), 28.3 (C*Me*$_3$), 22.7 (CH_2), –1.5 ($SiMe_3$); MS (ESI) *m/z* 342 [$(M + Na)^+$, 36], 320 [$(M + H)^+$, 19], 264 (39), 248 (100); HRMS (ESI) *m/z* calcd for $C_{18}H_{29}NO_2Si$ $(M + H)^+$ 320.2040, found 320.2035 (+1.6 ppm error).

Lab book Reference GB8/723

rac-2-Phenylpyrrolidine-1,2-dicarboxylic acid 1-_tert_-butyl ester 2-methyl ester _rac_-343

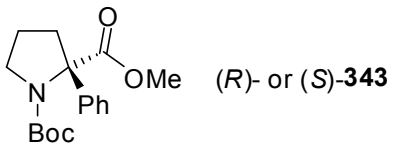


rac-**343**

Using general procedure Q, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine (*R*)-**77** (50 mg, 0.20 mmol, 97:3 er) in THF (4 mL) at 0 °C for 5 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**343** (50 mg, 82%, 50:50 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL min^{-1}) (*R*)-**343** 21.8 min, (*S*)-**343** 24.8 min.

Lab Book Reference GB9/809

(*R*)- or (*S*)-2-Phenylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (*R*)- or (*S*)-343



(*R*)- or (*S*)-**343**

(Table 6.4, entry 1)

Using general procedure Q, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine (*R*)-**77** (50 mg, 0.20 mmol, 97:3 er) in THF (4 mL) at –78 °C for 60 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**343** (19 mg, 31%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +13.1 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL

min^{-1}) major enantiomer 21.8 min, minor enantiomer 24.8 min and recovered (*R*)-**77** (31 mg, 62% recovery) as a colourless oil.
Lab Book Reference GB9/810

(Table 6.4, entry 2)
Using general procedure Q, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine (*R*)-**77** (50 mg, 0.20 mmol, 97:3 er) in THF (4 mL) at –50 °C for 10 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**343** (45 mg, 74%, 90:10 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +34.1 (*c* 0.73 in $CHCl_3$); CSP-HPLC: Chiralpcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL min^{-1}) major enanitomer **343** 21.8 min, minor enantiomer **343** 24.8 min.
Lab Book Reference GB9/813

(Table 6.4, entry 3)
Using general procedure Q, *n*-BuLi (64 μL of a 2.5 M solution in hexanes, 0.16 mmol) and phenyl pyrrolidine (*R*)-**77** (30 mg, 0.12 mmol, 97:3 er) in THF (4 mL) at –50 °C for 5 min and methyl chloroformate (23 mg, 19 μL, 0.24 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**343** (28 mg, 78%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +46.7 (*c* 0.525 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL min^{-1}) major enantiomer **343** 21.8 min, minor enantiomer **343** 24.8 min.
Lab Book Reference GB9/820

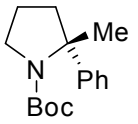
(Table 6.4, entry 4)
Using general procedure Q, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine (*R*)-**77** (50 mg, 0.20 mmol, 97:3 er) in THF (4 mL) at –40 °C for 5 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**343** (42 mg, 69%, 85:15 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +39.1 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL min^{-1}) major enantiomer **343** 21.8 min, minor enantiomer **343** 24.8 min.
Lab Book Reference GB9/812

(Table 6.4, entry 5)

Using general procedure Q, *n*-BuLi (104 μL of a 2.5 M solution in hexanes, 0.26 mmol) and phenyl pyrrolidine (*R*)-**77** (50 mg, 0.20 mmol, 97:3 er) in THF (4 mL) at –30 °C for 5 min and methyl chloroformate (38 mg, 31 μL, 0.40 mmol) gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**343** (48 mg, 79%, 65:35 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +17.5 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99.5:0.5 hexane-*i*-PrOH, 1 mL min^{-1}) major enantiomer **343** 21.8 min, minor enantiomer **343** 24.8 min.

Lab Book Reference GB9/811

(*R*)- or (*S*)-2-Methyl-2-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)- or (*S*)-334

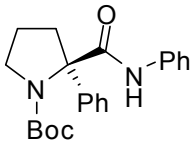


(*R*)- or (*S*)-**334**

Using general procedure R, *n*-BuLi (96 μL of a 2.5 M solution in hexanes, 0.24 mmol) and phenyl pyrrolidine (*R*)-**77** (46 mg, 0.18 mmol, 97:3 er) in THF (4 mL) and dimethyl sulfate (47 mg, 35 μL, 0.37 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**334** (41 mg, 87%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +6.4 (*c* 0.25 in $CHCl_3$); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1 mL min^{-1}) minor enantiomer **334** 6.53 min, major enantiomer **334** 7.43 min.

Lab Book Reference GB9:822

(*R*)- or (*S*)-2-Phenyl-2-phenylcarbamoylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*R*)- or (*S*)-347

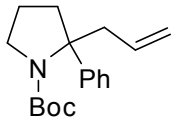


(*R*)- or (*S*)-**347**

Using general procedure R, *n*-BuLi (96 μL of a 2.5 M solution in hexanes, 0.24 mmol) and phenyl pyrrolidine (*R*)-**77** (46 mg, 0.18 mmol, 97:3 er) in THF (4 mL) and phenyl isocyanate (41 mg, 37 μL, 0.37 mmol) gave the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave pyrrolidine (*R*)- or (*S*)-**347** (55 mg, 83%, 95:5 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +21.3 (*c* 1.125 in $CHCl_3$); CSP-HPLC: Chiralpak AD (99:1 hexane-*i*-PrOH, 1 mL min^{-1}) minor enantiomer **347** 6.38 min, major enantiomer **347** 9.95 min.

Lab Book Reference GB9/823

rac-2-Allyl-2-phenylpyrrolidine-1-carboxylic acid _tert_-butyl ester _rac_-349



rac-**349**

Using general procedure R, *n*-BuLi (96 μL of a 2.5 M solution in hexanes, 0.24 mmol) and phenyl pyrrolidine (*R*)-**77** (46 mg, 0.18 mmol, 97:3 er) in THF (4 mL) and allyl bromide (45mg, 32 μL, 0.37 mmol) gave the crude product. Purification by flash column chromatography in silia with 9:1 petrol-Et_2O as eluent gave pyrrolidine *rac*-**349** (41 mg, 84%, 50:50 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 1 mL min^{-1}) 5.39 min, 5.99 min.

Lab Book Reference GB9/821

ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (–78 °C)

(Scheme 6.21)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt underAr. After cooling to –78 °C, a solution of 2-phenyl pyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 2 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 μL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred –78 °C for 12 min.

For 2-phenyl pyrrolidine **77**, a peak at 1696 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 2 min, partial

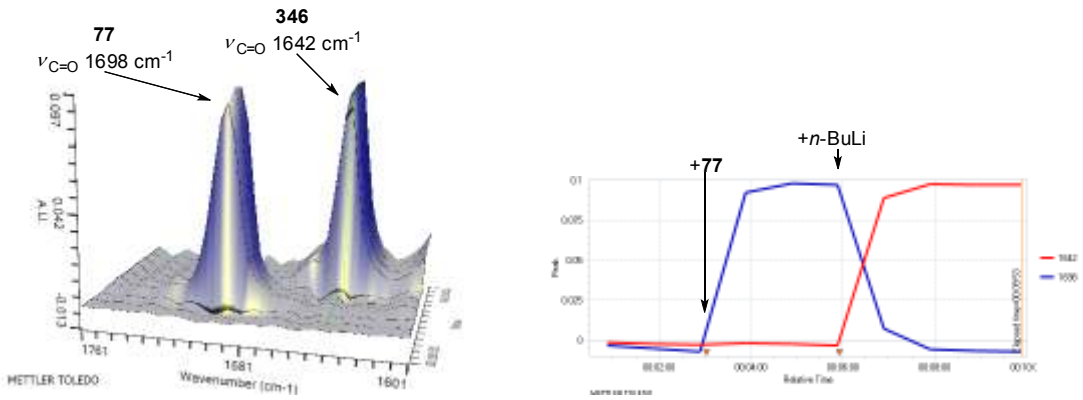
lithiation (~40%) of 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed. After a further 10 min incubation at –78 °C, no further lithiation was observed.
Lab Book Reference GB9/794

ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (0 °C)
(Scheme 6.22)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to 0 °C, a solution of 2-phenyl pyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 2 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at 0 °C for 5 min.

For 2-phenyl pyrrolidine **77**, a peak at 1701 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 2 min, complete lithiation of 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed.
Lab Book Reference GB9/793

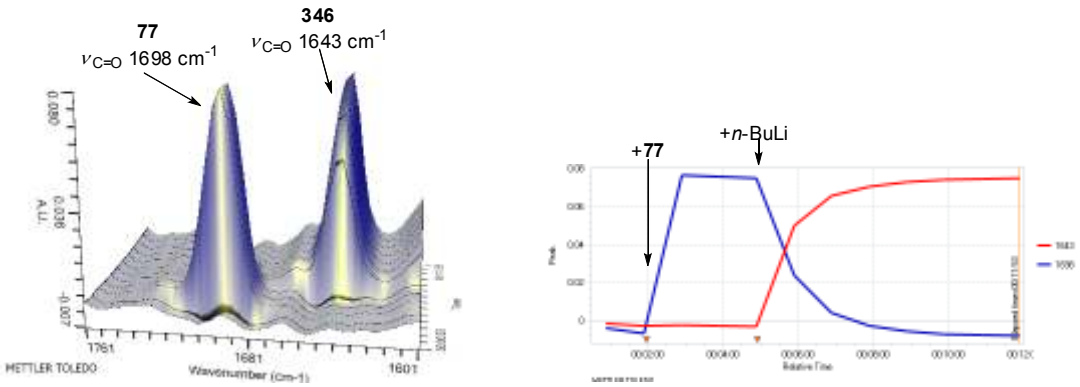
ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (–30 °C)
(Figure 6.2)



THF (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 2-phenyl pyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 2 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –30 °C for 5 min.

For 2-phenyl pyrrolidine **77**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1642 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 2 min, complete lithiation of 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed.
Lab Book Reference GB9/795

ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (–40 °C)
(Figure 6.2)

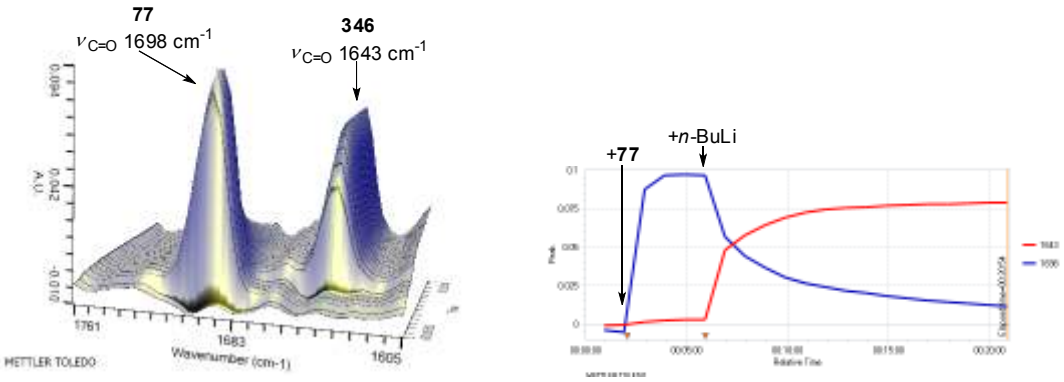


THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –40 °C, a solution of 2-phenylpyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 3 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –40 °C for 7 min.

For 2-phenyl pyrrolidine **77**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 3 min, complete lithiation of 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed.
Lab Book Reference GB9/797

ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (–50 °C)

(Figure 6.2)



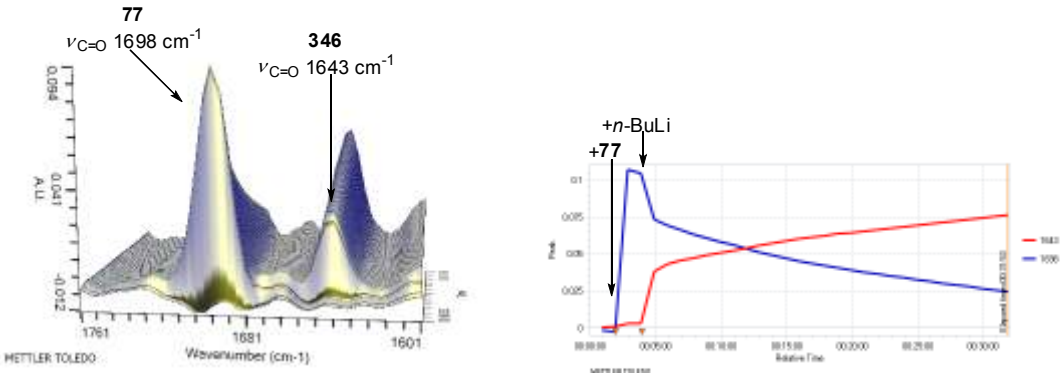
THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –50 °C, a solution of 2-phenyl pyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 3 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –50 °C for 15 min.

For 2-phenyl pyrrolidine **77**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 2 min, partial lithiation (~50%) of the 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed. After a further 13 min incubation at –50 °C, complete lithiation of 2-phenyl pyrrolidine77 to give lithiated intermediate **346** was observed.

Lab Book Reference GB9/796

ReactIR monitoring of the lithiation of phenyl pyrrolidine 77 (–60 °C)

(Figure 6.2)



THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –60 °C, a solution of 2-phenyl pyrrolidine **77** (247 mg, 1.0 mmol) in THF (2 mL) was added. The solution was stirred for 2 min (to verify the stability of readout on ReactIR). Then, *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol) was added dropwise. The solution was stirred at –60 °C for 30 min.

For 2-phenyl pyrrolidine **77**, a peak at 1698 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1643 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in lithiated intermediate **346**. After a lithiation time of 2 min, partial lithiation (~50%) of the 2-phenyl pyrrolidine **77** to give lithiated intermediate **346** was observed. After a further 27 min incubation at –60 °C, additional slow lithiation of 2-phenyl pyrrolidine **77** to lithiated intermediate **346** was observed.

Lab Book Reference GB9/798

Chapter Eight: References

1 A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita, and K. Suzuki, *Angew. Chem. Int. Ed.*, 2011, **50**, 2297.
2 J. Clayden, 'Organolithiums: Selectivity for Synthesis', Elsevier, 2002.
3 P. West and R. Waack, *J. Am. Chem. Soc.*, 1967, **89**, 4395.
4 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870.
5 M. J. McGrath and P. O'Brien, *J. Am. Chem. Soc.*, 2005, **127**, 16378.
6 J.-C. Kizirian, J.-C. Caille, and A. Alexakis, *Tetrahedron Lett.*, 2003, **44**, 8893.
7 J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, 1946, **68**, 1658.
8 P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356.
9 P. Beak and W. J. Zajdel, *Chem. Rev.*, 1984, **84**, 471.
10 P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552.
11 M. C. Whisler, S. MacNeil, V. Snieckus, and P. Beak, *Angew. Chem. Int. Ed.*, 2004, **43**, 2206.
12 P. Beak and D. B. Reitz, *Chem. Rev.*, 1978, **78**, 275.
13 P. Beak, B. G. McKinnie, and D. B. Reitz, *Tetrahedron Lett.*, 1977, **22**, 1839.
14 D. B. Reitz, A. Tse, and P. Beak, *J. Org. Chem.*, 1981, **46**, 4316.
15 P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34.
16 M. Al-Aseer, P. Beak, D. Hay, D. J. Kempf, S. Mills, and S. G. Smith, *J. Am. Chem. Soc.*, 1983, **105**, 2080.
17 P. Beak and W. J. Zadjel, *J. Am. Chem. Soc.*, 1984, **106**, 1010.
18 D. R. Hay, Z. Song, S. G. Smith, and P. Beak, *J. Am. Chem. Soc.*, 1988, **110**, 8145.
19 D. J. Pippel, M. D. Curtis, H. Du, and P. Beak, *J. Org. Chem.*, 1998, **63**, 2.
20 N. G. Rondan, K. N. Houk, P. Beak, W. J. Zajdel, J. Chandrasekhar, and P. v. R. Schleyer, *J. Org. Chem.*, 1981, **46**, 4108.
21 A. I. Meyers and S. Hellring, *J. Org. Chem.*, 1982, **47**, 2229.
22 A. I. Meyers, P. D. Edwards, W. F. Rieker, and T. R. Bailey, *J. Am. Chem. Soc.*, 1984, **106**, 3270.
23 A. I. Meyers and D. A. Dickman, *J. Am. Chem. Soc.*, 1987, **109**, 1263.
24 A. I. Meyers and G. Milot, *J. Org. Chem.*, 1993, **58**, 6538.
25 D. Seebach and D. Enders, *Angew. Chem. Int. Ed.*, 1975, **14**, 15.
26 D. Seebach, I. M. Huber, and M. A. Syfrig, *Helv. Chim. Acta.*, 1987, **70**, 1357.
27 C. Metallinos and S. Xu, *Org. Lett.*, 2010, **12**, 76.
28 D. M. Hodgson and J. Kloesges, *Angew. Chem. Int. Ed.*, 2010, **49**, 2900.
29 P. Beak and W.-K. Lee, *Tetrahedron Lett.*, 1989, **30**, 1197.
30 P. Beak and B. G. McKinnie, *J. Am. Chem. Soc.*, 1977, **99**, 5213.
31 P. Beak and E. M. Monroe, *J. Org. Chem.*, 1969, **34**, 589.

[32] N. J. R. v. E. Hommes and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 755.
[33] D. R. Anderson, N. C. Faibish, and P. Beak, *J. Am. Chem. Soc.*, 1999, **121**, 7553.
[34] D. Seebach and T. Hassel, *Angew. Chem. Int. Ed.*, 1978, **17**, 274.
[35] D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 932.
[36] D. Hoppe and T. Kramer, *Angew. Chem. Int. Ed. Engl.*, 1986, **98**, 171.
[37] T. Kramer and D. Hoppe, *Tetrahedron Lett.*, 1987, **28**, 5149.
[38] D. Hoppe and O. Zschage, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 69.
[39] D. Hoppe, F. Hintze, and P. Tebben, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 1422.
[40] E.-U. Wurthwein and D. Hoppe, *J. Org. Chem.*, 2005, **70**, 4443.
[41] M. Paetow, H. Ahrens, and D. Hoppe, *Tetrahedron Lett.*, 1992, **33**, 5323.
[42] F. Hintze and D. Hoppe, *Synthesis*, 1992, 1216.
[43] J. P. N. Papillon and R. J. K. Taylor, *Org. Lett.*, 2002, **4**, 119.
[44] M. Menges and R. Bruckner, *Eur. J. Org. Chem.*, 1998, 1023.
[45] E. Beckmann, V. Desai, and D. Hoppe, *Synlett*, 2004, 2275.
[46] G. Besong, K. Jarowicki, P. J. Kocienski, E. Sliwinski, and F. T. Boyle, *Org. Biomol. Chem.*, 2006, **4**, 2193.
[47] J. Bilke and P. O'Brien, *Angew. Chem. Int. Ed. Engl.*, 2008, **47**, 2734.
[48] J. L. Stymiest, G. Dutheuil, A. Mahmood, and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2007, **46**, 7491.
[49] J. W. Daly and T. F. Spande, *Alkaloids: Chemical and Biological Perspectives*, 1986, **4**.
[50] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, and J. Clardy, *Tetrahedron Lett.*, 1988, **29**, 4381.
[51] S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708.
[52] P. Beak, S. T. Kerrick, S. Wu, and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231.
[53] C. Strohman, K. Strohfeldt, D. Schildbach, M. J. McGrath, and P. O'Brien, *Organometallics*, 2004, **23**, 5389.
[54] M. J. Dearden, M. J. McGrath, and P. O'Brien, *J. Org. Chem.*, 2004, **69**, 5789.
[55] J.-P. R. Hermet, A. Viteisi, J. M. Wright, M. J. McGrath, P. O'Brien, A. C. Whitwood, and J. Gilday, *Org. Biomol. Chem.*, 2007, **5**, 3614.
[56] P. O'Brien, *Chem. Commun.*, 2008, 655.
[57] J.-P. R. Hermet, D. W. Porter, M. J. Dearden, J. R. Harrison, T. Koplin, P. O'Brien, J. Parmene, V. Tyurin, A. C. Whitwood, J. Gilday, and N. M. Smith, *Org. Biomol. Chem.*, 2003, **1**, 3977.
[58] C. Genet, M. J. McGrath, and P. O'Brien, *Org. Biomol. Chem.*, 2006, **4**, 1376.
[59] D. Stead, P. O'Brien, and A. Sanderson, *Org. Lett.*, 2008, **7**, 1409.
[60] I. Coldham, J. J. Patel, and G. Sanchez-Jimenez, *Chem. Commun.*, 2005, 3083.
[61] I. Coldham, S. Dufour, T. F. N. Haxell, S. Howard, and G. P. Vennall, *Angew. Chem. Int. Ed.*, 2002, **41**, 3887.
[62] I. Coldham, S. Dufour, T. F. N. Haxell, and G. P. Venall, *Tetrahedron*, 2005, **61**, 3205.
[63] I. Coldham, S. Dufour, T. F. N. Haxell, J. J. Patel, and G. Sanchez-Jimenez, *J. Am. Chem. Soc.*, 2006, **128**, 10943.
[64] W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma, and K. B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889.

[65] I. Coldham, P. O'Brien, J. J. Patel, S. Rainbault, A. J. Sanderson, D. Stead, and D. T. E. Whittaker, *Tetrahedron Asymmetry*, 2007, **18**, 2113.
[66] M. J. McGrath, J. Bilke, and P. O'Brien, *Chem. Commun.*, 2006, 2607.
[67] D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260.
[68] I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel, and N. S. Sheikh, *Chem. Eur. J.*, 2010, **16**, 4082.
[69] S. Li and R. K. Dieter, *J. Org. Chem.*, 2003, **68**, 969.
[70] M. Berkheij, L. v. d. Sluis, C. Sewing, D. J. d. Boer, J. W. Terpstra, H. Heimstra, W. I. Iwema, I. Bakker, A. v. d. Hoogenbrand, and J. H. v. Maarseveen, *Tetrahedron Lett.*, 2005, **46**, 2369.
[71] K. A. Miller, C. S. Shanahan, and S. F. Martin, *Tetrahedron*, 2008, **64**, 6884.
[72] B. P. McDermott, A. D. Campbell, and A. Ertan, *Synlett*, 2008, **6**, 875.
[73] S. P. Robinson, N. S. Sheikh, C. A. Baxter, and I. Coldham, *Tetrahedron Lett.*, 2010, **51**, 3642.
[74] I. Coldham, R. C. B. Copley, T. F. N. Haxell, and S. Howard, *Org. Lett.*, 2001, **3**, 3799.
[75] N. J. Ashweek, I. Coldham, T. F. N. Haxell, and S. Howard, *Org. Biomol. Chem.*, 2003, **1**, 1532.
[76] J. R. Harrison and P. O'Brien, *Tetrahedron Lett.*, 2000, **41**, 6161.
[77] D. Stead, P. O'Brien, and A. J. Sanderson, *Org. Lett.*, 2005, **7**, 4459.
[78] U. Jordis, M. Kesselgruber, and S. Nerdinger, *ARKIVOC*, 2001, **2**, 69.
[79] G. R. Krow, S. B. Herzon, G. Lin, F. Qiu, and P. E. Sonnet, *Org. Lett.*, 2002, **4**, 3151.
[80] F. F. Wagner and D. L. Comins, *Org. Lett.*, 2006, **8**, 3549.
[81] Q. Zhang, G. Tu, Y. Zhao, and T. Cheng, *Tetrahedron*, 2002, **58**, 6795.
[82] S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, 1997, **119**, 7165.
[83] A. Klapars, K. R. Campos, J. H. Waldman, D. Zewge, P. G. Dormer, and C.-y. Chen, *J. Org. Chem.*, 2008, **73**, 4986.
[84] F. Manfre and J. P. Pulicani, *Tetrahedron: Asymmetry*, 1994, **5**, 235.
[85] K. R. Dieter and S. Li, *Tetrahedron Lett.*, 1995, **36**, 3613.
[86] K. R. Dieter and S. Li, *J. Org. Chem.*, 1997, **62**, 7726.
[87] R. K. Dieter, C. M. Topping, K. R. Chandupatla, and K. Lu, *J. Am. Chem. Soc.*, 2001, **123**, 5132.
[88] R. K. Dieter, G. Oba, K. R. Chandupatla, C. M. Topping, K. Lu, and R. T. Watson, *J. Org. Chem.*, 2004, **69**, 3076.
[89] K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, and C.-y. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 3538.
[90] M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.
[91] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hiortsu, *J. Am. Chem. Soc.*, 1984, **106**, 158.
[92] K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069.
[93] S. E. Reisman, A. G. Doyle, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2008, **130**, 7198.
[94] E. A. Peterson and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2009, **48**, 6328.
[95] R. R. Knowles, S. Lin, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2010, **132**, 5030.
[96] K. M. B. Gross and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 315.
[97] N. J. Ashweek, P. Brandt, I. Coldham, S. Dufour, R. E. Gawley, F. Haeffner, R. Klein, and G. S.-. Jimenez, *J. Am. Chem. Soc.*, 2005, 449.

[98] S. Cho-Schultz, M. J. Patten, B. Huang, J. Elleraas, K. T. Gajiwala, M. J. Hickey, J. Wang, P. P. Mehta, P. Kang, M. R. Gehring, P.-P. Kung, and S. C. Sutton, *J. Comb. Chem.*, 2009, **11**, 860.
[99] I. Coldham and D. Leonori, *Org. Lett.*, 2008, **10**, 3923.
[100] T. K. Beng and R. E. Gawley, *Org. Lett.*, 2011, **13**, 394.
[101] S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, and P. Knochel, *J. Am. Chem. Soc.*, 2011, **133**, 4774.
[102] L. E. Burgess and A. I. Meyers, *J. Org. Chem.*, 1992, **57**, 1656.
[103] F. Manescalchi, A. R. Nardi, and D. Savoia, *Tetrahedron Lett.*, 1994, **35**, 2775.
[104] K. Higashiyama, H. Inoue, and H. Takahashi, *Tetrahedron*, 1994, **50**, 1083.
[105] K. M. Brinner and J. A. Ellman, *Org. Biomol. Chem.*, 2005, **3**, 2109.
[106] S. Wu, S. Lee, and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 715.
[107] C. A. Willoughby and S. L. Buchwald, *J. Org. Chem.*, 1993, **58**, 7627.
[108] S. J. Pastine, D. V. Gribkov, and D. Sames, *J. Am. Chem. Soc.*, 2006, **128**, 14220.
[109] D. V. Gribkov, S. J. Pastine, M. Schnurch, and D. Sames, *J. Am. Chem. Soc.*, 2007, **129**, 11750.
[110] E. Leemans, S. Mangelinckx, and N. D. Kimpe, *Chem. Commun.*, 2010, **46**, 3122.
[111] L. R. Reddy, S. G. Das, Y. Liu, and M. Prashad, *J. Org. Chem.*, 2010, **75**, 2236.
[112] L. R. Reddy and M. Prashad, *Chem. Commun.*, 2010, **46**, 222.
[113] M. A. Al-Aseer and S. G. Smith, *J. Org. Chem.*, 1984, **49**, 2608.
[114] M. A. Al-Aseer, B. D. Allison, and S. G. Smith, *J. Org. Chem.*, 1985, **50**, 2715.
[115] X. Sun, S. L. Kenkre, J. F. Remenar, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, 1997, **119**, 4765.
[116] X. Sun and D. B. Collum, *J. Am. Chem. Soc.*, 2000, **122**, 2452.
[117] J. L. Rutherford, D. Hoffmann, and D. B. Collum, *J. Am. Chem. Soc.*, 2002, **124**, 264.
[118] D. J. Pippel, G. A. Weisenburger, N. C. Faibish, and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 4919.
[119] P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109.
[120] J. F. Couch, *J. Am. Chem. Soc.*, 1936, **58**, 1296.
[121] A. J. Dixon, M. J. McGrath, and P. O'Brien, *Org. Synth.*, 2006, **83**, 141.
[122] T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2005, **127**, 3244.
[123] P. O'Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, and M. J. McGrath, *J. Am. Chem. Soc.*, 2004, **126**, 15480.
[124] S. J. Canipa, P. O'Brien, and S. Taylor, *Tetrahedron: Asymmetry*, 2009, **20**, 2407.
[125] D. M. Hodgson, G. P. Lee, R. E. Marriott, A. J. Thompson, R. Wisedale, and J. Witherington, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2151.
[126] J. J. Gammon, S. J. Canipa, P. O'Brien, B. Kelly, and S. Taylor, *Chem. Commun.*, 2008, 3750.
[127] C. Genet, S. J. Canipa, P. O'Brien, and S. Taylor, *J. Am. Chem. Soc.*, 2006, **128**, 9336.
[128] K. Kanda, K. Endo, and T. Shibata, *Org. Lett.*, 2010, **12**, 1980.
[129] J. L. Bilke and P. O'Brien, *J. Org. Chem.*, 2008, **73**, 6452.
[130] J. L. Bilke, S. P. Moore, P. O'Brien, and J. Gilday, *Org. Lett.*, 2009, **11**, 1935.

[131] M. J. McGrath and P. O'Brien, *Synthesis*, 2006, **13**, 2233.
[132] G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, T. Fazekas, S. Sangiah, C.-L. Chen, F. D. Schubot, and D. v. d. Helm, *J. Med. Chem.*, 1996, **39**, 2559.
[133] P. O'Brien and J. L. Bilke, *unpublished results*.
[134] K. R. Campos, *unpublished results*.
[135] F. F. Wagner and D. L. Comins, *Tetrahedron*, 2007, **63**, 8065.
[136] Z.-H. Jiang, T. Tanaka, C. Inutsuka, and I. Kouno, *Chem. Pharm. Bull.*, 2001, **49**, 737.
[137] T.-S. Kam and K.-M. Sim, *Phytochemistry*, 1998, **47**, 145.
[138] K. Saito, T. Yoshino, T. Sekine, S. Ohmiya, H. Kubo, H. Otomasu, and I. Murakoshi, *Phytochemistry*, 1989, **28**, 2533.
[139] Y.-H. Wang, K. Higashiyama, H. Kubo, J.-S. Li, and S. Ohmiya, *Heterocycles*, 1999, **51**, 3001.
[140] Y.-H. Wang, J.-H. Li, Z.-R. Jiang, H. Kubo, K. Higashiyama, and S. Ohmiya, *Chem. Pharm. Bull.*, 2000, **48**, 641.
[141] S. P. Arneric, J. P. Sullivan, C. A. Briggs, D. Donnelly-Roberts, D. J. Anderson, J. L. Raszkiewicz, M. L. Hughes, E. D. Cadman, P. Adams, and D. S. Garvey, *J. Pharm. Exp. Ther.*, 1994, **270**, 310.
[142] R. L. Papke, J. S. Thinschmidt, B. A. Moulton, E. M. Meyer, and A. Poirier, *B. J. Pharm.*, 1997, **120**, 429.
[143] A. Potter, J. Corwin, J. Lang, M. Piasecki, R. Lenox, and P. A. Newhouse, *Psycopharmacology*, 1999, **142**, 334.
[144] T. E. Wilens, J. Biederman, T. J. Spencer, J. Bostic, J. Prince, M. C. Monuteaux, J. Soriano, C. Fine, A. Abrams, M. Rater, and D. Polisner, *Am. J. Psychiatry*, 1999, **156**, 1931.
[145] N. D. P. Cosford, L. Bleicher, A. Herbaut, J. S. McCallum, J.-M. Vernier, H. Dawson, J. P. Whitten, P. Adams, L. C.-. Noriega, L. D. Correa, J. H. Crona, L. H. Mahaffy, F. Menzaghi, T. S. Rao, R. Reid, A. I. Sacaan, E. Santori, K. A. Stauderman, K. Whelan, G. K. Lloyd, and I. A. McDonald, *J. Med. Chem.*, 1996, **39**, 3235.
[146] K. Kawanishi, Y. Uhara, and Y. Hashimoto, *J. Nat. Prod.*, 1982, **45**, 637.
[147] J. Bastida, M. Selles, C. Codina, F. Viladomat, and J. L. L. d. l. Luz, *Planta Med.*, 1996, **62**, 575.
[148] J. B. Bodem and E. Leete, *J. Org. Chem.*, 1979, **44**, 4696.
[149] B. Siegmund, E. Leitner, and W. Pfannhauser, *J. Agric. Food Chem.*, 1999, **47**, 3113.
[150] A. Pinner, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 292.
[151] A. Pictet and A. Rotschy, *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 1225.
[152] C. G. Chavdarian, E. B. Sanders, and R. L. Bassfield, *J. Org. Chem.*, 1982, **47**, 1069.
[153] C. G. Chavdarian and E. B. Sanders, *Org. Prep. Proced. Int.*, 1981, **13**, 389.
[154] T. A. Bryson, J. C. Wisowaty, R. B. Dunlap, R. R. Fisher, and P. D. Ellis, *J. Org. Chem.*, 1974, **39**, 3436.
[155] C. Welter, R. M. Moreno, S. Streiff, and G. Helmchen, *Org. Biomol. Chem.*, 2005, **3**, 3266.
[156] K. Tissot-Croset, D. Polet, S. Gille, C. Hawner, and A. Alexakis, *Synthesis*, 2004, 2586.
[157] S. Girard, R. J. Robins, J. Villieras, and J. Lebreton, *Tetrahedron: Asymmetry*, 2001, **12**, 1121.

158 D. L. Comins and E. D. Smith, *Tetrahedron Lett.*, 2006, **47**, 1449.
159 F. F. Wagner and D. L. Comins, *J. Org. Chem.*, 2006, **71**, 8673.
160 F. F. Wagner and D. L. Comins, *Eur. J. Org. Chem.*, 2006, 3562.
161 M. Tominaga, M. Kato, T. Okano, S. Sakamoto, K. Yamaguchi, and M. Fukita, *Chem. Lett.*, 2003, **32**, 1012.
162 W. L. Fitch and C. Djerassi, *J. Am. Chem. Soc.*, 1974, **96**, 4917.
163 E. Gravel, E. Poupon, and R. Hocquemiller, *Tetrahedron*, 2006, **62**, 5248.
164 Z. Szakonyi, M. D'hooghe, I. Kanizsai, F. Fulop, and N. D. Kimpe, *Tetrahedron*, 2005, **61**, 1595.
165 P. J. Dransfield, P. M. Gore, I. Prokes, M. Shipman, and A. M. Z. Slawin, *Org. Biomol. Chem.*, 2003, **1**, 2723.
166 J. Wang, Y.-L. Liang, and J. Qu, *Chem. Commun.*, 2009, 5144.
167 M. Sakaitani and Y. Ohfune, *Tetrahedron Lett.*, 1985, **26**, 5543.
168 M. Sakaitani and Y. Ohfune, *J. Org. Chem.*, 1990, **55**, 870.
169 M. G. Pizzuti, A. J. Minnard, and B. L. Feringa, *Org. Biomol. Chem.*, 2008, **6**, 3464.
170 S. Krishnan, J. T. Bagdanoff, D. C. Ebner, Y. K. Ramtohul, U. K. Tambar, and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 13745.
171 B. L. Bourdonnec, A. J. Goodman, T. M. Graczyk, S. Belanger, P. R. Seida, R. N. DeHaven, and R. E. Dolle, *J. Med. Chem.*, 2006, **49**, 7290.
172 M. Guillaume, J. Cuypers, and J. Dingenen, *Org. Proc. Res. Dev.*, 2007, **11**, 1079.
173 P. Beak, S. Wu, E. K. Yum, and Y. M. Jun, *J. Org. Chem.*, 1994, **59**, 276.
174 D. B. Collum, *Acc. Chem. Res.*, 1992, **25**, 448.
175 M. P. Bernstein, F. E. Romesberg, D. J. Fuller, A. T. Harrison, D. B. Collum, Q.-Y. Liu, and P. G. Willard, *J. Am. Chem. Soc.*, 1992, **114**, 5100.
176 B. L. Lucht, M. P. Bernstein, J. F. Remenar, and D. B. Collum, *J. Am. Chem. Soc.*, 1996, **118**, 10707.
177 I. Hoppe, M. Marsch, K. Harms, G. Boche, and D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2158.
178 Y. S. Park, M. L. Boys, and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 3757.
179 K. M. B. Gross, Y. M. Jun, and P. Beak, *J. Org. Chem.*, 1997, **62**, 7679.
180 Z. Pakulski, M. Koprowski, and K. M. Pietrusiewicz, *Tetrahedron*, 2003, **59**, 8219.
181 S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, P. V. Bharatam, and A. K. Sharma, *J. Am. Chem. Soc.*, 2007, **129**, 4506.
182 J. Huang and P. O'Brien, *Chem. Commun.*, 2005, 5696.
183 G. Carbone, P. O'Brien, and G. Hilmersson, *J. Am. Chem. Soc.*, 2010, **132**, 15445.
184 R. Sott, M. Hakansson, and G. Hilmersson, *Organometallics*, 2006, **25**, 6047.
185 D. J. Gallagher, S. T. Kerrick, and P. Beak, *J. Am. Chem. Soc.*, 1992, **114**, 5872.
186 D. F. Aycock, *Org. Process Res. Dev.*, 2007, **11**, 156.
187 J. C. L. Armande and U. K. Pandit, *Tetrahedron Lett.*, 1977, **11**, 897.
188 S. Yamashita, N. Kurono, H. Senboku, M. Tokuda, and K. Orito, *Eur. J. Org. Chem.*, 2009, 1173.
189 R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, 1972, **37**, 560.
190 A. J. Duggan and F. E. Edwards, *Tetrahedron Lett.*, 1979, 595.
191 L. Spialter and C. W. Harris, *J. Org. Chem.*, 1966, **31**, 4263.
192 A. Krief, B. Kenda, P. Barbeaux, and E. Guittet, *Tetrahedron*, 1994, **50**, 7177.

193 P. D. Bartlett, S. Friedman, and M. Stiles, *J. Am. Chem. Soc.*, 1953, **75**, 1771.
194 I. Fleming, S. R. Mack, and B. P. Clark, *Chem. Commun.*, 1998, 713.
195 I. Coldham and D. Leonori, *J. Org. Chem.*, 2010, **75**, 4069.
196 M. Lautens, E. Fillion, and M. Sampat, *J. Org. Chem.*, 1997, **62**, 7080.
197 G. Carbone, P. O'Brien, and G. Hilmersson, *unpublished results*.
198 P. A. Loo, A. F. Braunwalder, M. Williams, and M. A. Sills, *Eur. J. Pharmacol.*, 1987, **135**, 261.
199 B. V. Clineschmidt, G. E. Martin, and P. R. Bunting, *Drug Dev. Res.*, 1982, **2**, 123.
200 J. W. McDonald, F. S. Silverstein, and M. V. Johnston, *Eur. J. Pharmacol.*, 1987, **140**, 359.
201 J. Olney, M. Price, K. S. Salles, J. Labruyere, and G. Frierdich, *Eur. J. Pharmacol.*, 1987, **141**, 357.
202 T. Harrison, B. J. Williams, and C. J. Swain, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2733.
203 G. A. Reichard, C. Stengone, S. Paliwal, I. Mergelsberg, S. Majmundar, C. Wang, R. Tiberi, A. T. McPhail, J. J. Piwinski, and N.-Y. Shih, *Org. Lett.*, 2003, **5**, 4249.
204 G. A. Molander and E. D. Dowdy, *J. Org. Chem.*, 1998, **63**, 8983.
205 T. Xu, S. Qiu, and G. Liu, *J. Organomet. Chem.*, 2011, **696**, 46.
206 V. Gandon, P. Bertus, and J. Szymoniak, *Synthesis*, 2002, 1115.
207 M. Shi, L.-P. Liu, and J. Tang, *Org. Lett.*, 2006, **8**, 4043.
208 W.-J. Shi, Y. Liu, P. Butti, and A. Togni, *Adv. Synth. Catal.*, 2007, **349**, 1619.
209 W. Rao and P. W. H. Chan, *Chem. Eur. J.*, 2008, **14**, 10486.
210 V. Lupi, M. Penso, F. Foschi, F. Gassa, V. Mihali, and A. Tagliabue, *Chem. Commun.*, 2009, 5012.
211 F. Foschi, D. Landini, V. Lupi, V. Mihali, M. Penso, T. Pilati, and A. Tagliabue, *Chem. Eur. J.*, 2010, **16**, 10667.
212 J. v. Betsbrugge, D. Tourwe, B. Kaptein, H. Kierkels, and R. Broxterman, *Tetrahedron*, 1997, **53**, 9233.
213 T. Kano, R. Sakamoto, H. Mii, Y.-G. Wang, and K. Maruoka, *Tetrahedron*, 2010, **66**, 4900.
214 J. A. Monn and K. C. Rice, *Tetrahedron Lett.*, 1989, **30**, 911.
215 J. A. Monn, A. Thurkauf, M. V. Mattson, A. E. Jacobson, and K. C. Rice, *J. Med. Chem.*, 1990, **33**, 1069.
216 A. I. Meyers and T. H. Nguyen, *Tetrahedron Lett.*, 1995, **36**, 5873.
217 N. C. Faibish, Y. S. Park, S. Lee, and P. Beak, *J. Am. Chem. Soc.*, 1997, **119**, 11561.
218 J. Clayden, L. Lemierge, and M. Pickworth, *Tetrahedron: Asymmetry*, 2008, **19**, 2218.
219 N. Voyer and J. Roby, *Tetrahedron Lett.*, 1995, **36**, 6627.
220 M. Schlosser and D. Limat, *J. Am. Chem. Soc.*, 1995, **117**, 12342.
221 S. L. Pira, T. W. Wallace, and J. P. Graham, *Org. Lett.*, 2009, **11**, 1663.
222 J. Clayden, J. Dufour, D. M. Grainger, and M. Helliwell, *J. Am. Chem. Soc.*, 2007, **129**, 7488.
223 J. Clayden, W. Farnaby, D. M. Grainger, U. Hennecke, M. Marcinelli, D. J. Tetlow, I. H. Hillier, and M. A. Vincent, *J. Am. Chem. Soc.*, 2009, **131**, 3410.
224 P. MacLellan and J. Clayden, *Chem. Commun.*, 2011, 3395.
225 R. Bach, J. Clayden, and U. Hennecke, *Synlett*, 2009, 421.

[226] D. Xiao, B. J. Lavey, A. Palani, C. Wang, R. G. Aslanian, J. A. Kozlowski, N.-Y. Shih, A. T. McPhail, G. P. Randolph, J. E. Lachowicz, and R. A. Duffy, *Tetrahedron Lett.*, 2005, **46**, 7653.
[227] A. F. Burchat, J. M. Chong, and N. Nielsen, *Organomet. Chem.*, 1997, 281.
[228] L. A. Carpino, E. M. E. Mansour, C. H. Cheng, J. R. Williams, R. MacDonald, K. Knapczyk, and M. Carman, *J. Org. Chem.*, 1983, **48**, 661.
[229] M. Obiedzinski and P. O'Brien, *Unpublished results*.
[230] T. R. Herrin, J. M. Pauvlik, E. V. Shuber, and A. Gieszler, *J. Med. Chem.*, 1975, **18**, 1216.
[231] R. Varala, S. Nuvula, and S. R. Adapa, *J. Org. Chem.*, 2006, **71**, 8283.
[232] F. X. Felpin, S. Girard, G. Vo-Thanh, R. J. Robins, J. Villieras, and J. Lebreton, *J. Org. Chem.*, 2001, **66**, 6305.
[233] P. Magnus, C. Hulme, and W. Weber, *J. Am. Chem. Soc.*, 1994, **116**, 4501.
[234] T. Horiuchi, T. Ohta, E. Shirakawa, K. Nozaki, and H. Takaya, *J. Org. Chem.*, 1997, **62**, 4285.
[235] S. Y. Ablordeppey, R. Altundas, B. Bricker, X. Y. Zhu, Y. V. K. S. Kumar, T. Jackson, A. Khan, and B. L. Roth, *Bioorg. Med. Chem.*, 2008, **16**, 7291.
[236] F. Muhlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. S. Prakash, and T. Back, *J. Am. Chem. Soc.*, 2006, **128**, 9668.
[237] R. E. Gawley, E. Low, Q. Zhang, and R. Harris, *J. Am. Chem. Soc.*, 2000, **122**, 3344.
[238] R. Kuwano, M. Kashiwabara, M. Ohsumi, and H. Kusano, *J. Am. Chem. Soc.*, 2008, **130**, 808.
[239] P. Majewski, *Phosphorous, Sulfur Silicon Relat. Elem.*, 2009, **184**, 942.