Use of Organometallic Intermediates in Organic Synthesis

This Thesis is Submitted in Partial Fulfilment of The Requirements for The Degree of Doctor of Philosophy (PhD)

By

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This thesis is sincerely dedicated to my loving parents and my wife

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Abbrevations

Et_2O	Diethyl ether
THF	Tetrahydrofuran
DCM	Dichloromethane
EtOAc	Ethyl acetate
DMF	*N*,*N*-Dimethylformamide
TEA	Triethylamine
DMA	Dimethylamine
MsCl	Methanesulfonyl chloride
RLi	Alkyllithiums
n-BuLi	*n*-Butyllithium
t-BuLi	*tert*-Butyllithium
sec-BuLi	*sec*-Butyllithium
MeLi	Methyllithium
LDA	Lithium diisopropylamide
LTMP	2,2,6,6-Tetramethylpiperidide
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
DMG	Directing metallation group
TLC	Thin layer chromatography
o-	*ortho*-
TMS	Tetramethylsilane
Boc	*tert*-Butoxycarbonyl
DMSO-*d*6	Deuterated dimethylsulfoxide
$CDCl_3$	Deuterated chloroform
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon nuclear magnetic resonance
DEPT	Distortionless Enhancement by Polarization Transfer
J	Coupling constants
δ	Chemical shifts
MS (EI)	Mass spectra (Electron impact)

Abbrevations

MS (CI)	Mass spectra (Chemical ionization)
APCI-MS (APCI)	Mass spectra (Atmospheric pressure chemical ionization)
MS (ES)	Mass spectra (Electrospray)
IR	Infrared
Mp	Melting point
Calc.	Calculated
Anal.	Analysis
min	Minutes
h	Hour
s	Singlet
d	Doublet
dd	Double doublet
dt	Double triplet
dq	Double quartet
ddq	Double double quartet
app.	Apparent

Summary

Chapter One

Chapter one describes a historical overview and the practical consideration of lithiation reactions and highlight of some of the factors that could influence the site of lithiation. It also provides reviews of the directed and side-chain lithiation of substituted aromatics.

Chapter Two

Chapter two deals with lithiation of *N′*-phenethyl-*N*,*N*-dimethylurea with three equivalents of *t*-BuLi in THF at –78 °C followed by reaction with various electrophiles to give side-chain substituted products due to lithiation and substitution at the CH_2 next to the phenyl ring (α-lithiation). The 2-lithio isomer can be obtained *via* Br–Li exchange of 2-bromo derivative using MeLi followed by *t*-BuLi in THF at –78 °C. The lithium reagents thus obtained react with various electrophiles to give the corresponding 2-substituted derivatives in excellent yields. Lithiation of *N′*-(3-phenylpropyl)-*N*,*N*-dimethylurea takes place on the α-CH_2 with *t*-BuLi at 0 °C. On the other hand, lithiation of *N′*-(4-phenylbutyl)-*N*,*N*-dimethylurea with *t*-BuLi at 0 °C takes place on one of the methyl groups of the urea unit.

Chapter Three

Chapter three includes lithiation of *N′*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea with three equivalents of *n*-BuLi in THF at 0 °C followed by reaction with various electrophiles to give side-chain products in excellent yields due to α-lithiation. Similarly, lithiation of the pivalamide derivative followed by reaction with benzophenone as a representative electrophile gave the corresponding α-substituted product in high yield. Surprisingly, no products resulting from lateral lithiation were observed under the conditions tried, which sharply contrast with the reported results for lateral lithiation of the carbamate derivative.

Chapter Four

In this chapter, *N*-(2-(4-methoxyphenyl)ethyl)amine derivatives are reported to undergo directed *ortho*-lithiation next to the directing group with *n*-BuLi at 0 ºC, followed by treatment with various electrophiles, to give high yields of the corresponding substituted products. This contrasts sharply with the earlier results for the α-substitution of the pivaloyl derivative using *t*-BuLi at a lower temperature.

Chapter Five

Chapter five includes variations in the site of lithiation of *N*-acyl-3-(aminomethyl)pyridine derivatives with different *N*-substituents using different lithiating reagents. Ring lithiation has been achieved by the use of *t*-BuLi at –78 °C followed by reaction with various electrophiles to give the corresponding 4-substituted products in high yields. On the other hand, the reaction was regioselective towards the side-chain when LDA was used as the lithium reagent at –20 to 0 °C. A mixture of ring and side-chain substitution products was obtained when *n*-BuLi was the lithium reagent.

Chapter Six

Chapter six investigates the use of various chiral ligands containing different coordinating groups in Matteson homologation. Some stereoselectivity (de = 2–52%) was obtained depending on the type of chiral catalyst used. The best %de (52%) was obtained when $Yb(OTf)_3$ as a Lewis acid and (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol as a chiral ligand were used in combination. However, significant %de (46%) could be obtained with the diol chiral ligand in the absence of the Lewis acid, which is very interesting and open windows for further improvement.

List of Publications of the Author

- **Published Papers:**

1. Smith, K.; El-Hiti, G. A.; Alshammari, M. B. Lithiation and Substitution of *N′*-(ω-Phenylalkyl)-*N*,*N*-dimethylureas *Synthesis* **2012**, 44, 2013–2022, doi: 10.1055/s-0031-1291008.
2. Smith, K.; El-Hiti, G. A.; Fekri, A.; Alshammari, M. B. Side-Chain Lithiation of 2- and 4-Substituted Pyridines: Synthesis of More Complex Substituted Pyridines, *Heterocycles* **2012**, 86, 391–410, doi: 10.3987/COM-12-S(N)33.
3. Smith, K.; El-Hiti, G. A.; Alshammari, M. B. Variation in the Site of Lithiation of 2-(2-Methylphenyl)ethanamine Derivatives, *J. Org. Chem*. **2012**, *77*, 11210–11215, doi: 10.1021/jo3023445.
4. Smith, K.; El-Hiti, G. A.; Alshammari, M. B. Variations in Site of Lithiation of *N*-[2-(4-Methoxyphenyl)ethyl]pivalamide Use in Ring Substitution, *Synlett* **2013**, *24*, 117–119, doi: 10.1055/s-0032-1317859.
5. Smith, K.; El-Hiti, G. A.; Alshammari, M. B. Unexpected Site of Lithiation of 2-(4-Methoxyphenyl)ethanamine Derivatives. Research article in preparation.
6. Smith, K.; El-Hiti, G. A.; Alshammari, M. B.; Fekri, A. Synthesis of Substituted Pyridines via Directed and Side-Chain Lithiation of 3-Substituted Pyridines. Research article in preparation.
7. Smith, K.; El-Hiti, G. A.; Alshammari, M. B. Variations in Site of Lithiation of Simple Aromatics: Ring and Side-Chain Substitution. Review article in preparation.

- **Posters Represented:**

1. Cardiff Spring Conference, Cardiff University, 14–15 May 2012
2. RSC Roadshow conference, Cardiff University, 7 July 2012
3. The 6th Saudi Scientific International Conference, 11–14 October 2012
4. The South West Regional Meeting of the Organic Division of the Royal Society of Chemistry, School of Chemistry, Cardiff University, Cardiff, United Kingdom, 11 January 2013.

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Chapter One

Lithiation of Simple Aromatic Compounds

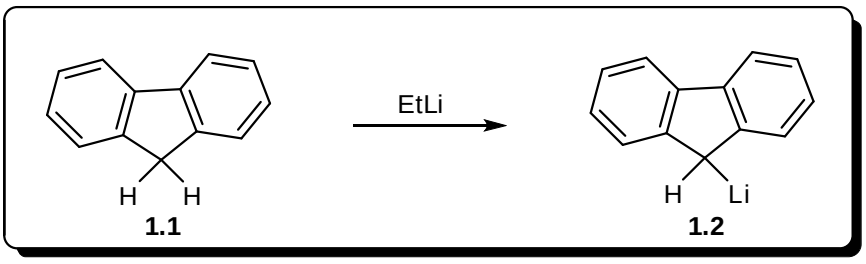
Chapter One

Lithiation of Simple Aromatic Compounds

1.1 Introduction

Electrophilic aromatic substitution reactions are extremely useful in the synthesis of pharmaceutical and other valuable aromatic compounds. Many reactions such as aromatic nitration, halogenation, sulfonation, and Friedel-Crafts acylation and alkylation reactions are well studied electrophilic aromatic substitution reactions.[1] However, such reactions often suffer from serious disadvantages such as low regioselectivity and use of stoichiometric quantities of Lewis acid or other activators. Solid catalysts provide a route for *para*-substitution selectively *via* shape selectivity. On the other hand, directed lithiation can provide a route for the production of *ortho*-disubstituted aromatics.[2]

In 1928 Schlenk and Bergmann reported the first lithiation reaction in which fluorene **1.1** was lithiated with ethyllithium (Scheme 1.1).[3a-d]



Scheme 1.1 Lithiation of fluorene (**1.1**) using ethylithium by Schlenk and Bergmann[3a-d]

In 1939-1940, the independent discovery by Gilman[3e] and Wittig[3f] of *ortho* deprotonation of anisole by *n*-BuLi constituted a new conceptual framework in synthetic aromatic chemistry. Gilman and Wittig also discovered halogen–metal exchange methodology which could be used efficiently for the production of the corresponding lithium reagents when directed lithiation failed.[3g-j] Lithium reagents began to be used industrially in the 1970s as polymerization catalysts, which led to their commercial availability.[3k, l] Over the years, the *ortho*-lithiation reaction has evolved to become a significant fundamental methodology for the regiospecific construction of

polysubstituted aromatic and heteroaromatic compounds and has become one of the most widely used processes for synthesis of organic compounds.[3m, n]

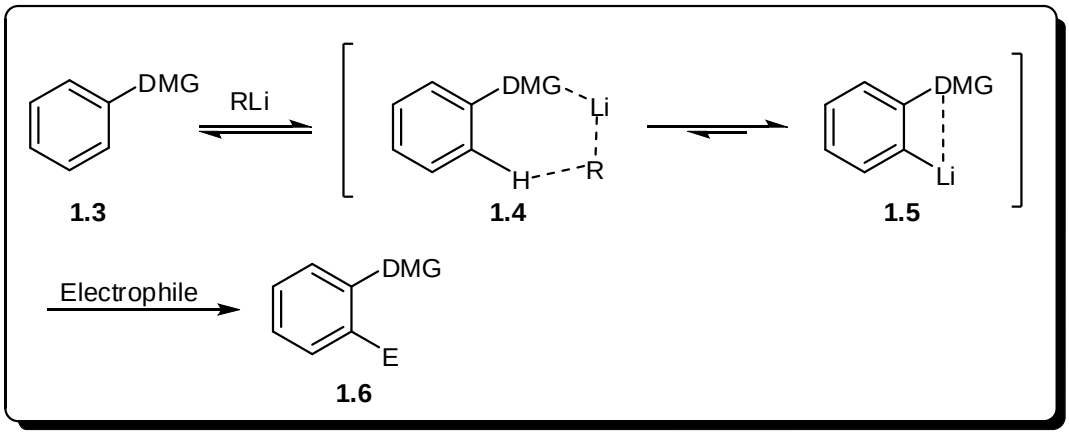
Lithiation is described as a process by which a hydrogen atom is replaced by a lithium atom using lithium metal, a radical anion lithium salt or a lithium reagent. Organolithium reagents are most widely used for organic synthesis; generally they are soluble in organic solvents (*e.g*. hexane and ethers), very reactive, but less toxic or less reactive with ethers at low temperatures compared with some other organometallics, such as organomercury, organosodium and organopotassium reagents.[4]

Several organolithium reagents are made commercially, some of them on a considerable scale. *n*-Butyllithium (*n*-BuLi), *sec*-butyllithium (*sec*-BuLi) and *tert*-butyllithium (*t*-BuLi) in hydrocarbon solvents, for example, are sold in tonnage quantities due to their reasonable stability at room temperature. The addition of coordinating ligands such as *N*,*N*,*N'*,*N'*-tetramethylethlenediamine (TMEDA) to lithium reagents tends to lower the degree of aggregation by providing the electron density needed to the deficient lithium atom *via* coordination.[2]

The lithiation of benzene, naphthalene or other simple arenes requires "superbasic" reagents since the presence of acidic hydrogen is an important requisite for lithiation. Although protons attached to sp^2 carbons are more acidic than protons attached to sp^3 carbons, the acidity of simple unsubstituted arenes is not great enough for lithiation by ordinary organolithium reagents. In some substituted aromatic rings and various heterocycles, however, alkyllithium reagents could deprotonate an sp^2 hybridized carbon atom on the ring. The protons that need to be removed should be more acidic than the alkane corresponding to the alkyllithium.[2] However, the acidity of the aromatic protons is affected by the presence of substituents.[4] Factors which increase the acidity of the hydrogens, such as electron-withdrawing groups (nitrile and carboxyl) facilitate lithiation,[5] while methyl and other alkyl deactivate the ring towards lithiation.[6]

Directed lithiation of substituted aromatics **1.3** is a powerful way of functionalizing aromatic systems regioselectively. Directing the attack of an organolithium reagent to the target positions (Scheme 1.2) requires a directing metalating group (DMG). This has to possess donor substituents containing a coordinating atom such as oxygen or nitrogen to bind to the Lewis acidic organolithium reagent and direct the nucleophile to the neighbouring proton to be removed. Therefore,

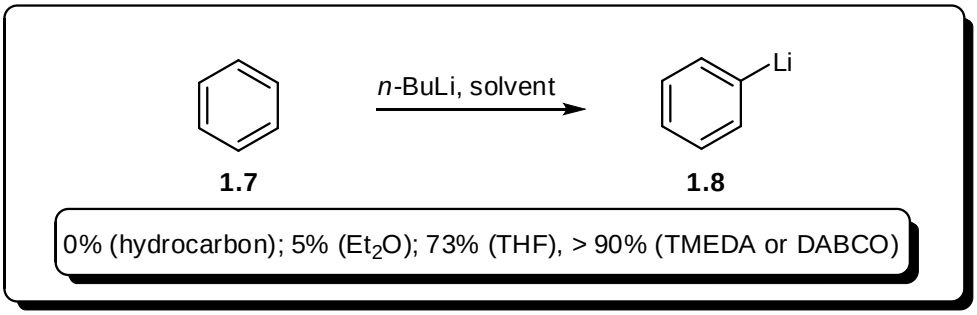
the functional group 'guides' the lithium reagent to attack adjacent protons by forming a complex with the Lewis acidic lithium atom.[2,3] Lithium reagents **1.4** and **1.5** are produced *in situ* and on reaction with an electrophile give the corresponding 2-substituted derivatives **1.6**.[2,3]



Scheme 1.2 Directed lithiation of substituted aromatics **1.3** followed by reaction with an electrophile[2,3]

The direct lithiation of substituted benzenes relies on a number of elements, such as the nature of the DMG, the lithium reagent, additives used, temperature, solvents, nature of the substituent on the benzene ring, and how far the directing group is away from the ring.[2,3]

Aggregation brings down the reactivity of organolithium reagents, but such aggregates can be broken up and activated by complexation with an electron donor such as a Lewis basic solvent (*e.g.* diethyl ether or THF) or an additive (*e.g.* TMEDA, 1,4-diazabicyclo[2.2.2]octane (DABCO), or potassium *tert*-butoxide (*t*-BuOK), which also enhance the reactivity of organolithiums by increasing the ionic character of the Li–C bond (increased negative charge on the carbanion).[2] For example, lithiation of benzene (**1.7**) using *n*-BuLi in hydrocarbon solvent, where the *n*-BuLi exists as a hexamer, does not take place. In diethyl ether and/or THF, where the *n*-BuLi exists as tetramer, it does not occur much better (about 5% yield of **1.8**). However, in the presence of TMEDA or DABCO, where the *n*-BuLi exists as either a dimer or monomer, at least 90% yield of phenyllithium is observed (Scheme 1.3).[2]



Scheme 1.3 Lithiation of benzene (**1.7**) using *n*-BuLi in different conditions[2]

The reactivity gained from the complexation between a lithium reagent and a solvent can be deleterious under certain conditions (*e.g*. high temperature or long time), because they may react with each other. One typical pathway for a reaction of an organolithium reagent with an ethereal solvent involves ether cleavage leading to an alkene and lithium alkoxide.[2]

These additives could affect the regioselectivity of the lithiation site. For example, during lithiation of 4-methoxy-(*N*,*N*-dimethylaminomethyl)benzene (**1.9**, Figure 1.1) with *n*-BuLi, the nitrogen atom binds to the Li (Lewis acid), and directs the carbanion to the *ortho*-position, *meta* to the methoxy group. On the other hand, in the presence of TMEDA or *t*-BuOK, which increase the basicity of the metalating reagent, the more acidic protons, next to the methoxy group, are deprotonated.[2c]

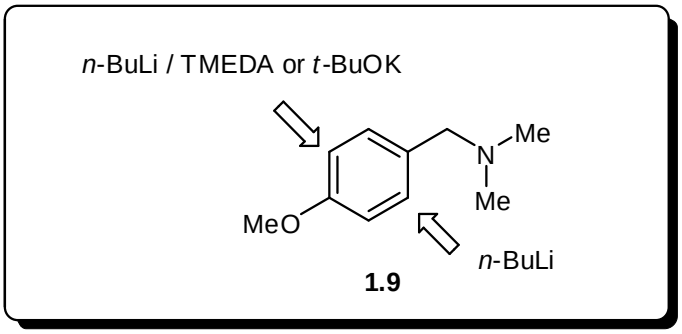


Figure 1.1 Regioselective lithiation of 4-methoxy-(*N*,*N*-dimethylaminomethy)lbenzene (**1.9**)[2c]

In another example, lithiation of *tert*-butyl 2-(3-methoxyphenyl)ethylcarbamate (**1.10**, Figure 1.2) with *n*-BuLi took place at the *ortho*-position, powered by coordination from both the methoxy and carbamate groups as well as the acidity of the proton to be attacked. The use of *t*-BuLi as lithium reagent lithiated the less hindered

benzylic site (α-lithiation), where it still benefitted from coordination with the carbamate group. When the Lewis acidity of the Li atom in *t*-BuLi was decreased by the addition of a Lewis base such as TMEDA the most acidic and less hindered proton, at position 4, was deprotonated and the lithium reagent produced was presumably stabilised *via* coordination.[7]

Also, the reaction temperature can have a significant effect in lithiation reactions; it could affect the reaction rate, the regioselectivity, the stability of the intermediates, or isomerization, as well as creating or preventing side products.

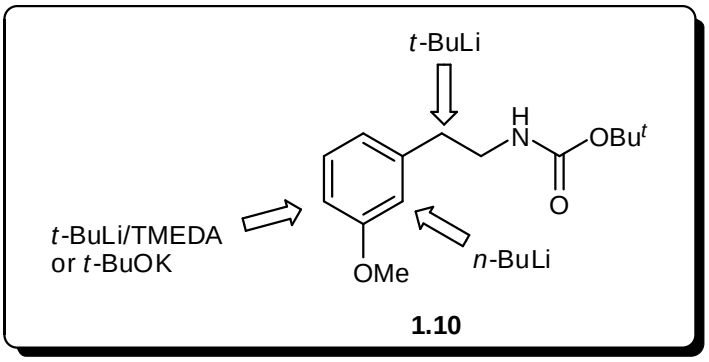
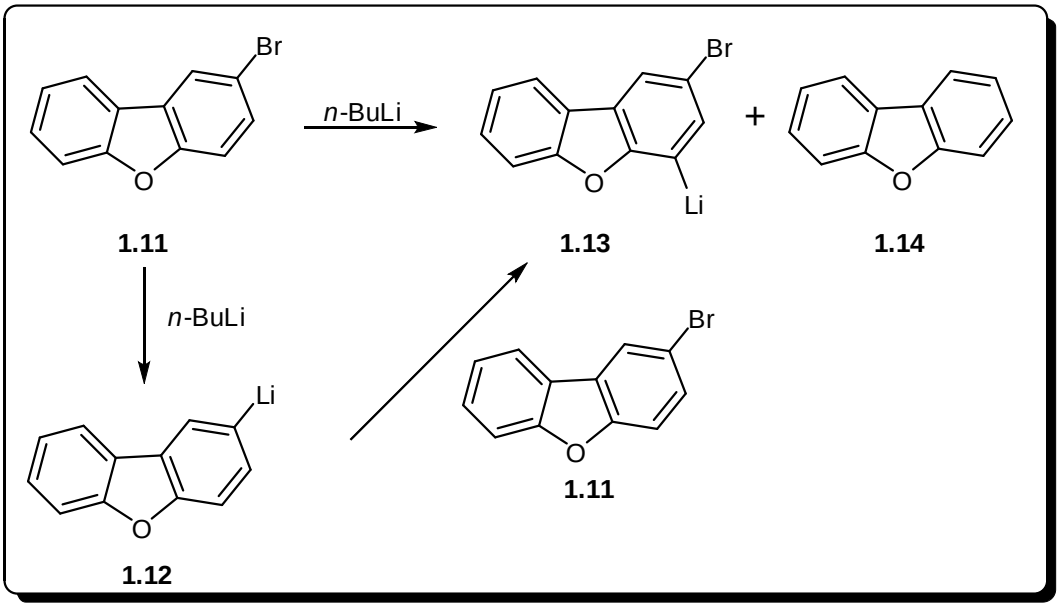


Figure 1.2 Regioselective lithiation of *tert*-butyl 2-(3-methoxyphenyl)ethylcarbamate (**1.10**)[7]

While it may be possible to predict the product of a specific lithiation reaction, it is never safe to conclude with certainty that this is the product unless it is supported experimentally. In some cases, the lithiation product does not reflect where the lithiation initially occurred during the course of the reaction. For example, treatment of 2-bromodibenzofuran (**1.11**) with *n*-BuLi initially resulted in halogen–metal exchange to give 2-lithiodibenzofuran (**1.12**), which then lithiated unreacted 2-bromodibenzofuran to give dibenzofuran (**1.14**) along with 2-bromo-4-lithiodibenzofuran (**1.13**; Scheme 1.4), based on the structure of the carboxylation product obtained.[8]



Scheme 1.4. Reaction of 2-bromodibenzofuran (**1.11**) with *n*-butyllithium[8]

α-Lithiation is favoured by strongly acidifying groups or strongly coordinating groups that stabilise the organolithium even if they decrease the acidity. Despite the electron-withdrawing effect of oxygen and nitrogen atoms, lithiation next to them (*e.g.* next to NMe_2 and OMe groups) is unfavoured due to the low stability of the lithium intermediates formed (Figure 1.3A) as a result of the antibonding interaction of these atoms' lone pairs with the electrons of the C–Li bond. But lithiation next to such atoms could be favoured by decreasing the lone pair's energy by delocalisation such as conjugation with a carbonyl group (*e.g.* $CONMe_2$, $CONHBu^t$) that will reduce the repulsion between the antibonding lone pair with the C–Li bond (Figure 1.3B).[2]

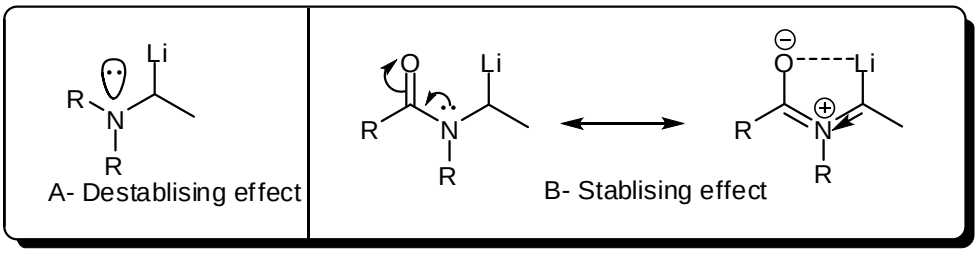


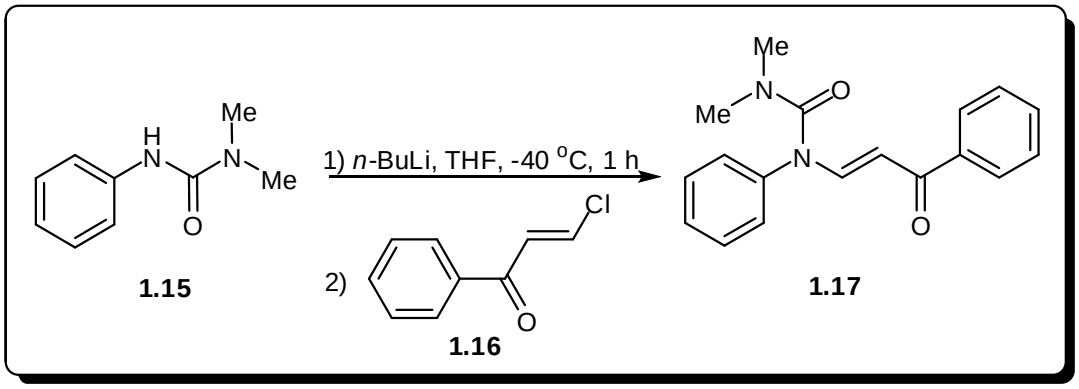
Figure 1.3 Stabilising and destabilising effects of lithium intermediates[2]

The direct *ortho* functionalization of aniline derivatives has been the subject of several recent publications.[9a] Due to their excellent coordination ability towards alkyllithium reagents, the urea, pivalamide and carbamate groups can exert a powerful

ortho-directing effect on the lithiation of protected anilines.[9b] The following section will try to highlight the effect of such groups, type of lithium reagents and/or temperature on the site of lithiation of the corresponding substituted anilines.

1.2 Lithiation of *N′*-phenyl-*N*,*N*-dimethylurea (1.15)

Lithiation of *N′*-phenyl-*N*,*N*-dimethylurea (**1.15**) with *n*-BuLi (1.2 equivalents) at –40 °C in THF for 1 h followed by reaction with 3-chloro-1-phenyl-2-propen-1-one (**1.16**) gave the corresponding *N*-substituted product **1.17** in 82% yield (Scheme 1.5).[10] This demonstrates that the first proton removed from such urea derivatives is the NH proton, which is the most acidic proton.

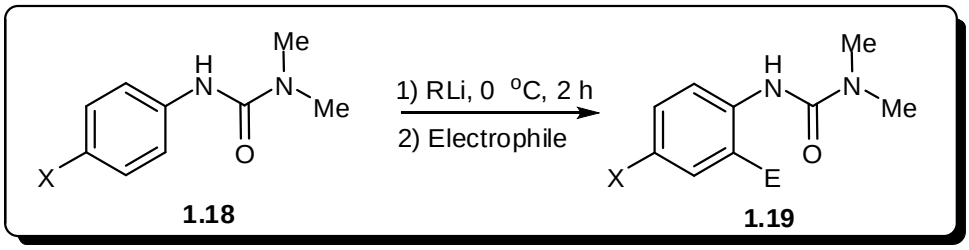


Scheme 1.5 Lithiation and substitution of *N′*-phenyl-*N*,*N*-dimethylurea (**1.15**)[10]

Double lithiation of various *N′*-aryl-*N*,*N*-dimethylureas **1.18** takes different courses depending on the substituent on the aryl ring. For example, lithiation of *N′*-(4-chlorophenyl)-*N*,*N*-dimethylurea (**1.18**; X = Cl) occurred smoothly and rapidly with *n*-BuLi (2.5 equivalents) at 0 °C in THF. The dilithium reagent produced *in situ* was reacted with electrophiles to afford the corresponding *ortho*-products **1.19** (X = Cl) in high yields (Table 1.1).[11]

Lithiation of *N′*-(4-fluorophenyl)-*N*,*N*-dimethylurea (**1.18**; X = F) was not successful with *n*-BuLi. However, *ortho*-lithiation was achieved by the use of *t*-BuLi (2.5 equivalents) at 0 °C for 2 h in THF.[11] Reaction of the dilithium reagent produced *in situ* with electrophiles at 0 °C gave the corresponding *ortho*-products **1.19** (X = F) in good yields (Table 1.1). *N′*-(4-Trifluoromethylphenyl)-*N*,*N*-dimethylurea (**1.18**; X = CF_3) provided low yields (31%) under similar reaction conditions when benzophenone was used as a representative electrophile.

Table 1.1 Directed lithiation of *N'*-(4-substituted phenyl)-*N*,*N*-dimethylureas **1.18**[11]

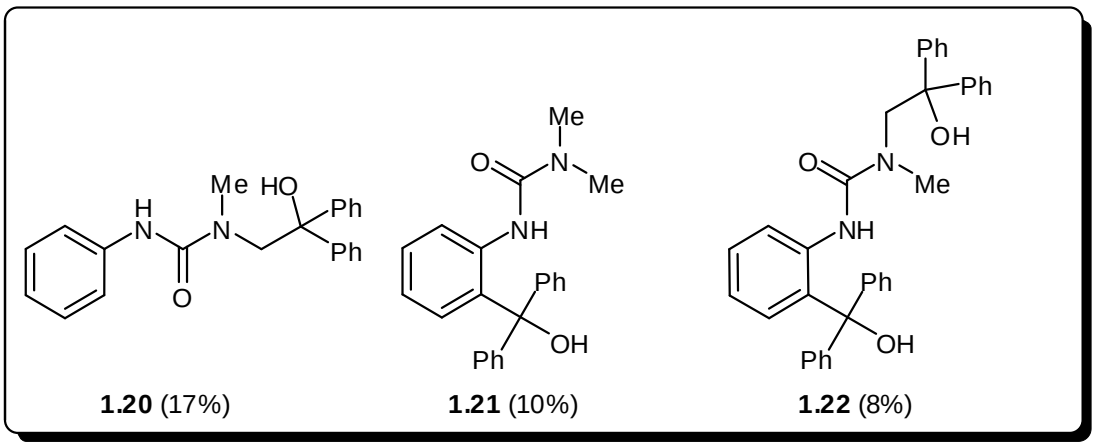


1.18 **1.19**

X	RLi	Electrophile	E	Yields of **1.19** (%)[a]
Cl	*n*-BuLi	D_2O	D	83
Cl	*n*-BuLi	$(Ph)_2CO$	$(Ph)_2C(OH)$	82
Cl	*n*-BuLi	PhCHO	PhCH(OH)	78
Cl	*n*-BuLi	PhNCO	PhNHCO	80
Cl	*n*-BuLi	PhNCS	PhNHCS	72
F	*t*-BuLi	D_2O	D	88
F	*t*-BuLi	$(Ph)_2CO$	$(Ph)_2C(OH)$	78
F	*t*-BuLi	PhCHO	PhCH(OH)	77
CF_3	*t*-BuLi	$(Ph)_2CO$	$(Ph)_2C(OH)$	31[b]

[a] Yield of pure isolated products.
[b] Starting material (61%) was recovered.

Attempted double lithiations of unsubstituted *N'*-phenyl *N*,*N*-dimethylurea (**1.15**) and *N'*-(4-methylphenyl)-*N*,*N*-dimethylurea (**1.18**; X = CH_3) were not successful using *n*-BuLi at 0 °C and starting materials were recovered quantatitively.[11] However, double lithiation of *N'*-phenyl *N*,*N*-dimethylurea (**1.15**) was achieved by use of *t*-BuLi (2.2 equivalents) at 0 °C, but with poor selectivity, a mixture of products **1.20** (17%), **1.21** (10%) and **1.22** (8%) (Figure 1.4) being produced when benzophenone was used as electrophile.[11] Unidentified highly polar materials which adsorbed at the top of the column explain the low overall yield isloated.[11]

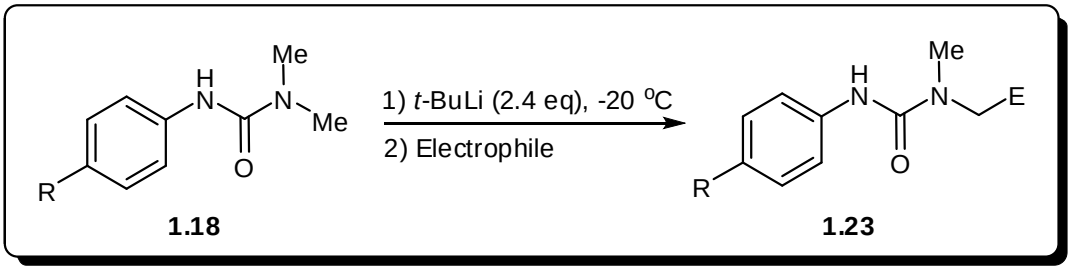


1.20 (17%) **1.21** (10%) **1.22** (8%)

Figure 1.4 Structures of products **1.20–1.22**[11]

The selectivity was improved with *t*-BuLi (2.4 equivalents) at –20 °C for 2 h followed by the reaction with electrophiles (1.2 equivalents) to give corresponding side-chain substituted products **1.23** in high yields (Table 1.2).[11] *N′*-(4-Methylphenyl)-*N*,*N*-dimethylurea (**1.18**; X = CH_3) gave similar results (Table 1.2).[11]

Table 1.2 Side-chain lithiation of *N′*-(substituted phenyl)-*N*,*N*-dimethylureas **1.18**[11]

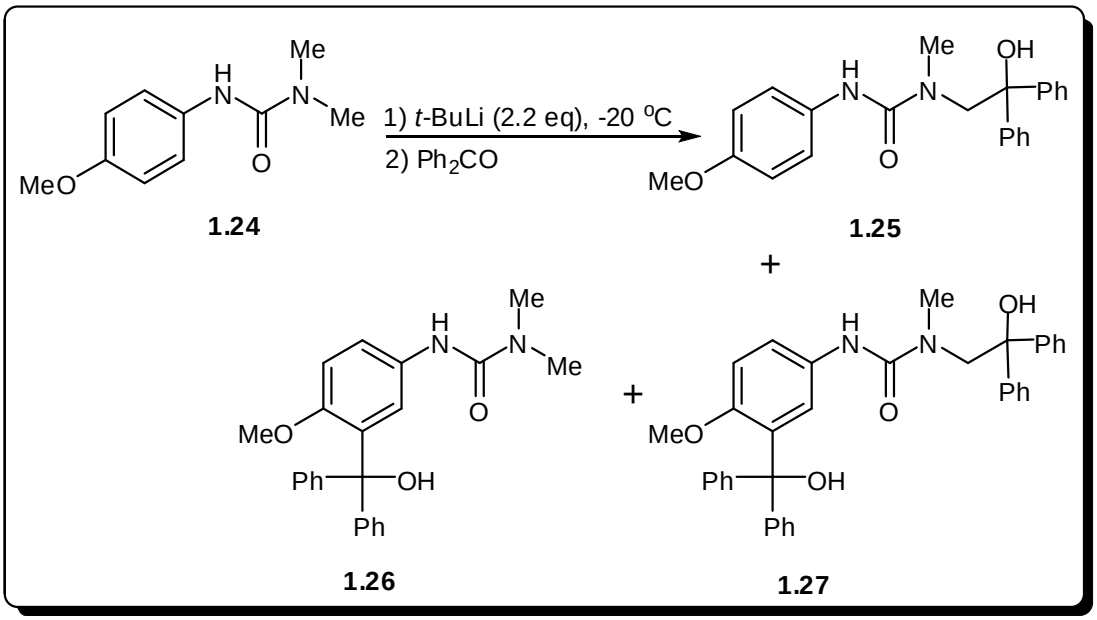


1.18 **1.23**

R	Electrophile	E	Yield (%)
H	Ph_2CO	$Ph_2C(OH)$	82
H	D_2O	D	92
H	PhCHO	PhCH(OH)	78
Me	Ph_2CO	$Ph_2C(OH)$	79
Me	D_2O	D	90
Me	PhCHO	PhCH(OH)	75

Attempted lithiation of *N′*-(4-methoxyphenyl)-*N*,*N*-dimethylurea (**1.24**) with *n*-BuLi, *t*-BuLi or LDA at −78 °C was not successful.[11] However, lithiation of **1.24** (Scheme 1.6) with *t*-BuLi (2.2 equivalents) at -20°C followed by reaction with

benzophenone (2.2 equivalents) led to a mixture of products formed by side-chain substitution (**1.25**, 50%), ring substitution next to methoxy group (**1.26**, 2%) and disubstitution (**1.27**, 16%).[11] The disubstituted product **1.27** was produced in 87% yield (Table 1.3) as the only product when excess *t*-BuLi (3.3 equivalents) and benzophenone (2.2 equivalents) were used.[11] Similar results were obtained when 4-*tert*-butylcyclohexanone was used as the electrophile.



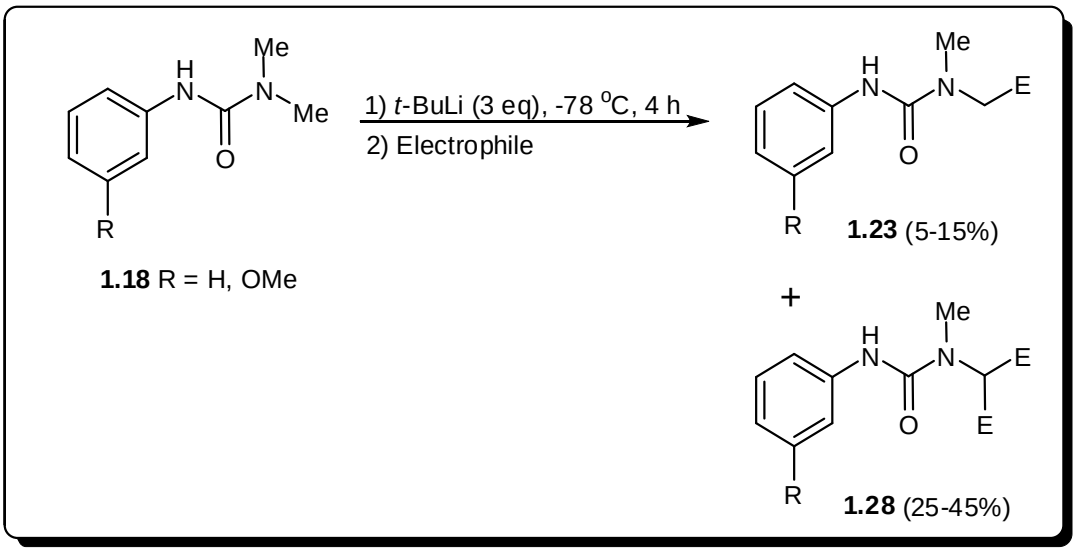
Scheme 1.6 Lithiation and substitution of *N*′-(4-methoxyphenyl)-*N*,*N*-dimethylurea (**1.24**)[11]

Table 1.3 Lithiation of *N*′-(4-methoxyphenyl)-*N*,*N*-dimethylurea (**1.24**) under various reaction conditions followed by reactions with benzophenone[11]

t-BuLi (mmol)	Reaction temperature (°C)	Yield of products (%)		
		1.25	**1.26**	**1.27**
2.2	0	62	2	4
2.2	–20	50	2	16
2.2	–78	—	—	—
3.3	0	2	2	77
3.3	–20	—	—	87

Ring substitution could be achieved *via* bromine–lithium exchange of *N'*-(2-bromophenyl)-*N*,*N*-dimethylurea or *N'*-(2-bromo-4-methylphenyl)-*N*,*N*-dimethylurea with one mole equivalent of MeLi to deprotonate the nitrogen, followed by 2 mole equivalents of *t*-BuLi at 0 °C to achieve the bromine–lithium exchange, followed by reaction with benzophenone. The corresponding substituted derivatives were obtained in 85% and 86% isolated yields, respectively.[11]

Rauf and Brown[12] have reported that lithiation of *N'*-phenyl-*N*,*N*-dimethylurea and *N'*-(3-methoxyphenyl)-*N*,*N*-dimethylurea **1.18** with *t*-BuLi (3 equivalents) for 3 h at –78 °C followed by reaction with Me_3SiCl or $(Ph_2MeSi)_2$ (3 equivalents) gave mixtures of products from *N*-methyl substitution (**1.23**, 5-15%) and double *N*-methyl substitution (**1.28**, 25–45%; Scheme 1.7).[12]



Scheme 1.7 Lithiation and substitution of *N'*-(substituted phenyl)-*N*,*N*-dimethylureas **1.18**[12]

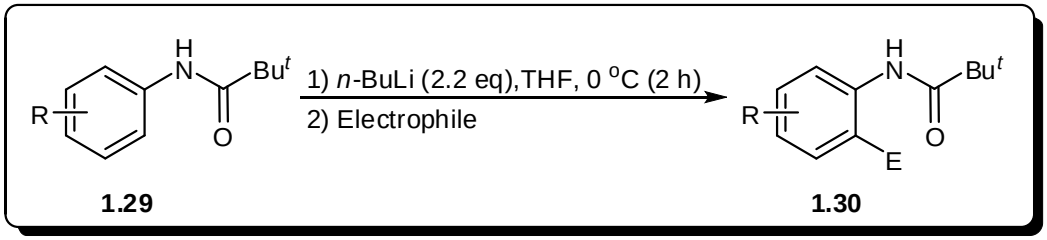
Lithiation of *N'*-(4-nitrophenyl)-*N*,*N*-dimethylurea was not successful with *n*-BuLi or *t*-BuLi under various reaction conditions.[11]

1.3 Lithiation of *N*-phenylpivalamides

Double lithiation of *N*-phenylpivalamide with *s*ec-BuLi and *n*-BuLi (with or without TMEDA) at low temperatures (–78 to –20 °C) in THF followed by reactions with electrophiles provided the corresponding *ortho*-substituted derivatives in moderate

yields (30–85%).[13] Similarly, substituted *N*-phenylpivalamides **1.29** were doubly lithiated with *n*-BuLi at 0 °C for 2 h in THF and the dilithium reagents obtained were reacted with electrophiles to give the corresponding 2-substituted products **1.30** in good yields (Table 1.4).[14]

Table 1.4 Synthesis of various substituted *N*-phenylpivalamides **1.30**[14]



1.29 **1.30**

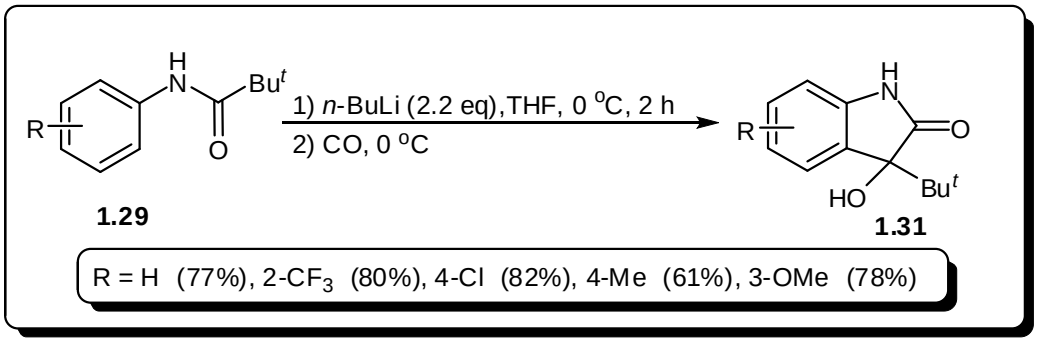
R	Electrophile	E	Yields (%)
H	$(MeS)_2$	MeS	78
H	DMF	CHO	53
3-OMe	$(MeS)_2$	MeS	82
3-OMe	PhCHO	PhCH(OH)	79
4-OMe	$(MeS)_2$	MeS	38[a]
4-Cl	$(MeS)_2$	MeS	79
4-Cl	MeI	Me	71

[a] 21% of disusbtituted products (next to directing group and the methoxy group) was obtained along with 18% of starting material.

High yields (79–82%) were obtained in the case of the 3-methoxy derivative **1.29** (R = 3-OMe) as a result of the combined *ortho*-directing effect exerted by the pivalamide and the methoxy groups. However, the yield was low (38%) for the 4-methoxy derivative **1.29** (R = 4-OMe), from which the disubstituted product was obtained in 21% yield.[15] The competitive effect of two directing metallating groups affected the lithiation site but the pivalamide group was slightly more effective than the methoxy group.[14]

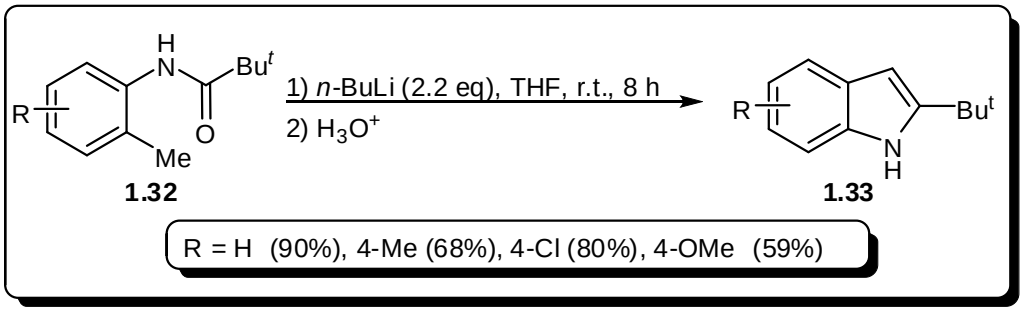
The utility of the reaction presented in Scheme 1.8 has been demonstrated by carbonylation of doubly lithiated *N*-pivaloylanilines **1.29**, with carbon monoxide, under

similar conditions, to give the corresponding 3-*tert*-butyl-3-hydroxyindolin-2-ones **1.31** in high yields (Scheme 1.8).[15]



Scheme 1.8 Lithiation of substituted *N*-phenylpivalamides **1.29** followed by reaction with carbon monoxide[15]

Lateral lithiation of **1.32** followed by cyclisation led to the corresponding 2-*tert*-butylindoles in good yields (Scheme 1.9).[15]

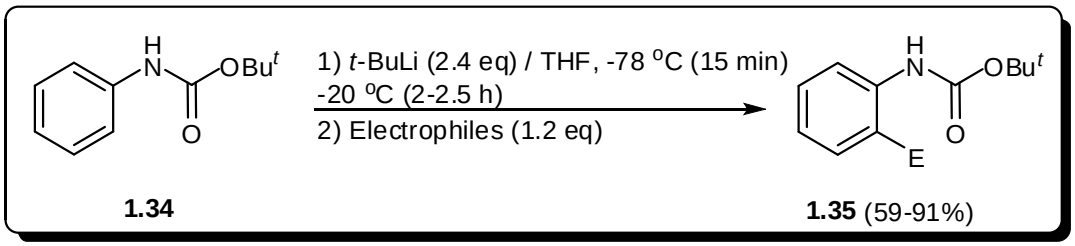


Scheme 1.9 Lateral lithiation followed by cyclization of substituted *N*-(2-methylphenyl)pivalamides **1.32**[15]

1.4 Lithiation of *tert*-butyl phenylcarbamate

Ring lithiation and substitution of *tert*-butyl phenylcarbamate **1.34** was achieved by the use *t*-BuLi at low temperature followed by reactions with electrophiles to give the corresponding products **1.35** in 59–91% yields (Table 1.5).[16] However, no *C*-lithiation took place, even after several hours at room temperature, when *n*-BuLi (2.5 equiv), in the presence or absence of TMEDA, or *sec*-BuLi was used as the lithium reagent.[16]

Table 1.5 Synthesis of various *tert*-butyl (2-substituted phenyl)carbamates **1.35**[16]



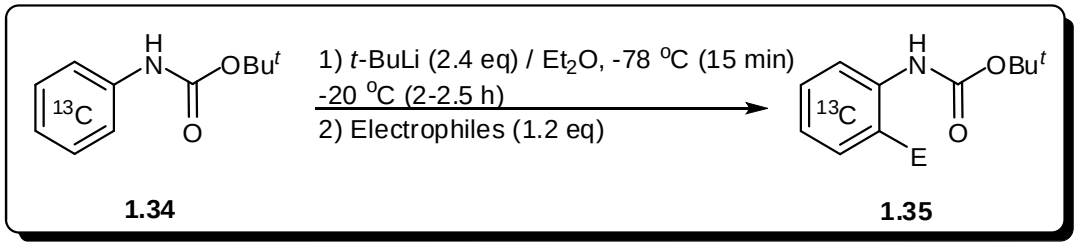
1.34 **1.35** (59-91%)

Time with Electrophile (h); Temp. (°C)	Electrophile	E	Yields (%)
0.5 (–20)	MeI	Me	59[a]
2 (–20)	$(PhS)_2$	PhS	91
2.5 (–20)	PhCHO	PhCH(OH)	67
2 (–20)	Ph_2CO	$Ph_2C(OH)$	78
1 (–20), 2 (r.t.)	Me_2NCHO	CHO	65
2 (r.t)	CO_2	CO_2H	73
2 (–20), 1 (r.t.)	PhNCS	PhNHCS	69

[a] Dimethylated product was obtained in 82% yield when MeI (4 equivalent) was used.

The number of electrophiles used in the process represented in Table 1.5 has been extended by using other electrophiles such as phenyl cyanate, but in Et_2O as a solvent.[17,18] Similarly, borates were used as electrophiles (1.2 equivalents) to provide the corresponding derivatives, but in low yields (8–47%) when *t*-BuLi (2.4 equivalents) at –20 °C in Et_2O was used even in the presence or absence of additives (Table 1.6).[19]

Table 1.6 Synthesis of various *tert*-butyl (2-substituted phenyl)carbamates **1.35**[19]



1.34 **1.35**

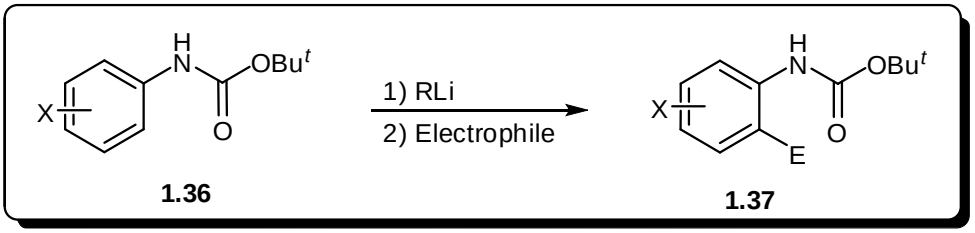
Electrophile	E	Additive	Yield (%)[a]
$B(OMe)_3$	$B(OMe)_2$	—	47(52)[b]
$B(O^iPr)_3$	$B(O^iPr)_2$	—	35
$B(O^iPr)_3$	$B(O^iPr)_2$	2,2-dimethylpropane-1,3-diol	32
O_2	OH	—	8
O_2	OH	$Ti(O^iPr)_4$	11

[a] The yield of products after oxidation of the boron compounds.
[b] When THF was used as solvent. No product was obtained when *n*-BuLi at −20 °C was used.

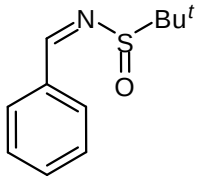
Ring lithiation of various substituted *tert*-butyl phenylcarbamates **1.36** with *sec*-BuLi (2 equivalents) in presence of TMEDA at −20 °C for 2 h followed by reaction with (*Z*)-*N*-benzylidene-2-methylpropane-2-sulfinamide successfully gave the corresponding 2-substituted derivatives **1.37** in high yields (Table 1.7).[20] Previous reports had indicated that lithiation of **1.34** was not successful with *sec*-BuLi as the lithium reagent.[16]

Higher yields (74–81%) were obtained when electron-withdrawing substituents were attached to the phenyl ring.[20] A lower yield (30%) was obtained in the case of the electron-donating methoxy group.[20] However, other reports have indicated that the yield of the methoxy derivative could be improved to 55%[21] and 86%[22] when 2.2 and 2.5 equivalents of *t*-BuLi in Et_2O were used, respectively. Similarly, 2-bromo derivatives **1.37** were obtained in high yields (Table 1.7, Entries 6–16) from lithiation of **1.36** with *t*-BuLi in THF at –50 °C followed by reaction with CBr_4 as the elctrophile.[24]

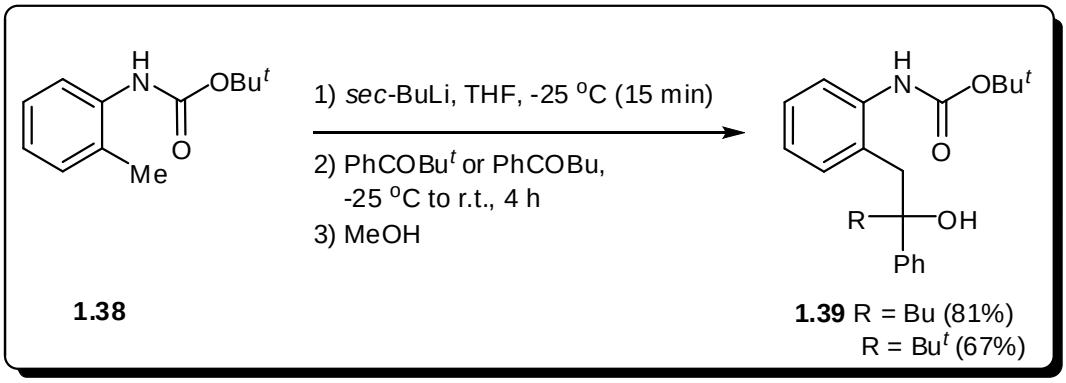
Table 1.7 Synthesis of various *tert*-butyl (substituted) phenylcarbamates **1.37**[20–23]



1.36 **1.37**

Entry	X	RLi (mole equiv, condition)	Electrophile	Yields (%)
1	H	*sec*-BuLi (2 equiv),		61
2	4-Cl	TMEDA (2 equiv), THF,		79
3	4-F	-78 °C (15 min), -20 °C		74
4	4-CF_3	(2–2.5 h)		81
5	4-OMe			30
6	H	*t*-BuLi (2 equiv), THF,	CBr_4	78
7	2-F	–78 °C (15 min), –50 °C		82
8	3-F	(3 h)		75
9	4-F			66
10	2-CF_3			64
11	3-CF_3			77
12	4-CF_3			94
13	2-OCF_3			46
14	4-OCF_3			81
15	2,4-*bis*-CF_3			63
16	2-F-3-OMe			62

Lateral lithiation and substitution of *tert*-butyl (2-methylphenyl)carbamate (**1.38**) took place with either *sec*-BuLi[24] at –25 °C (Scheme 1.10) or *t*-BuLi at –20 °C[25] and subsequent reactions with representative electrophiles gave the corresponding substituted derivatives (Scheme 1.10) in high yields.



Scheme 1.10 Lateral lithiation and substitution of *tert*-butyl (2-methylphenyl)carbamate (**1.38**)[24]

1.5 Lithiation of *N'*-benzyl-*N,N*-dimethylureas

Lithiation of *N'*-benzyl-*N,N*-dimethylureas with *sec*-BuLi (2 equivalents) in THF at −78 °C for 4 h followed by reaction with carbon dioxide has been reported to afford the *ortho*−substituted product in 82% yield. The yield increased to 90% when *t*-BuLi was used as the lithium reagent. Various *N'*-(substituted benzyl)-*N,N*-dimethylureas (*e.g.* 2-, 3- and 4-methoxy and 2-, 3- and 4-fluoro derivatives) were lithiated and the results are illustrated in Figure 1.5.[26]

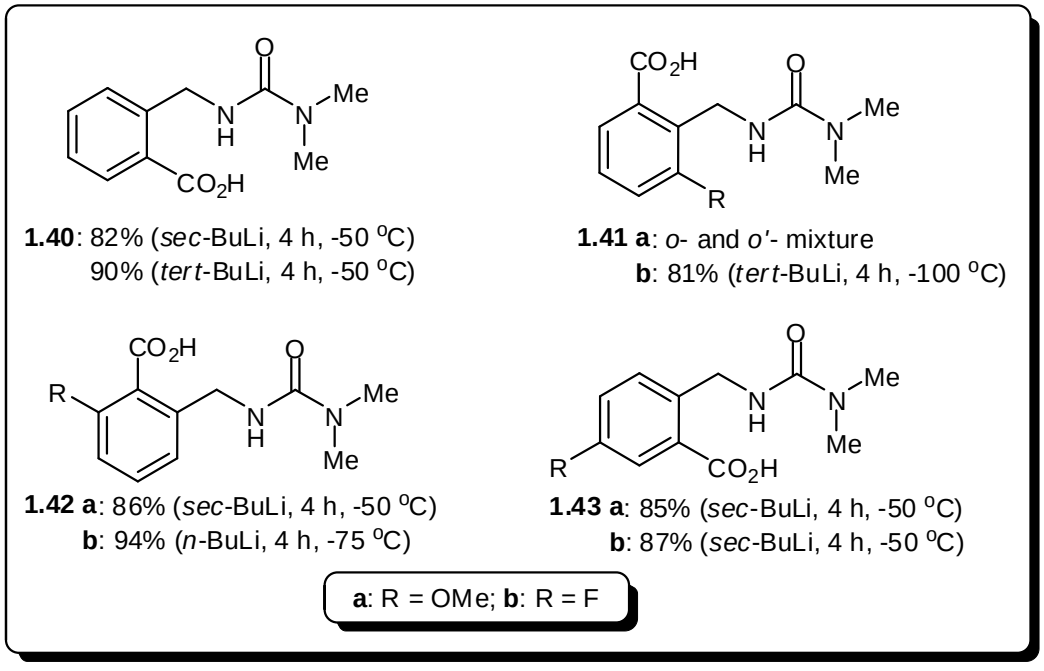
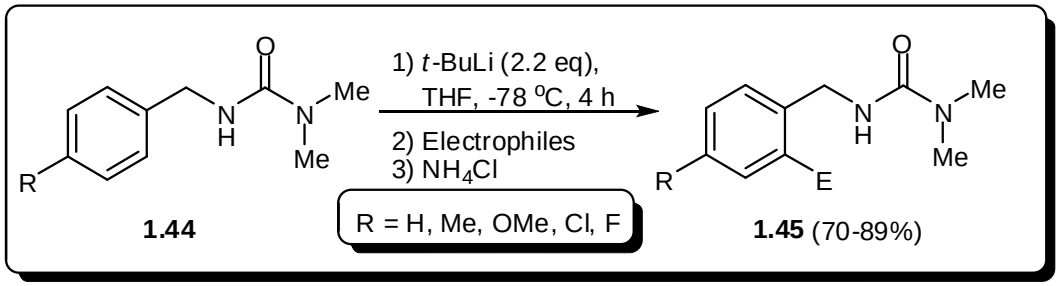


Figure 1.5 Products from lithiation of *N'*-(substituted benzyl)-*N,N*-dimethylureas under different conditions followed by reaction with carbon dioxide[26]

Thus, Schlosser proved that the urea group is an excellent *ortho*-directing group with various lithium reagents in such systems, even in the presence of another DMG (*e.g*. methoxy group). However, in the case of the 2-methoxy derivative, a mixture of unseparated products *ortho* to the directing group (*o*-product) and *ortho* to the OMe group (*o'*-product) were produced on reaction of carbon dioxide with the dilithium reagents produced *in situ*.[26]

A detailed study of the lithiation of various substituted *N'*-benzyl-*N*,*N*-dimethylureas **1.44** to test the generality of the process was recently reported.[27] It was found that lithiation of **1.44** with *t*-BuLi (2.2 equivalents) in anhydrous THF at −78 °C followed by reaction with various electrophiles indeed afforded *ortho*-substituted products **1.45** in high yields (Table 1.8).[27]

Table 1.8 Lithiation and substitution of various substituted *N'*-benzyl-*N*,*N*-dimethylureas **1.44** [27]



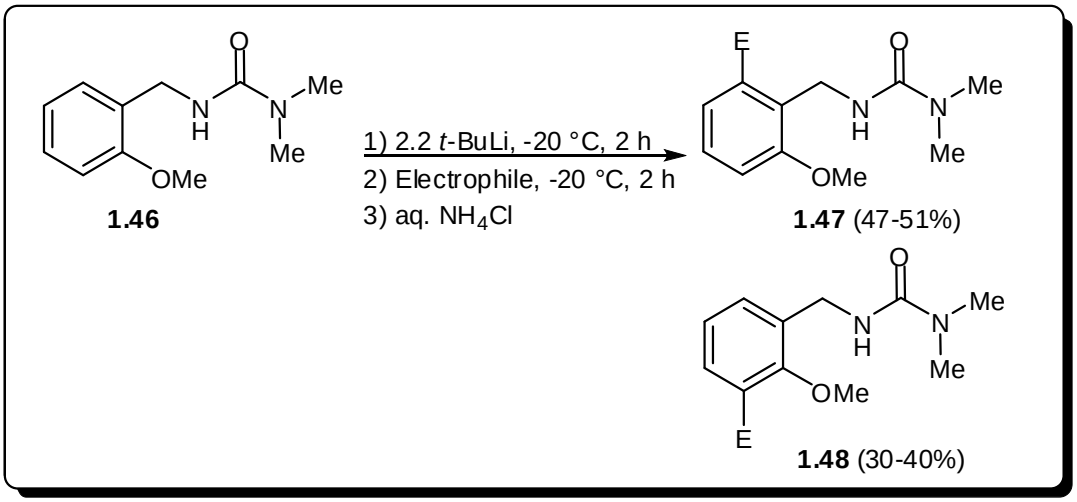
R	Electrophile	E	Yields (%)
H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	86
H	PhCHO	PhCH(OH)	82
H	Ph_2CO	$Ph_2C(OH)$	84
H	MeI	Me	80
H	D_2O	D	89
Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	76
Me	PhCHO	PhCH(OH)	70
Me	Ph_2CO	$Ph_2C(OH)$	72
Me	EtI	Et	80
Me	D_2O	D	86
OMe	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	85
OMe	PhCHO	PhCH(OH)	89

Table 1.8: Continued

OMe	Ph_2CO	$Ph_2C(OH)$	84
OMe	D_2O	D	86
OMe	EtI	Et	88
Cl	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	79
Cl	PhCHO	PhCH(OH)	79
Cl	EtI	Et	78
Cl	D_2O	D	79
F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
F	PhCHO	PhCH(OH)	83

Lithiation of *N′*-(2-methoxybenzyl)-*N*,*N*-dimethylurea (**1.46**) with *t*-BuLi followed by reactions with electrophiles were investigated in detail by Smith's group and shown to give mixtures of two products, **1.47** and **1.48**, in *ca*. 49/35 ratio (Table 1.9).[27] Such results were in agreement with the initial findings by Schlosser.[26]

Table 1.9 Lithiation and substitution of *N′*-(2-methoxybenzyl)-*N*,*N*-dimethylureas **1.46**[27]



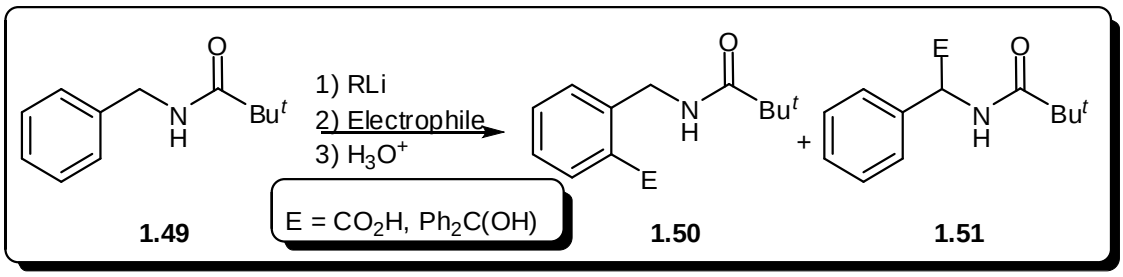
Electrophile	E	Yields (%)**1.47**	Yields (%)**1.48**
4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	49	40
PhCHO	PhCH(OH)	51	38
Ph_2CO	$Ph_2C(OH)$	47	30
MeI	Me	51	40
D_2O	D	51	38

Lateral lithiation of *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea was successfully achieved under the conditions used for other derivatives to afford the laterally-substituted products in high yields (74–84%).[28]

1.6 Lithiation of *N*-benzylpivalamides

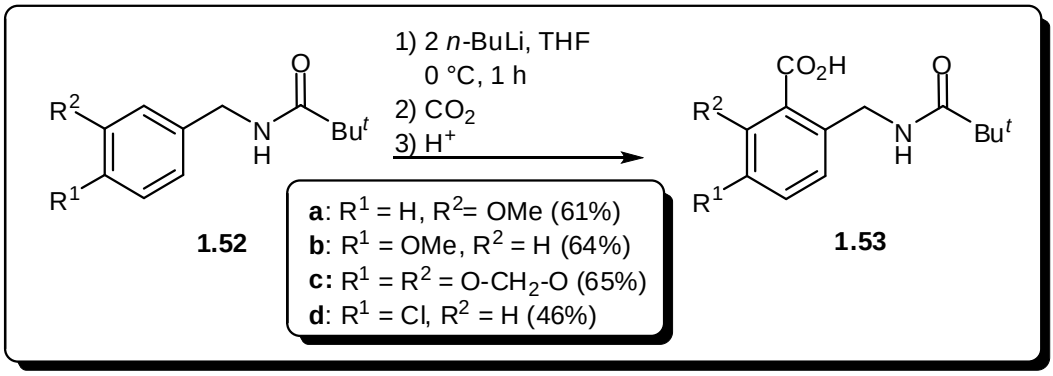
The lithiation of *N*-benzylpivalamide (**1.49**) with *sec*-BuLi (2 equivalents) in THF at −50 °C for 4 h followed by reaction with carbon dioxide was first reported by Schlosser.[29] A mixture of *ortho* product **1.50** (36%) and a side-chain product **1.51** (20%) (Scheme 1.11) was obtained, possibly as a result of coordination and steric effects.[29] In the presence of TMEDA or *t*-BuOK the side-chain product **1.51** was obtained exclusively.[29]

The lithiation was investigated further by the Smith's group using various lithium reagents including *t*-BuLi, *sec*-BuLi and *n*-BuLi, at −78 °C and 0 °C.[27] It was found that *t*-BuLi gave a higher overall yield (71 %) of the two products at 0 °C, under which conditions **1.50** (34%) and **1.51** (37%) were produced when benzophenone was used as electrophile (Scheme 1.11).[27]



Scheme 1.11 Lithiation and substitution of *N*-benzylpivalamide **1.49**[27,29]

Lithiation of various substituted *N*-benzylpivalamides **1.52** by *n*-BuLi at 0 °C for 1 h followed by reaction with carbon dioxide gave *ortho* substituted products **1.53** in moderate yields (Scheme 1.12).[29]

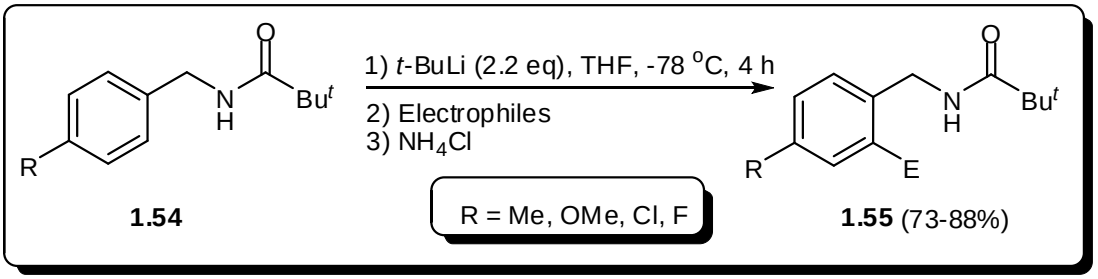


Scheme 1.12 Lithiation and substitution of various substituted *N*-benzylpivalamides **1.52**[29]

Evidently, the pivaloylamino group is a superior *ortho*-directing group than an alkoxy group. On the other hand, when these two substituents occupy positions *meta*- to each other they each activate the CH group in between and deprotonation occurs preferentially at that position.[29]

The yields of *ortho* products **1.55** from the lithiation of substituted *N*-benzylpivalamides **1.54** were improved by using *t*-BuLi (2 equivalents) at −78 °C in excellent yields (Table 1.10).[27]

Table 1.10 Lithiation and substitution of various substituted *N*-benzylpivalamides **1.54** with *t*-BuLi[27]



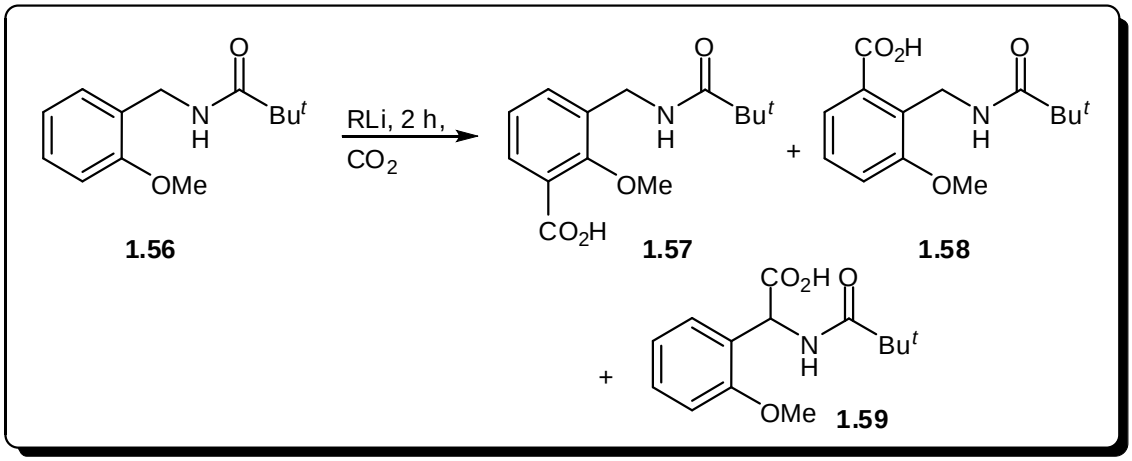
R	Electrophile	E	Yields of **1.55** (%)
Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	81
Me	PhCHO	PhCH(OH)	79
Me	Ph_2CO	$Ph_2C(OH)$	81
Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	82

Table 1.10: Continued

Me	D_2O	D	88
Me	MeI	Me	80[b]
Me	EtI	Et	81
OMe	MeI	Me	81[c]
OMe	Ph_2CO	$Ph_2C(OH)$	80
OMe	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	77
OMe	MeCOBu	MeC(OH)Bu	78
OMe	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	82
OMe	D_2O	D	88
Cl	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
Cl	PhCHO	PhCH(OH)	82
Cl	Ph_2CO	$Ph_2C(OH)$	79
Cl	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	73
Cl	EtI	Et	79
Cl	D_2O	D	88
F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78
F	PhCHO	PhCH(OH)	79
F	Ph_2CO	$Ph_2C(OH)$	76
F	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	82
F	EtI	Et	82
F	D_2O	D	85

Double lithiation of *N*-(2-methoxybenzyl)pivalamide (**1.56**) under the conditions used for other derivatives, followed by reaction with carbon dioxide as electrophile, gave a mixture of three products as a result of *ortho* substitution next to the methoxy group (**1.57**, 8–87%), *ortho* substitution next to the pivaloylaminomethyl group (**1.58**, 19–30%) and side-chain substitution (**1.59**, 7–40%).[27] The proportion of products depended on the type of lithium reagent and the temperature (Table 1.11).[27]

Table 1.11 Lithiation of *N*-(2-methoxybenzyl)pivalamide **1.56**[27]



		Yields of products (%)			
RLi	T (°C)	**1.56**	**1.57**	**1.58**	**1.59**
t-BuLi	–78	2	87	—	7
t-BuLi	0	—	49	19	26
sec-BuLi	–78	22	—	36	34
sec-BuLi	0	9	—	48	38
n-BuLi	–78	97	—	—	—
n-BuLi	0	17	8	30	40

The results showed interesting variations in both rates and product proportions. The extent of lithiation at –78 °C ranged from virtually quantitative with *t*-BuLi to virtually zero with *n*-BuLi, while all three reagents brought about substantial lithiation at 0 °C. Both *n*-BuLi and *sec*-BuLi gave mixtures indicative of lithiation on the side-chain and at the 6-position, as reported by Schlosser with *n*-BuLi.[29] There was very little lithiation at the 3-position with these reagents, whereas this was predominant with *t*-BuLi at 0 °C and almost exclusive at –78 °C. It was assumed that lithiation of **1.56** with *t*-BuLi in THF at –78 °C occurred *ortho*- to the methoxy group because the *t*-BuLi, which was the most basic of the reagents tried, preferred to attack the most acidic and least sterically hindered position while *n*-BuLi and *sec*-BuLi gave mixtures involving lithiation at two other sites, at which stabilisation of the lithium intermediate *via* coordination possibly became the superior factor.[27]

Lateral lithiation of *N*-(2-methylbenzyl)pivalamide using two mole equivalents of *t*-BuLi at –78 °C and reaction of the lithium reagent obtained with a variety of electrophiles gave the corresponding laterally-substituted products in high yields (76-89%).[28]

1.7 Lithiation of *tert*-butyl benzylcarbamates

Lithiation of *tert*-butyl benzylcarbamate (**1.65**) with *sec*-BuLi (2 equivalents) in THF at –50 °C for 4 h followed by reaction with carbon dioxide afforded α–substituted product **1.61** in 79% yield (Figure 1.6).[26] Lithiations of 2-, 3- and 4-methoxy- and 2-, 3- and 4-fluoro derivatives were also reported, but mostly using a different lithium reagent under different reaction conditions (Figure 1.6).[26]

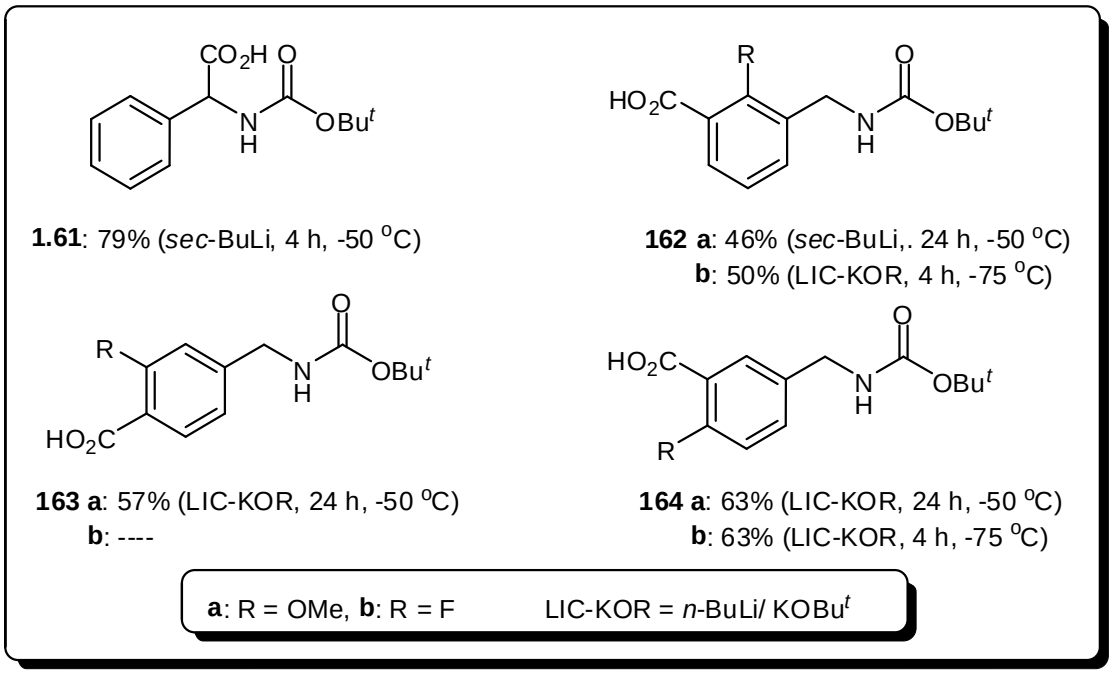
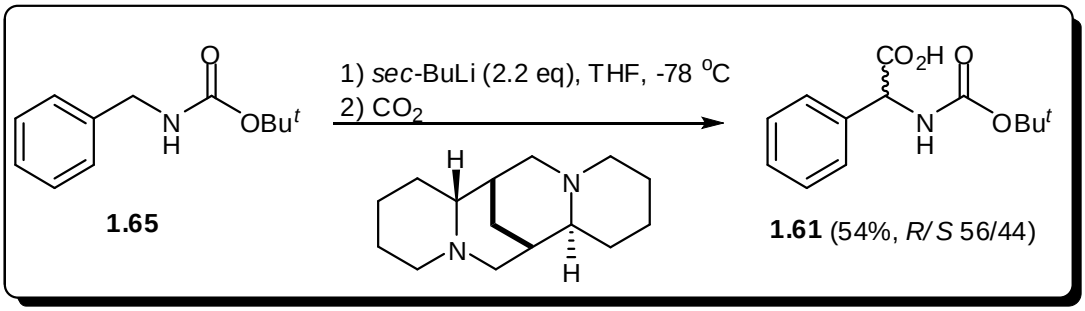


Figure 1.6 Products of lithiation of *tert*-butyl benzylcarbamates under different conditions[26]

It was clear from Schlosser's studies[26] on *tert*-butyl benzylcarbamate that the carbamate group was not a particularly good *ortho* directing group when attached *via* a CH_2 group.[26]

Lithiation of *tert*-butyl benzylcarbamate (**1.65**) was attempted using (–)-sparteine *sec*-BuLi complex as a chiral base (Scheme 1.13) at low temperature,

followed by reaction with carbon dioxide.[30] The corresponding α-substituted acid **1.61** was produced in 54% yield with the disappointing enantiomeric ratio of 56/44.[30]



Scheme 1.13 Asymmetric deprotonation of *tert*-butyl benzylcarbamate **1.65**[30]

Also, lithiation of **1.65** with *sec*-BuLi (3 equivalents) at −78 °C for 3 h in presence of TMEDA followed by reaction with acrolein (prop-2-enal) gave the corresponding α−substituted product **1.66** (Figure 1.7) in 49% yield.[31]

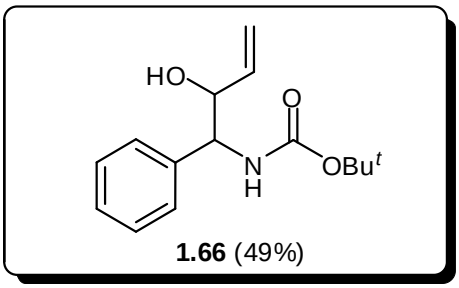
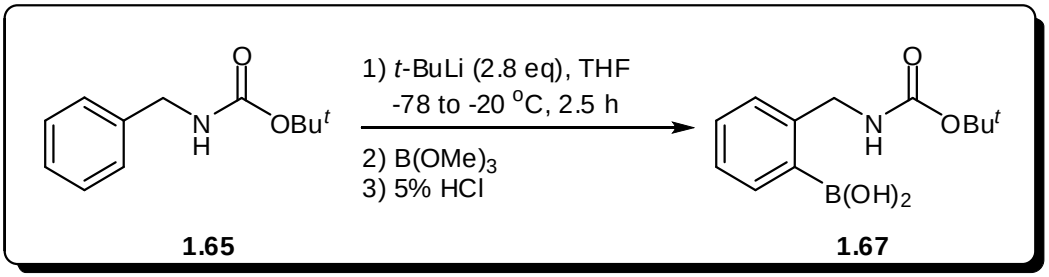


Figure 1.7 Structure of compound **1.66**

The *ortho*-substitution product was however produced in high yield (~85%) when *tert*-butyl benzylcarbamate (**1.65**) was lithiated with *t*-BuLi (2.8 equivalents) in THF at −78 °C to −20 °C for 2.5 h followed by reaction with trimethyl borate (Scheme 1.14).[32]



Scheme 1.14 Lithiation of *tert*-butyl benzylcarbamate **1.65**[32]

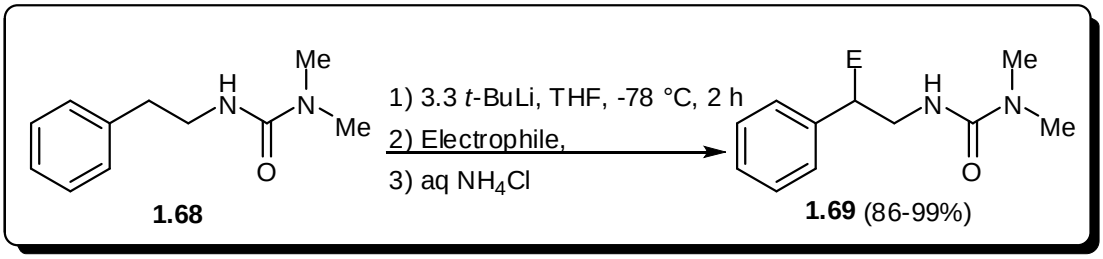
The *N*-substitution product was obtained in 90% yield from lithiation of **1.65** with 1.2 equivalents of *n*-BuLi in THF at –78 °C for 30 min followed by reaction with methyl chloromethyl ether as electrophile.[33a] Similarly, lithiation of **1.65** under the same conditions followed by reaction with ethyl bromoacetate and then alkaline hydrolysis provided the corresponding *N*-substituted acid in 78% yield.[33b]

Lateral lithiation of *tert*-butyl 2-methylbenzylcarbamate was reported using various lithium reagents (*t*-BuLi, *sec*-BuLi, *n*-BuLi) with or without TMEDA at low temperatures (–78 and –20 °C) in THF and the substitution products were produced in high yields (up to 95%).[24b, 34]

1.8 Lithiation of *N′*-(2-phenylethyl)-*N*,*N*-dimethylureas

Lithiation of *N′*-(2-phenylethyl)-*N*,*N*-dimethylurea (**1.68**) took place on the side-chain at the CH_2 group next to the phenyl ring (α-lithiation) with *t*-BuLi (3 equivalents) in THF at -78 °C.[35] Reactions of the lithium reagents with various electrophiles gave the corresponding substituted products **1.69** (Table 1.12) in high yields.[35] The details of this work are reported in Chapter Two.

Table 1.12: Lithiation and substitution of *N′*-(2-phenylethyl)-*N*,*N*-dimethylurea (**1.68**)[35]



1.68 **1.69** (86-99%)

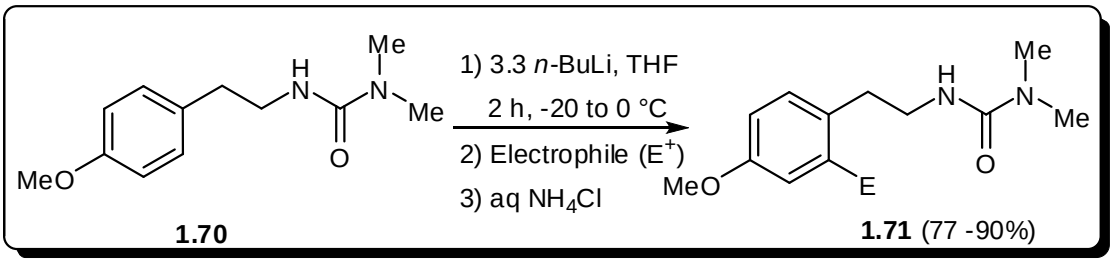
Electrophile	E	Yield of **1.69** (%)[a]
PhCHO	PhCH(OH)	97[b]
PhCOMe	PhC(OH)Me	96[b]
Ph_2CO	$Ph_2C(OH)$	98
Me_2CO	$Me_2C(OH)$	98
$(CH_2)_5CO$	$(CH_2)_5C(OH)$	98
EtI	Et	86
D_2O	D	99

[a] Yield of pure product after isolation.

Similarly, *N'*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea was lithiated with *n*-BuLi (3 equivalents) at 0 °C for 2 h, followed by reactions with various electrophiles, to afford the corresponding side-chain substituted products in high yields (78-93%).[36] The details of this work are reported in Chapter Three.

N-(2-(4-Methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**1.70**) underwent mainly ring lithiation with *n*-BuLi at 0 ºC.[37] Reactions of the 2-lithio reagent with several electrophiles gave the corresponding 2-substituted derivatives **1.71** in high yields (Table 1.13).[37] Side products (6-17%) were obtained due to lithiation and substitution on one methyl of the urea unit.[37] The details of this work are represented in Chapter Four.

Table 1.13 Lithiation and substitution of *N'*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**1.70**)[37]

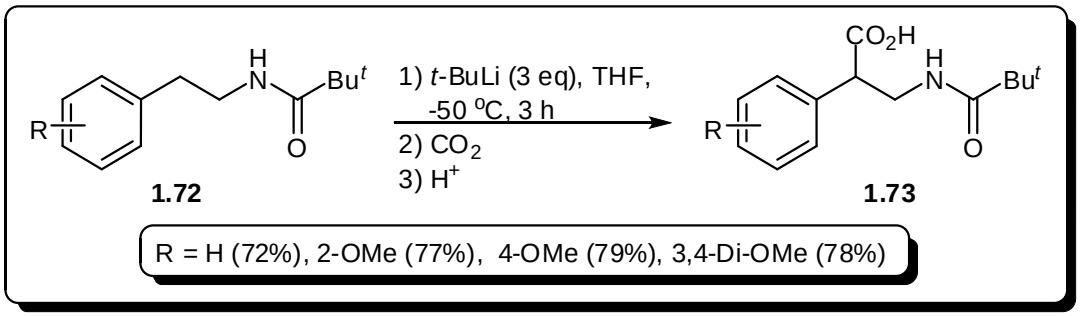


Electrophile	E	Yield of **1.71**(%)[a]
Ph_2CO	$Ph_2C(OH)$	85
4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)Me$	82
$(CH_2)_5CO$	$(CH_2)_5C(OH)$	77
4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	80
PhCHO	PhCH(OH)	82
EtI	Et	86[b]
Me_2NCHO	CHO	90

[a] Yield of the isolated pure product after column chromatography.
[b] The diethyl derivative was produced in 9% yield.

1.9 Lithiation of *N*-phenethylpivalamides

Lithiation of *N*-phenethylpivalamide and its 2-methoxyphenyl, 4-methoxyphenyl and 3,4-dimethoxyphenyl analogues **1.72** with *t*-BuLi at –50 °C for 3 h took place on the side-chain.[7] The lithium reagents produced reacted with carbon dioxide to give the corresponding substituted products **1.73** in high yields (Scheme 1.15).[7]



Scheme 1.15 Lithiation of substituted *N*-phenethylpivalamides **1.72**[7]

Lithiation of *N*-(2-(3-methoxyphenyl)ethyl)pivalamide was studied intensively by Schlosser, using various lithium reagents under different reaction conditions, and the lithiation sites were found to be dependent on the type of lithium reagent used and the temperature (Figure 1.8).[38]

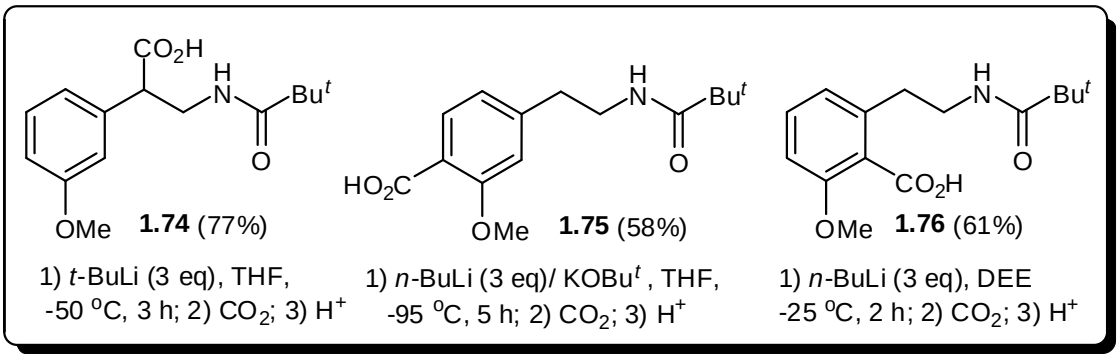
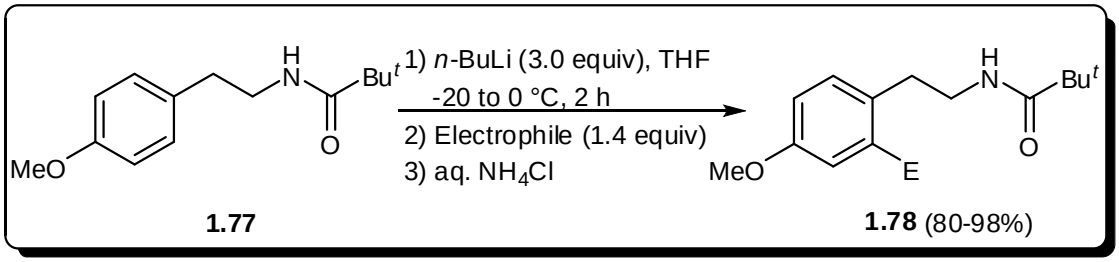


Figure 1.8 Products of the lithiation of *N*-(2-(3-methoxyphenyl)ethyl)pivalamide under various conditions[38]

In contrast with Schlosser's result,[7] lithiation of *N*-(2-(4-methoxyphenyl)-ethyl)pivalamide (**1.77**) with *n*-BuLi (3 equivalents) at 0 °C followed by the reaction with various electrophiles gave the corresponding 2-substituted products **1.78** in high yields (Table 1.14).[37] The details of this work are reported in Chapter Four.

Table 1.14 lithiation and substitution of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide **1.77**[37]

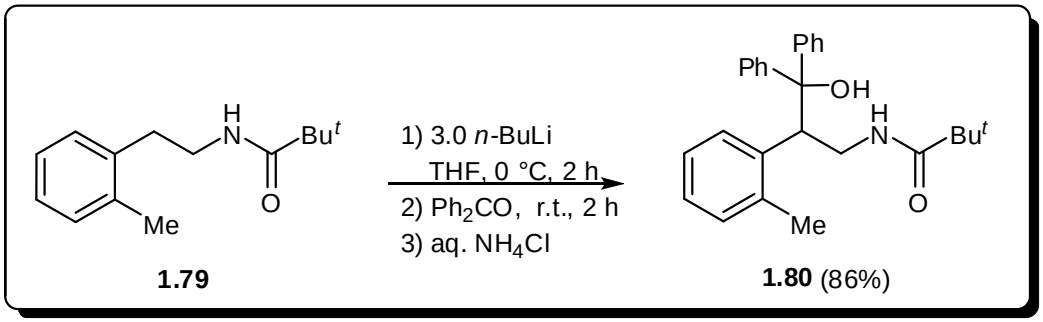


1.77 **1.78** (80-98%)

Electrophile	E	Yield of **1.78** (%)[a]
Ph_2CO	$Ph_2C(OH)$	92
$(CH_2)_5CO$	$(CH_2)_5C(OH)$	88
EtCOMe	EtC(OH)Me	95
4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	80
4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	90
Me_2NCHO	CHO	98
I_2	I	89

[a] Yield of isolated product after purification by flash column chromatography.

Lithiation of *N*-(2-(2-methylphenyl)ethyl)pivalamide (**1.79**) with *n*-BuLi (3 equivalents) at 0 °C for 2 h followed by the reaction with benzophenone gave the corresponding α-substituted product **1.80** in 86% yield (Scheme 1.16).[36]

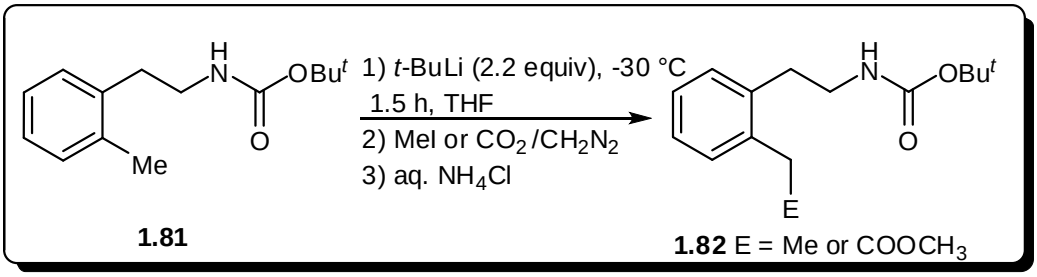


1.79 **1.80** (86%)

Scheme 1.16 Lithiation and substitution of **1.79** followed by reaction with benzophenone

1.10 Lithiation of *tert*-butyl 2-phenylethylcarbamates

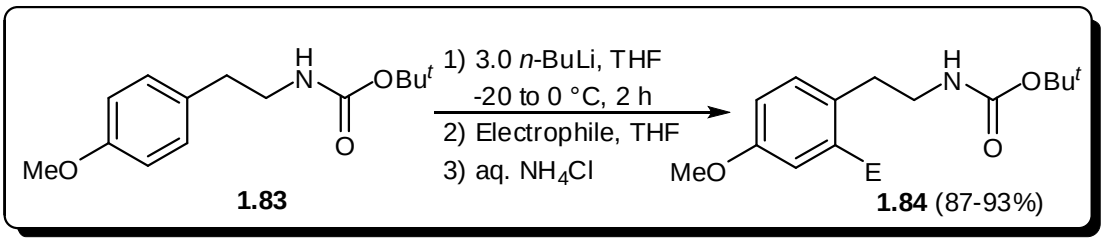
There is no report for lithiation of *tert*-butyl 2-phenylethylcarbamate published till now. However, lateral lithiation of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**1.81**) was achieved with *t*-BuLi (2.2 equivalents) at –30 °C for 1.5 h.[34a] Reaction of the lithium reagent produced with MeI and CO_2 (in the presence of diazomethane CH_2N_2) gave the corresponding substituted products **1.82** (Scheme 1.17) in 80% and 67%, respectively.[34a]



Scheme 1.17 lithiation of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**1.81**)

Ring lithiation of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate **1.83** was achieved with *n*-BuLi (3 equivalents) at 0 °C for 2 h; reaction with various electrophiles gave the corresponding substituted products **1.84** in high yields (Table 1.15).[37] The details of this work are reported in Chapter Three.

Table 1.15 Lithiation and substitution of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate (**1.83**)[37]



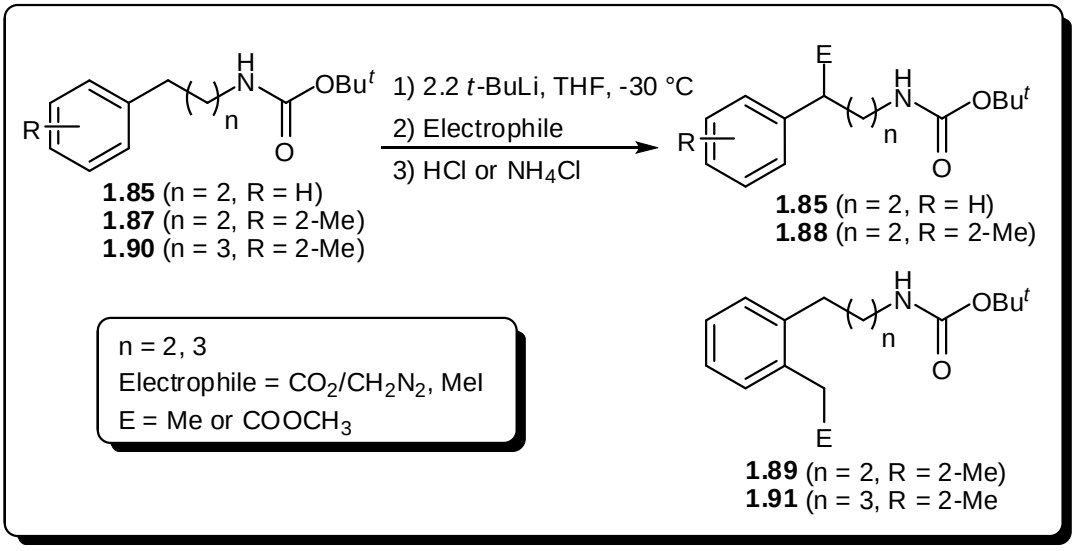
Electrophile	E	Yield of **1.82** %[a]
Ph_2CO	$Ph_2C(OH)$	89
4-$Me_2NC_6H_4COH$	4-$Me_2NC_6H_4C(OH)H$	93
Me_2NCHO	CHO	87
EtI	Et	90

[a] Yield of isolated product after purification by flash column chromatography.

1.11 Lithiation of other urea and carbamate derivatives

Lithiation of *N′*-(3-phenylpropyl)-*N*,*N*-dimethylurea with *t*-BuLi in THF at 0 °C followed by reaction with benzophenone gave the corresponding α-substituted product in 89% yield (Chapter Two). By contrast, lithiation and substitution of *N′*-(4-phenylbutyl)-*N*,*N*-dimethylurea under similar conditions took place on one of the methyl groups of the urea unit to produce the corresponding substituted derivative in 89% yield (Chapter Two).[35]

Lithiation of *tert*-butyl *N*-(3-phenylpropyl)carbamate (**1.85**) with *t*-BuLi (2.2 equivalents) at –30 °C for 1.5 h followed by the reaction with CO_2 (in the presence of diazomethane CH_2N_2) afforded the corresponding α-substituted ester **1.86** in 65% yield.[34a] *N*-(3-(2-Methylphenyl)propyl)carbamate (**1.87**; n = 2, R = 2-Me) under the same conditions, except that the lithiation time was 6 h, followed by reaction with MeI, afforded a mixture of **1.88** and **1.89** (E = Me, n = 2) in 1/4 ratio in 82% overall yield, but lithiation of *N′*-(4-(2-methylphenyl)butyl)carbamate (**1.90**; n = 3) was selective and took place laterally on the 2-methyl group to give **1.91** (n = 3; Scheme 1.18), but low yields (35–40%) were reported for the reactions with carbon dioxide and iodomethane as electrophiles.[34a]



Scheme 1.18 Lithiation and substitution of *N*-(phenylalkyl)carbamates

1.12 Conclusions

N-Phenylpivalamide is relatively easy to lithiate using *n*-BuLi at 0 °C. On the other hand a more nucleophilic lithium reagent (*t*-BuLi or *sec*-BuLi/TMEDA) is needed to lithiate either *N'*-phenyl-*N*,*N*-dimethylurea or *tert*-butyl *N*-phenylcarbamate. In terms of lithiation site, both the pivalamide and the carbamate groups are efficient *ortho* directing groups but simpler conditions are needed for the pivalamide derivative. Also, the substituted pivalamide derivatives are produced in higher yields compared with the corresponding carbamates. However, lithiation of *N'*-phenyl-*N*,*N*-dimethylurea takes place mainly on one of the methyl groups of the urea unit with *t*-BuLi at –20 °C.

Directed lithiation of *N*-(substituted phenyl)pivalamides can be achieved with *n*-BuLi at 0 °C but the 4-methoxy derivative produces a mixture of products due to ring lithiation next to the pivalamide group and dilithiation next to both the methoxy and the pivalamide groups in a ratio of 3:2. Successful ring lithiation of various substituted carbamates was achieved with either *t*-BuLi or *sec*-BuLi/TMEDA at –50 or –10 °C, respectively but the yield of substitution product in the case of the 4-methoxy derivative was low. The site of lithiation in the case of *N'*-(substituted phenyl)-*N*,*N*-dimethylureas with either *n*-BuLi or *t*-BuLi at 0 °C is dependent on the type of substituents. Electron-withdrawing groups (*e.g*. Cl, F, CF_3) at the 4-position provide *ortho* substitution products in excellent yields. On the other hand, the 4-methyl derivative provides products due to lithiation and substitution on one of the methyl groups of the urea unit with *t*-BuLi at –20 °C. Lithiation of the 4-methoxy derivative with *t*-BuLi at –20 or 0 °C takes place mainly on one of the methyl groups of the urea units and *ortho* to the methoxy group, but also gives minor products due to double substitution at both positions.

Lithiation of the corresponding benzylamine derivatives is dependent on the nature of the directing metallating group (*e.g*. pivalamide, carbamate and urea) with *n*-BuLi, *sec*-BuLi or *t*-BuLi at low temperature (–78 °C). In term of the selectivity, the urea derivative is a powerful *ortho* directing group even in presence of different substituents, such as 3-OMe, 4-OMe, 2-F, 3-F, 4-F and 4-Me. However, lithiation with *t*-BuLi at –20 °C and substitution of *N'*-(2-methoxybenzyl)-*N*,*N*-dimethylurea gives a mixture of products due to ring lithiation next to both the methoxy and urea-containing groups.

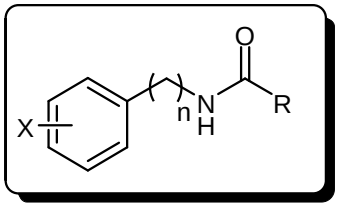
N-Benzylpivalamide is less selective, giving *ortho* and side-chain substitution products in nearly equal proportions. However, use of a mixture of *sec*-BuLi and TMEDA provides the α-substituted product only by lithiation on the CH_2 group. Lithiation of *tert*-butyl *N*-benzylcarbamate takes place only on the side-chain with *sec*-BuLi at low temperatures (−50 and −78 °C) and only on the *ortho* position with *t*-BuLi at somewhat higher temperature (−20 °C).

Substituted *N*-benzylpivalamides are more selective than the corresponding carbamates towards ring lithiation. For example, lithiation of the pivalamide derivatives provides high yields of products due to ring lithiation next to the directing metallating group. However, lithiation of the 2-methoxybenzyl derivative gives a mixture of substituted products due to lithiation on the side-chain and on the ring next to the methoxy group. Lithiation of the corresponding carbamate derivative takes place on the ring, but next to the methoxy substituent rather than next to the DMG.

Lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea and *N*′-phenethylpivalamide with *n*-BuLi or *t*-BuLi takes place only on the side-chain and the corresponding α-substituted products can be obtained in high yields. Similar side-chain substitution products are obtained from *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea and *N*′-(2-(2-methylphenyl)ethyl)pivalamide, while *tert*-butyl *N*′-(2-(2-methylphenyl)ethyl)carbamate leads to lateral substitution.

Lithiation *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea, *N*′-(2-(4-methoxyphenyl)ethyl)pivalamide and *tert*-butyl *N*′-(2-(4-methoxyphenyl)ethyl)-carbamate with *n*-BuLi followed by reaction with various electrophiles provides the products of *ortho* substitution next to the directing metalting group. Side products (6-17% yields) are obtained in the case of the urea derivative due to lithiation and substitution on one of the methyl groups of the urea unit.

1.13 Summary of lithiation sites of urea, pivalamide and carbamate derivatives under various conditions



1.13.1 Dimethylureas

n	X	RLi (eq)	T (°C)	t (h)	Lithiation site (Yield; %)	Ref
0	H	*n*-BuLi (1.1)	–30	1	NH (82)	10
	4-Cl	*n*-BuLi (2.5)	0	2	*ortho* to DMG (72–83)	11
	4-F				No reaction	
	4-F	*t*-BuLi (2.5)			*ortho* to DMG (77–88)	
	4-CF_3				*ortho* to DMG (31)	
	H	*t*-BuLi (2.2)			NMe (17), *ortho* to DMG (10), both (8)	
	H, 2-Me	*t*-BuLi (2.4)	–20		NMe (75–92)	
	4-OMe	*t*-BuLi, *sec*-BuLi, *n*-BuLi	–78		No reaction	
		t-BuLi (2.2)	0		NMe (62), *ortho* to OMe (2), both (4)	
			–20		NMe (50), *ortho* to OMe (2), both (16)	
		t-BuLi (3.3)	0		NMe (2), *ortho* to OMe (2), both (77)	
			–20		both (87)	
	H, 3-OMe	*t*-BuLi (3) in Et_2O	–78	4	NMe (5–15), NMe_2 (25–45)	12
1	H	*sec*-BuLi (2)	–78	4	*ortho* to DMG (82)	26
	H	*t*-BuLi (2)			*ortho* to DMG (90)	
	3-OMe, 4-OMe, 4-F	*sec*-BuLi (2)	–50		*ortho* to DMG (~86)	
	2-F	*t*-BuLi (2)	–100		*ortho* to DMG (81)	
	3-F	*n*-BuLi (2)	–75		*ortho* to DMG (94)	
	H, 4-Me, 4-OMe, 4-Cl, 4-F	*t*-BuLi (2.2)	–78		*ortho* to DMG (70–89)	27
	2-Me				Me (lateral, 74–84)	28
	2-OMe		–20	2	*ortho* to DMG (47–51), *ortho* to OMe (30–40)	27
2	H	*t*-BuLi (3.3)	–78	2	Side-chain (86–99)	35
	2-Me	*n*-BuLi (3)	0		Side-chain (78–93)	
	4-OMe	*n*-BuLi (3.3)	0		NMe (6–17), *ortho* to DMG (77–90)	

1.13.2 Pivalamides

n	X	RLi (eq)	T (°C)	t (h)	Lithiation site (Yield; %)	Ref
0	H	*n*-BuLi (2) /TMEDA, *sec*-BuLi (2)	–78 to -20	2	*ortho* to DMG (30–85)	13
	H, 3-OMe, 4-OMe, 4-Cl, 4-Me, 4-CF_3	*n*-BuLi (2)	0		*ortho* to DMG (38–82)	14
	H, 4-OMe, 4-Cl, 4-Me	*n*-BuLi (2)	r.t		*ortho* to DMG (59–90)	15
1	H	*sec*-BuLi (2)	–50	2	*ortho* to DMG (36), side-chain (20)	29
		sec-BuLi (2) /TMEDA			side-chain	
		n-BuLi or *sec*-BuLi (2.2)	–78		*ortho* to DMG (7), side-chain (4)	27
		t-BuLi (2)			*ortho* to DMG (10), side-chain (6)	
			0		*ortho* to DMG (34), side-chain (37)	
			20		*ortho* to DMG (17), side-chain (42)	
	4-Me, 4-OMe, 4-Cl, 4-F	*t*-BuLi (2)		4	*ortho* to DMG (73–88)	
	3-OMe, 4-OMe, 4-Cl, 4-CF_3, 3,4-(O-CH_2-O)	*n*-BuLi (2)	0	1	*ortho* to DMG (46–65)	29
	2-OMe	*t*-BuLi (2)	–78	2	*ortho* to OMe (87), side-chain (7)	27
			0		*ortho* to OMe (49), side-chain (16), *ortho* to DMG (19)	
		sec-BuLi (2)	–78		*ortho* to DMG (36), side-chain (34)	
			0		*ortho* to DMG (48), side-chain (38)	
		n-BuLi	–78		No reaction	
			0		*ortho* to OMe (8), sidechain (40), *ortho* to DMG (30)	
	2-Me	*t*-BuLi (2)	–78		lateral (76–89)	28
2	H, 2-OMe, 3-OMe, 4-OMe, 3,4-OMe	*t*-BuLi (3)	–50	3	side-chain (72–79)	30
	3-OMe				side-chain (78–93)	
		n-BuLi (3)	–95	5	*ortho* to OMe(58)	
			–25	2	*ortho* to DMG (61)	
	2-Me		0		side-chain (86)	36
	4-OMe				*ortho* to DMG (80–98)	37

1.13.3 Carbamates

n	X	RLi (eq)	T (°C)	t (h)	Lithiation site (Yield %)	Ref
0	H	*n*-BuLi (2) /TMEDA, *sec*-BuLi (2)	Several		No reaction	16
		t-BuLi (2.4) in Et_2O	–20	2	*ortho* to DMG (59–91)	
					ortho to DMG (8–47)	19
	H, 4-OMe, 4-Cl, 4-F, 4-CF_3	*sec*-BuLi (2) /TMEDA	–10		*ortho* to DMG (30-81)	20
	H, 2-F, 3-F, 4-F, 2-CF_3, 3-CF_3, 4-CF_3, 2-OCF_3, 4-OCF_3, 2,4-bis CF_3, 2-F-3-OCH_3	*t*-BuLi (2)	–50	3	*ortho* to DMG (46–94)	23
	4-OMe	*t*-BuLi (2.2) in Et_2O	–10		*ortho* to DMG (55)	21
		t-BuLi (2.5) in Et_2O			*ortho* to DMG (86)	22
	2-Me	*t*-BuLi or *sec*-BuLi (2.2)	–20	2	lateral (*ca*. 98%)	24 25
1	H	*sec*-BuLi (2)	–78	4	side-chain (79)	26
	2-OMe	*sec*-BuLi (2)	–50	24	*ortho* to OMe (46)	
	3-OMe	LiC-KOR			*ortho* to OMe (63)	
	4-OMe				*ortho* to OMe (57)	
	2-F		–75	4	*ortho* to F (50)	
	3-F				*ortho* to F (63)	
	H	*sec*-BuLi (1.1)/ (-)-sparteine	–78	4	side-chain (50-54)	30
		sec-BuLi (3)/ TMEDA	–78	3	side-chain (49)	31
		t-BuLi (2.8)	–20	2.5	*ortho* to DMG (85)	32
		n-BuLi (1.2)	–78	0.5	*N*-lithiated (78–90)	33
	2-Me	*n*-BuLi, *sec*-BuLi, *t*-BuLi (2); with or without TMEDA	–78 –20	2	lateral (high)	24 b, 34
2	2-Me	*t*-BuLi (2.2)	–30	1.5	lateral (67–80%)	34a
	4-OMe	*n*-BuLi (3)	0	2	*ortho* to DMG (87–93)	37

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Chapter Two

Lithiation and Substitution of N'-(ω-Phenylalkyl)-N,N-dimethylureas

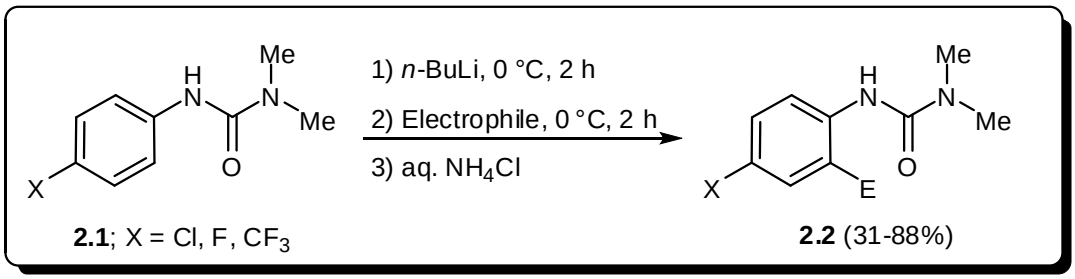
Chapter Two

Lithiation and Substitution of *N′*-(ω-Phenylalkyl)-*N,N*-dimethylureas

2.1 Introduction

Many aromatic compounds undergo lithiation *ortho* to a functional group,[1–4] and the organolithium reagents produced *in situ* in such reactions are useful intermediates for the synthesis of *ortho*-disubstituted aromatics.[5] Moreover, *ortho*-lithiation has been applied to various heterocycles to produce the corresponding substituted derivatives.[6]

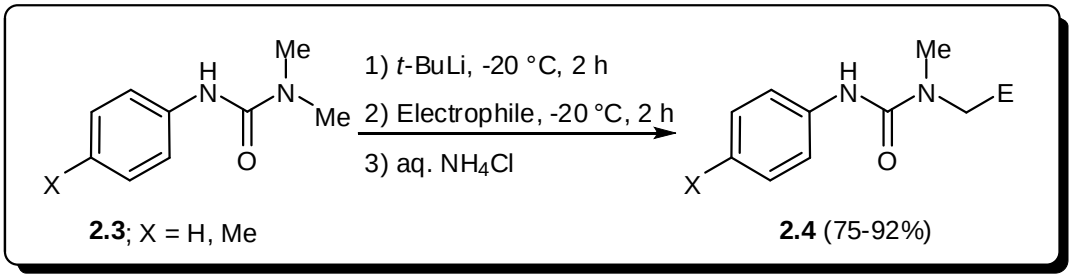
The research group of Smith has developed several efficient lithiation procedures for the synthesis of various substituted aromatics and heteroaromatics that might be difficult to prepare by other means.[7] As part of such studies they have successfully achieved lithiation and substitution of various *N*-(substituted benzyl)pivalamides and *N′*-(substituted benzyl)-*N,N*-dimethylureas selectively using *n*-butyllithium (*n*-BuLi) or *tert*-butyllithium (*t*-BuLi) in anhydrous tetrahydrofuran (THF) under nitrogen.[8–10] For example, they have demonstrated lithiation procedures that allow electrophilic substitution of *N′*-aryl-*N,N*-dimethylureas to provide efficient syntheses of substituted ureas.[11] Electron-withdrawing groups (*e.g.* Cl, F, CF_3) on the phenyl ring of the urea induce ring substitution to provide substituted derivatives **2.2** in high yields for the chloro and fluoro derivatives and in lower yield for the trifluoromethyl derivative (Scheme 2.1).[11]



Scheme 2.1 Lithiation and substitution of *N′*-aryl-*N,N*-dimethylureas (**2.1**)

On the other hand, lithiation and substitution of *N′*-phenyl- and *N′*-(4-methylphenyl)-*N,N*-dimethylureas **2.3** with *t*-BuLi at –20 °C followed by reaction

with electrophiles gave the corresponding substituted products **2.4** where lithiation and substitution took place on one of the methyl groups of the urea moiety (Scheme 2.2).[11]



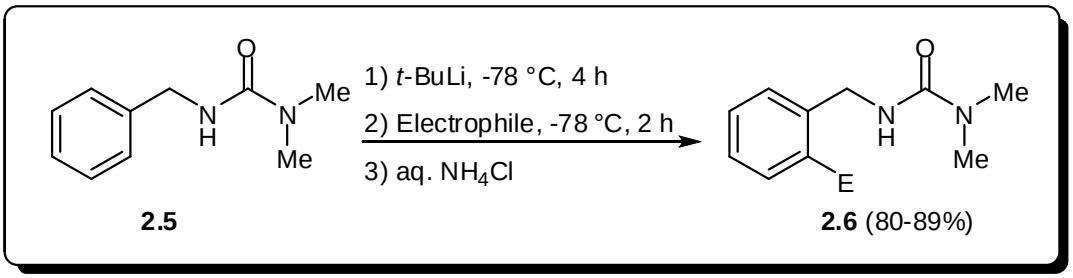
2.3; X = H, Me

2.4 (75-92%)

Scheme 2.2 Lithiation and substitution of *N′*-phenyl- and *N′*-(4-methylphenyl)-*N,N*-dimethylureas **2.3**

For other electron-donating groups such as a methoxy substituent at the 4-position, some ring substitution was observed, but next to the methoxy group rather than next to the urea-containing group, with the major product being derived from methyl substitution, as for other electron-donating groups such as the methyl group.[11]

Also, directed lithiation of *N′*-benzyl-*N,N*-dimethylurea (**2.5**) was achieved with *t*-BuLi at −78 °C and the dilithium reagent produced *in situ* was allowed to react with various electrophiles to give the corresponding substituted derivatives **2.6** in high yields (Scheme 2.3).[9] On the other hand lithiation of *N′*-benzylpivalamide under similar conditions gave a mixture of ring and side-chain substitution.[9] The lithiation processes have been also applied for the production of substituted isoindoline and isoquinoline derivatives in high yields.[12–14]



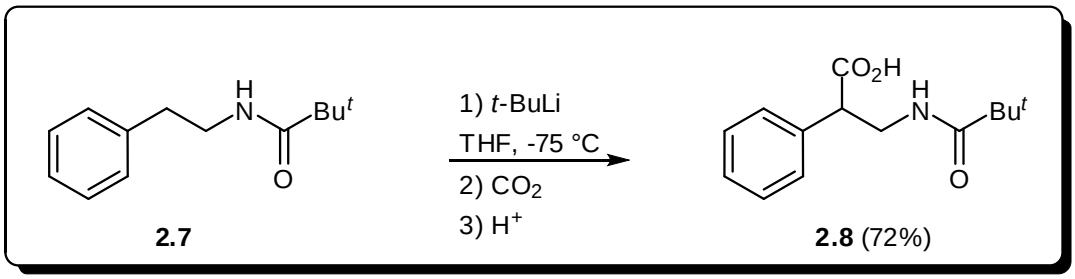
2.5

2.6 (80-89%)

Scheme 2.3 Lithiation and substitution of *N′*-benzyl-*N,N*-dimethylurea (**2.5**)

We became interested in directed lithiation of *N′*-phenethyl-*N,N*-dimethylureas. Lithiation of *N*-phenethylpivalamide derivatives has been reported by Schlosser.[15,16] For

example, lithiation of *N*-phenethylpivalamide (**2.7**) took place on the side-chain (α-lithiation) with three equivalents of *t*-BuLi in THF at –75 °C (Scheme 2.4).[15] Reaction of the dilithium reagent thus obtained with carbon dioxide, the only electrophile tried, gave the corresponding acid **2.8** in 72% yield (Scheme 2.4).[15]



2.7 **2.8** (72%)

Scheme 2.4 Lithiation of *N*-phenethylpivalamide (**2.7**) followed by reaction with carbon dioxide

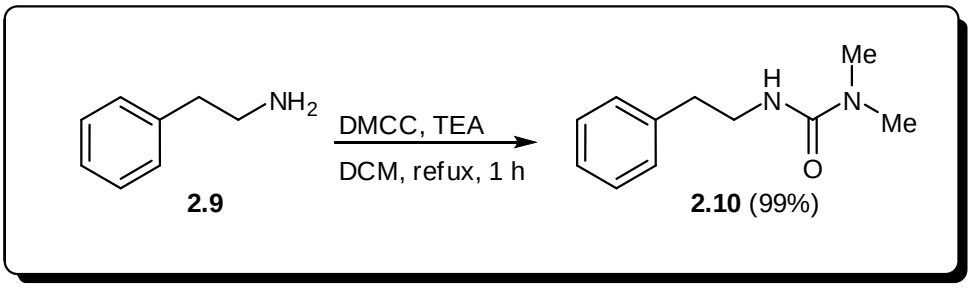
However, there are no reports of lithiation and substitution of *N′*-phenethyl-*N*,*N*-dimethylurea, and pivalamide and dimethylurea derivatives do not always behave in an identical manner towards lithiation,[9] while the urea derivatives are more generally useful for synthesis.[13,14] Also, it was of interest to see what effect an extra CH_2 unit could have on the site of lithiation compared with **2.5** itself. Moreover, the effect of extra methylene groups will be tested by investigating lithiation of both *N′*-(3-phenylpropyl)-*N*,*N*-dimethylurea (three CH_2 groups) and *N′*-(4-phenylbutyl)-*N*,*N*-dimethylurea (four CH_2 groups).

In this chapter we report the successful lithiation and substitution of *N′*-(ω-phenylalky)l-*N*,*N*-dimethylureas using a simple, general and efficient α-lithiation procedure using *t*-BuLi. We also report a procedure for ring-substitution by Br–Li exchange with methyllithium (MeLi) followed by *t*-BuLi in THF at –78 °C. The results of this study have been published.[17]

2.2 Synthesis of *N′*-phenethyl-*N*,*N*-dimethylurea (2.10)

The first tasks were to synthesise *N′*-phenethyl-*N*,*N*-dimethylurea[18] and to try to find conditions under which its lithiation could be effected. Reaction of phenethylamine (**2.9**) with dimethylcarbamoyl chloride (DMCC) in dichloromethane (DCM) in the presence of triethylamine (TEA) under reflux for one hour gave *N′*-phenethyl-*N*,*N*-dimethylurea (**2.10**; Scheme 2.5) as a colourless crystalline solid in 99% yield after

crystallisation from a mixture of ethyl acetate and diethyl ether (1:3 by volume). The structure of compound **2.10** was confirmed by various spectroscopic techniques (see Section 2.14.2).



Scheme 2.5 Synthesis of *N′*-phenethyl-*N*,*N*-dimethylurea (**2.10**)

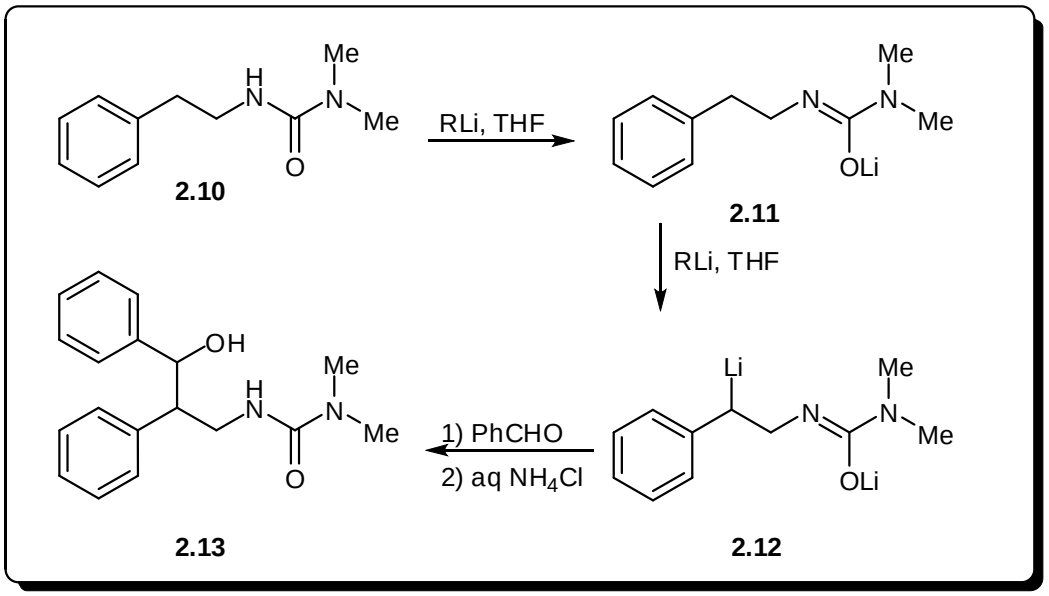
Having successfully produced **2.10** our attention was next turned to attempt its lithiation and substitution under various reaction conditions.

2.3 Lithiation and substitution of *N′*-phenethyl-*N*,*N*-dimethylurea (2.10)

Initially the reaction of **2.10** with *n*-BuLi (2.2 equivalents) was carried out in anhydrous THF under a nitrogen atmosphere at –78 °C. Initial addition of *n*-BuLi provided a pale yellow solution, presumably because of formation of the monolithium reagent **2.11**, until approximately one equivalent had been added, then gave a deep yellow solution as the remaining *n*-BuLi was added, presumably because of formation of a dilithium reagent. The mixture was stirred for two hours at -78 °C. Benzaldehyde (1.1 equivalents) was added and the mixture was stirred for another two hours (Scheme 2.6) at –78 °C and then quenched by the addition of aqueous ammonium chloride solution. The crude product was tested by TLC and showed the presence of starting material **2.10** along with a new compound. The crude product was purified by column chromatography (silica gel; diethyl ether–hexane, 1:3) to give the starting material **2.10** in 95% yield and the new product as a white solid.

The electron–impact mass spectrum of the new compound showed a low intensity molecular ion peak at *m/z* = 298 and the high resolution mass spectrum of this peak confirmed the formula as $C_{18}H_{22}N_2O_2$ (M). Clearly, lithiation followed by reaction with benzaldehyde had taken place. The ^{1}H NMR spectrum of the new product showed the presence of two racemic diastereoisomers in approximately equal proportions,

which would arise from creation of two stereogenic carbons during lithiation at the side-chain. Also, the NMR spectra showed the presence of one CH_2 group and two CH groups, indicating that lithiation had taken place on the other CH_2 group. It also showed diastereotopicity for the CH_2 protons. The chemical shifts for such groups indicated that lithiation followed by substitution had taken place on the CH_2 next to the phenyl ring. Therefore, the new compound was identified as the α-substituted product **2.13** and the dilithium reagent was therefore **2.12** (Scheme 2.6).



Scheme 2.6 Lithiation and substitution of **2.10** followed by reaction with benzaldehyde

Several experiments were conducted to try to improve the yield of **2.13** or to find conditions under which *ortho*-lithiation could be achieved instead. Double lithiations of **2.10** with various lithium reagents (*n*-BuLi, *t*-BuLi and lithium diisopropylamide, LDA) at various reaction temperatures (–78 and 0 °C) for 2 h followed by reaction with benzaldehyde were attempted. The crude products were analysed by ^{1}H NMR spectroscopy and the approximate yields of **2.13** obtained are summarised in Table 2.1.

It was found that use of *n*-BuLi, *t*-BuLi and LDA (2.2 or 3.3 molar equivalents) at high temperature (0 °C) gave a complex mixture of unidentified products. Purification of the reaction mixtures provided no pure products (Table 2.1; Entries 2–5) but dark coloured highly polar materials were adsorbed at the top of the column.

At lower temperature (–78 °C) *n*-BuLi (2.2 molar equivalents) was not efficient as a lithium reagent and provided very low yield of product **2.13** (Table 2.1; Entry 1). However, *t*-BuLi was highly efficient as a lithium reagent under similar reaction conditions and as a result product **2.13** was produced in 62% yield (Table 2.1; Entry 6). Use of three molar equivalents of *t*-BuLi give **2.13** in 97% yield (Table 2.1, Entry 7) after purification by column chromatography.

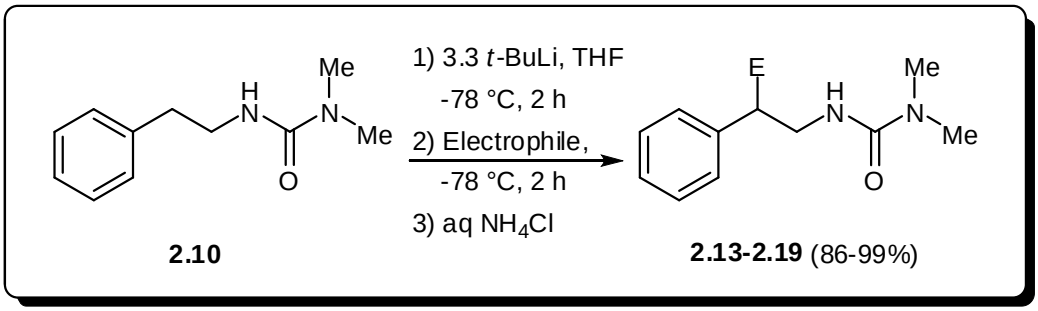
Table 2.1: Synthesis of **2.13** under various reaction conditions according to Scheme 2.6

Entry	Lithium reagent (mole equiv.)	T (°C)	Yield (%)
1	*n*-BuLi (2.2)	–78	2[a,b]
2	*n*-BuLi (2.2)	0	—[c]
3	*t*-BuLi (2.2)	0	—[c]
4	*t*-BuLi (3.3)	0	—[c]
5	LDA (2.2)	0	—[c]
6	*t*-BuLi (2.2)	–78	62[d]
7	*t*-BuLi (3.3)	–78	97[d]

[a] Yield by ^{1}H NMR analysis.
[b] Starting material **2.10** was recovered in significant quantities.
[c] A complex mixture of unidentified products was formed.
[d] Yield of **2.13** after purification by column chromatography.

In principle, at least two molar equivalents of *t*-BuLi were necessary to produce the dilithium reagent **2.12**. The need for excess of *t*-BuLi could possibly be due to either THF not being very dry or the concentration of lithium reagent being lower than stated. In order to test such possibilities, dry THF from different sources was used. However, 3.3 molar equivalents of *t*-BuLi were needed to produce a high yield of the substituted product **2.13** where benzaldehyde was used as electrophile. Also, the concentration of *t*-BuLi was measured *via* titration and its concentration was found to be similar to that originally thought. Clearly, 3.3 equivalents of *t*-BuLi are needed and indeed, the literature revealed that such excess of the lithium reagent has been used previously in similar cases.[15]

It was of interest to see if the reaction of the lithium intermediate **2.12** with other electrophiles would be useful and general. Consequently, reactions of **2.12**, prepared *in situ* from **2.10** under the conditions described above (Table 2.1; Entry 7), with various other electrophiles (acetophenone, benzophenone, acetone, cyclohexanone, iodoethane and deuterium oxide) were carried out. Each reaction was conducted under identical conditions. The crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3), to give the corresponding substituted derivatives **2.14**-**2.19** (Scheme 2.7) in excellent yields (Table 2.2).



Scheme 2.7 Lithiation and substitution of *N′*-phenethyl-*N*,*N*-dimethylurea (**2.10**)

Table 2.2: Synthesis of substituted *N′*-phenethyl-*N*,*N*-dimethylureas **2.13–2.19** according to Scheme 2.7

Product	Electrophile	E	Yield (%)[a]
2.13	PhCHO	PhCH(OH)	97[b]
2.14	PhCOMe	PhC(OH)Me	96[b]
2.15	Ph_2CO	$Ph_2C(OH)$	98
2.16	Me_2CO	$Me_2C(OH)$	98
2.17	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	98
2.18	EtI	Et	86
2.19	D_2O	D	99

[a] Yield of pure product after isolation.
[b] The ^{1}H NMR showed the presence of two diastereoisomers in approximately equal proportions.

The structures of the products were confirmed by various spectroscopic techniques (see Section 2.14.3 for details). The ^{1}H NMR spectrum of product **2.14**

showed the presence of two racemic diastereoisomers in approximately equal proportions. In the ^{13}C NMR spectrum of compound **2.15** the carbons of the two phenyl groups appeared as separated signals, verifying that the phenyl groups are diastereotopic. Similarly, the carbons of the two methyl groups originating from acetone in compound **2.16** and the two sides of the cyclohexane ring in compound **2.17** appeared as separated signals in their ^{13}C NMR spectra. Also, the NMR spectra of all compounds showed that the signals of the two hydrogens of the CH_2 group are diastereotopic. As indicated in Scheme 2.6 and Table 2.2, therefore, substitution of **2.10** took place on the side-chain (α-substitution) in all cases.

There is at least one possible explanation for the side-chain lithiation of **2.10**. The dilithium intermediate **2.12**, produced *in situ* from side-chain lithiation of **2.10**, could be stabilised *via* chelation between oxygen and lithium atoms through a six-membered ring (Figure 2.1). However, directed *ortho*-lithiation of **2.10** would involve formation of dilithium reagent **2.20** (Figure 2.1), which is expected to be less stable than **2.12** because the chelation between oxygen and lithium atoms requires formation of an eight-membered ring. Also, the hydrogen of the CH_2 next to the phenyl ring is expected to be slightly more acidic, due to the electron-withdrawing effect of the phenyl ring, than the hydrogen of the phenyl *ortho* to the urea-containing group.

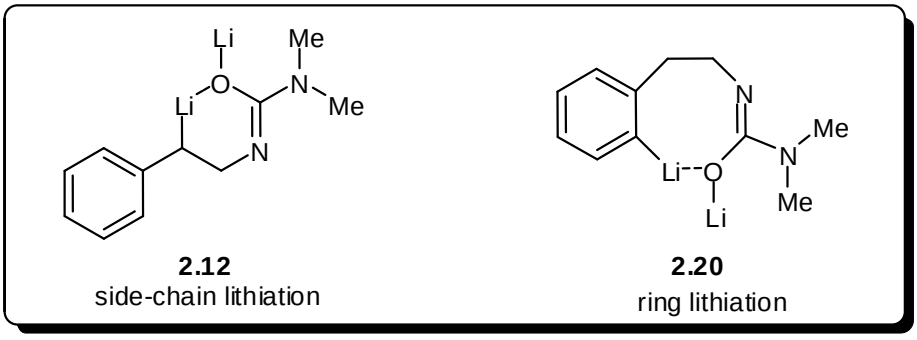


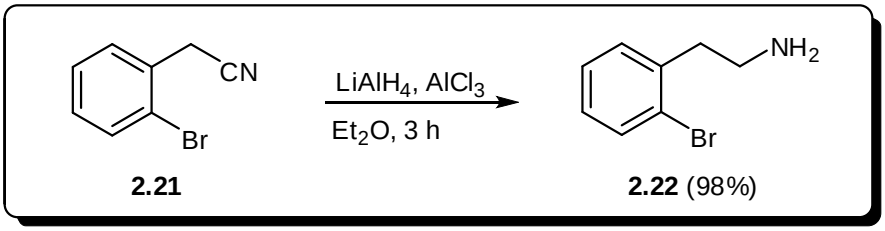
Figure 2.1 The structures of dilithium intermediates **2.12** and **2.20**

It appears that directed *ortho*-lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea (**2.10**) was not achievable under the conditions tried. However, ring substitution could in principle be achieved *via* bromine–lithium exchange of the corresponding bromo substrate. Therefore, we decided to synthesise *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea and attempt its bromine–lithium exchange followed by reactions with

electrophiles. The next task was therefore the synthesis (2-bromophenyl)ethylamine (**2.22**) by the reduction of its corresponding nitrile **2.21**.

2.4 Synthesis of (2-bromophenyl)ethylamine (2.22)

2-(2-Bromophenyl)ethylamine (**2.22**) was synthesised based on a literature procedure[19] from the reduction of (2-bromophenyl)acetonitrile (**2.21**) using lithium aluminium hydride ($LiAlH_4$; 2.2 molar equivalents) in the presence aluminium chloride ($AlCl_3$; 0.75 equivalents) as a catalyst (Scheme 2.8). Following work-up pure **2.22** was produced in 98% yield as oil. The structure of compound **2.22** was confirmed by various spectroscopic techniques (see Section 2.14.4).

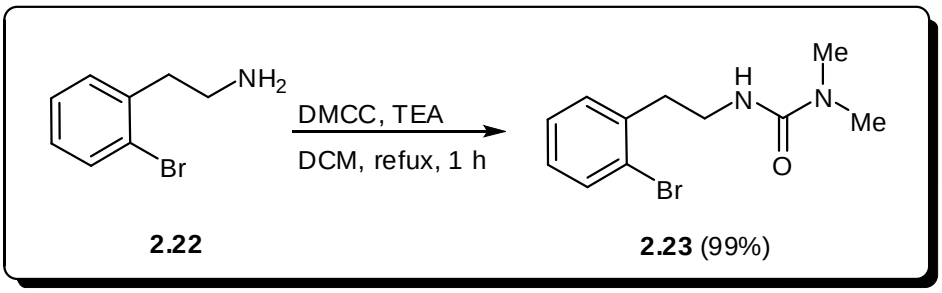


Scheme 2.8 Synthesis of 2-(2-bromophenyl)ethylamine (**2.22**)

Our attention was next turned to the reaction of 2-(2-bromophenyl)ethylamine (**2.22**) with dimethylcarbamoyl chloride in the presence of a base to synthesise *N′*-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**2.23**).

2.5 Synthesis of *N′*-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (2.23)

N′-2-(2-Bromophenyl)ethyl-*N*,*N*-dimethylurea (**2.23**) was synthesised based on a literature procedure for analogous compounds.[18] Reaction of 2-(2-bromophenyl)ethylamine (**2.23**) with dimethylcarbamoyl chloride (1.2 equivalents) in the presence of triethylamine as a base gave the corresponding urea derivative **2.23** in 99% yield (Scheme 2.9).



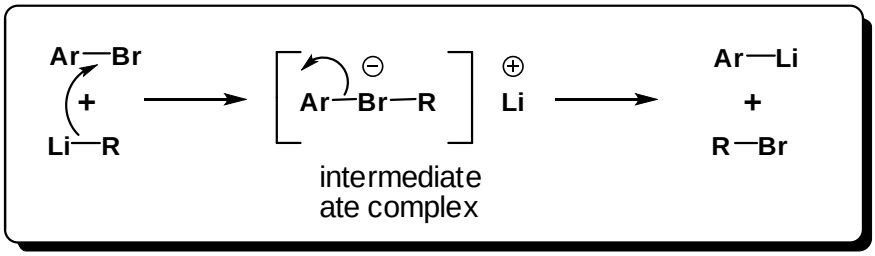
Scheme 2.9 Synthesis of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**2.23**)

The structure of **2.23** was confirmed by IR, NMR, MS and HRMS spectral data. For example, the electron-impact mass spectrum of **2.23** showed two pseudo molecular ion peaks (MH) at *m/z* = 273 and 271. The high resolution mass spectrum of the molecular ion peak at *m/z* = 271 confirmed the formula as $C_{11}H_{16}{}^{79}BrN_2O$. The ^1H NMR spectrum showed an apparent quartet (*J* = 7 Hz) at 3.41 ppm due to the CH_2 protons next to NH and a triplet (*J* = 7 Hz) at 2.90 ppm due to the CH_2 protons next to the aryl ring (see Section 2.14.5 for details).

Having successfully synthesised **2.23**, our attention was next turned to investigate its bromine–lithium exchange followed by reactions of various electrophiles in an attempt to produce the corresponding derivatives substituted at the 2-position of the phenyl ring.

2.6 Bromine–lithium exchange and substitution of *N′*-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (2.23)

Bromine–lithium exchange of aryl bromides is generally favoured over directed lithiation (deprotonation on the ring) at low temperatures. This rapid reaction allows the insertion of a lithium atom at a specific position on the ring. The bromine–lithium exchange of aryl bromides is likely to proceed through nucleophilic substitution at the bromine *via* formation of an ate complex as intermediate (Scheme 2.10).[1,20,21] Many examples of bromine–lithium exchange to produce the corresponding aryllithiums have been reported.[1,21]



Scheme 2.10 Bromine–lithium exchange of aryl bromide *via* formation of intermediate ate complex

In principle, bromine-lithium exchange of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**2.23**) could be achieved by use of three mole equivalents of *t*-BuLi. One mole would be to deprotonate the nitrogen, another to exchange the bromine and the third to eliminate the bromide ion from *t*-BuBr to produce isobutane and isobutene.

Successful bromine–lithium exchange of **2.23**, which possesses a proton-donating group (PDG), followed by trapping of the organolithium reagent with an electrophile, relies on clean initial deprotonation of the urea group (Scheme 2.11). If bromine–lithium exchange should precede deprotonation, then the incipient organolithium reagent could self-quench to give species **2.10** (Scheme 2.6). However, there are also other potential complications. For example, the initially formed intermediate **2.24** could complex further organolithium reagent RLi and provide intramolecular assistance for bromine–lithium exchange. If this process becomes faster than the initial deprotonation, the new organolithium intermediate can then compete with the added organolithium for deprotonation of further **2.23**, which would ultimately lead to recovery of **2.10**.

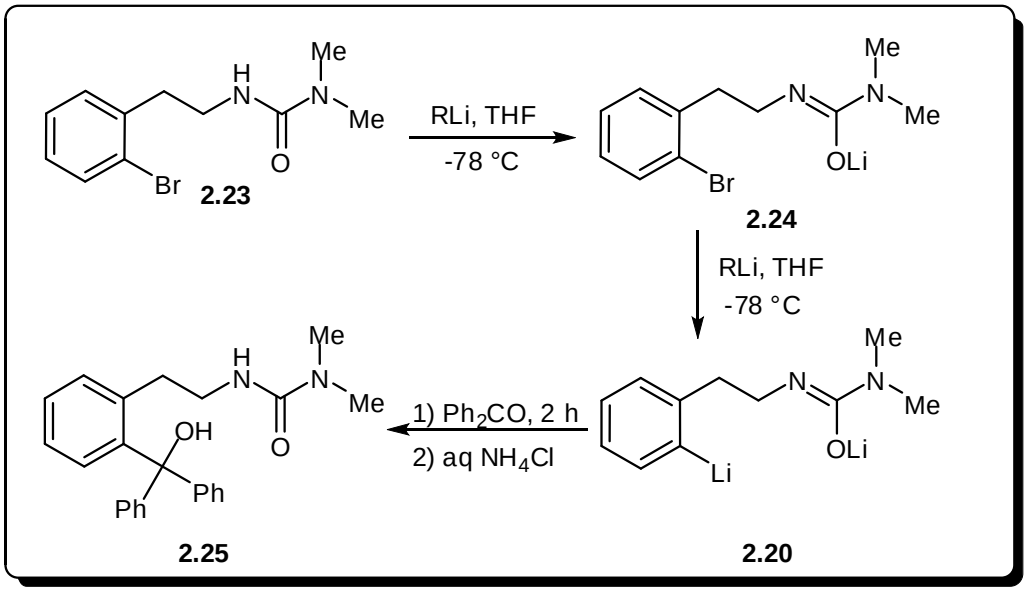
Some of these issues were investigated by Beak et al. for 2-bromo-*N*-ethylbenzamide and other substrates possessing PDGs, but primarily from a mechanistic rather than synthetic perspective.[22] For other PDG-containing substrates a Japanese group has used the less reactive dibutylmagnesium to effect the initial deprotonation, prior to bromine–lithium exchange,[23] but this suffers from the complication that the waste products of the reaction will contain two different metals, making recovery of the metals more difficult. The same group has also used mesityllithium for initial deprotonation of substrates containing active methylene groups,[24] but mesityllithium is more expensive and less widely available than common organolithium reagents, is more

wasteful of organic material, and produces a by-product that is less volatile and more difficult to remove. However, Smith's group has found that bromine-lithium exchange of *N*′-(2-bromoaryl)-*N,N*-dimethylurea and *N*-(2-bromobenzyl)pivalamide was more successfully achieved by the sequential use of MeLi (1.1 equivalents – to remove the NH proton) and *t*-BuLi (2.2 equivalents) at -78 °C.[9] This method was more attractive to us and therefore we proposed to investigate this method in the first instance if simple use of *tert*-butyllithium alone should prove unsatisfactory for Br–Li exchange of **2.23**.

Against this background, Br–Li exchange of **2.23** was attempted, initially by treatment with *t*-BuLi (2.5 equivalents) at –78 °C for 5 minute, followed by reaction with benzophenone as an electrophile, in the hope of producing *ortho* substituted product. Following work-up the crude product was tested by TLC and showed the presence of three components. The mixture was separated and purified by column chromatography (silica gel; Et_2O–hexane, 1:3).

One compound was identified as the starting material **2.23** (38%) and the other one was compound **2.10** (40%). Compound **2.10** was produced *via* Br–Li exchange followed by protonation. The structure of the third component was identified by various spectroscopic techniques (IR, ^1H, ^{13}C NMR, MS and HRMS). The ^1H NMR spectrum showed an apparent quartet (J = 7 Hz) at 3.37 ppm and a triplet (J = 7 Hz) at 2.68 ppm due to CH_2 protons next to NH and aryl groups, respectively. It also showed the presence of fourteen aromatic protons and two methyl protons of the urea unit. Clearly, bromine–lithium exchange followed by reaction with benzophenone has taken place. The new product was identified as **2.25** (Scheme 2.11) and was obtained in 19% yield. The ^{13}C NMR spectrum of **2.25** showed all the expected signals and was consistent with that predicted by ChemDraw. The structure of **2.25** was confirmed further by the low and high resolution mass spectra. The electron-impact mass spectrum of **2.25** showed a peak at *m/z* = 356, the HRMS of which identified its formula as $C_{24}H_{24}N_2O$ (corresponding to the molecular ion of **2.25** – H_2O).

It is clear that monolithium reagent **2.24** and dilithium reagent **2.20** were produced *in situ* on reaction of **2.23** with lithium reagent (Scheme 2.11).

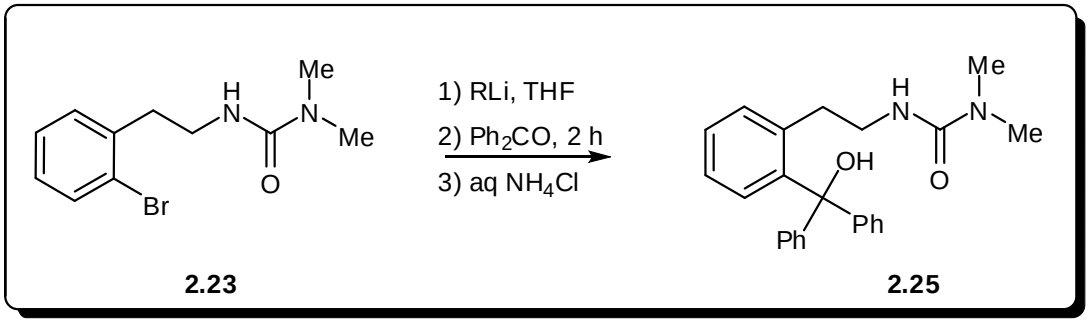


Scheme 2.11 Bromine–lithium exchange of **2.23** followed by reaction with benzophenone

However, the product **2.25** was isolated in only 19% yield along with debrominated starting material **2.10** (40%) and starting material **2.23** (38%) was recovered. Clearly, either other processes were competing with the desired process or the reaction had not gone to completion. Therefore, the reaction was carried out under a variety of different conditions. Various lithium reagents, various molar equivalents of lithium reagents and benzophenone, different reaction times and temperatures were used in an attempt to improve the yield of product **2.25**. The results obtained are recorded in Table 2.3. A very low yield (8%) of **2.25** was obtained under similar reaction conditions when dry diethyl ether was used as a solvent instead of THF (Table 2.3; Entry 1) along with **2.10** (15%). A similar result was obtained when the reaction was carried out at 0 °C when the lithiation time was 1 h (Table 2.3; Entry 4).

A better yield (23%) of **2.25** was obtained when the reaction time was increased to 2 h on using *t*-BuLi (2.5 equivalents) at –78 °C (Table 2.3; Entry 2) along with **2.10** (44%). The yield of **2.25** was increased further to 30% when three molar equivalents of *t*-BuLi were used under similar conditions (Table 2.3; Entry 3) along with **2.10** (53%). The yield of **2.25** was improved to 46% when MeLi (1.2 equivalents) and *t*-BuLi (2.5 equivalents) along with two molar equivalents of benzophenone were used at –78 °C and the time for the lithiation step was 15 minutes (Table 2.3; Entry 5). Under such conditions **2.10** was obtained in 4% yield.

Table 2.3: Synthesis of **2.25** under various reaction conditions according to Scheme 2.11



2.23 **2.25**

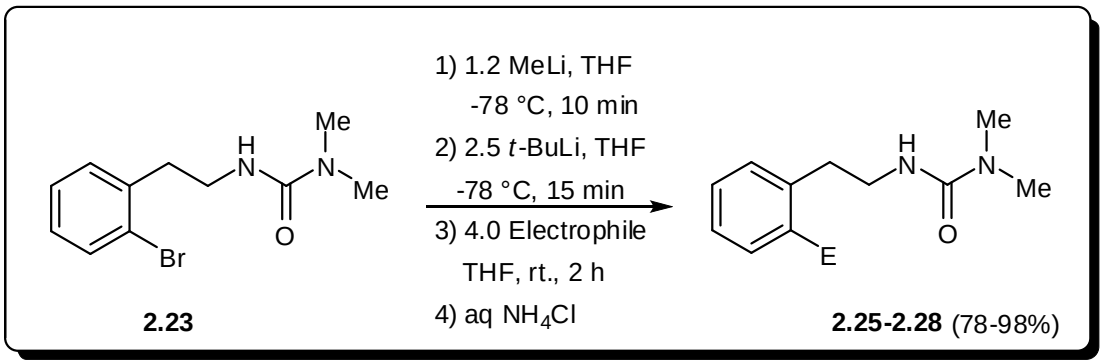
Entry	Lithiation step (–78 °C) RLi (mole equiv.), Time			Reaction with Ph_2CO Temp., mole equiv.		Yield of **2.25** (%)[a]
	MeLi	*t*-BuLi	Time (min)	T (°C)	mole equiv.	
1	—	2.5	5	–78	1.2	19 (8)[b]
2	—	2.5	120	–78	1.2	23
3	—	3.3	120	–78	1.2	30
4	—	2.5	60	0	1.2	9
5	1.2	2.5	15	–78	2.0	46
6	1.2	2.5	15	20	1.2	72
7	1.2	2.5	15	20	2.0	82
8	1.2	2.5	15	20	3.0	86
9	1.2	2.5	15	20	4.0	95
10	1.2	2.5	60	20	2.0	90

[a] Yield of pure **2.25**.
[b] The figure in parentheses is for a similar reaction in dry Et_2O.

The results reported in Table 2.3 showed that treatment of **2.23** with MeLi (1.2 equivalents), to deprotonate the nitrogen to give the monolithium reagent **2.24**, and then 2.5 equivalents of *tert*-butyllithium, to effect the bromine–lithium exchange[9.11] to give the dilithium reagent **2.20**, followed by reaction with benzophenone, provided **2.25** in 72–95% yields (Table 2.3; Entries 6–10). It is clear that **2.25** was produced in high yield (86–95%: Table 2.3; Entries 8 and 9) when the reaction time was short (15 minutes) and excess benzophenone (3 to 4 equivalents) was used. Also, a high yield (90%: Table 2.3;

Entry 10) of **2.25** was produced when a longer reaction time (1 h) and two equivalents of benzophenone were used.

Reactions of dilithium reagent **2.20**, prepared *in situ* from **2.23** under the highest−yielding conditions, with other representative electrophiles (benzaldehyde, 4-anisaldehyde and deuterium oxide; 4.0 equivalents) were carried out at room temperature for two hours. Purification of the crude products by column chromatography (silica gel; Et_2O–hexane, 1:3) gave the corresponding substituted derivatives **2.26**–**2.28** (Scheme 2.12) in high yields (Table 2.4).



Scheme 2.12 Lithiation and substitution of *N′*-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**2.23**)

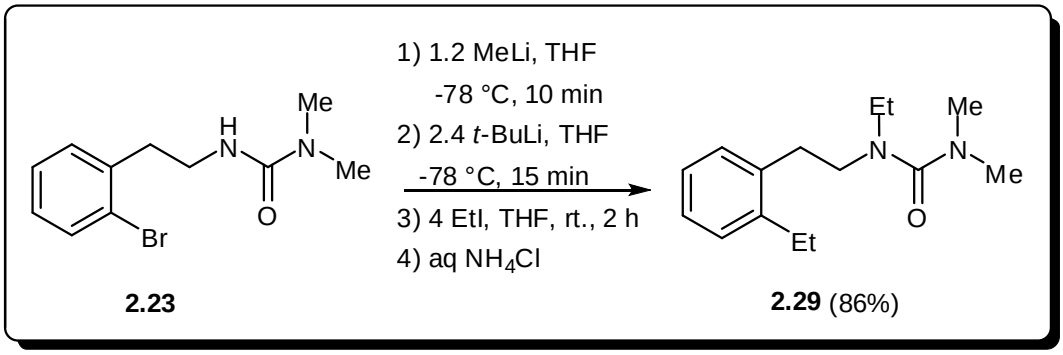
The structures of the new products were confirmed by various spectroscopic techniques (see Section 2.14.6 for details). The ^{1}H NMR spectra of compounds **2.26** and **2.27** showed that the two hydrogens of each of the two CH_2 groups are diastereotopic.

Table 2.4: Synthesis of *N'*-(2-(substituted phenyl)ethyl)-*N*,*N*-dimethylureas **2.25–2.28** according to Scheme 2.12

Product	Electrophile	E	Yield (%)[a]
2.25	Ph_2CO	$Ph_2C(OH)$	95
2.26	PhCHO	PhCH(OH)	90
2.27	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	87
2.28	D_2O	D	98

[a] Yield of pure product after isolation.

Reaction of the dilithium reagent **2.20**, obtained from **2.23**, with excess of iodoethane (4.0 equivalents) gave rise to the diethyl derivative **2.29** in 86% isolated yield (Scheme 2.13). Although we did not attempt to prepare the monoethyl derivative in this case, there is ample precedent to show that *C*-ethylation occurs much more readily than *N*-ethylation (see formation of **2.18**, Table 2.2, for example), so that simple *C*-ethylated products are generally easily obtained when the amount of iodoethane is restricted to one equivalent.



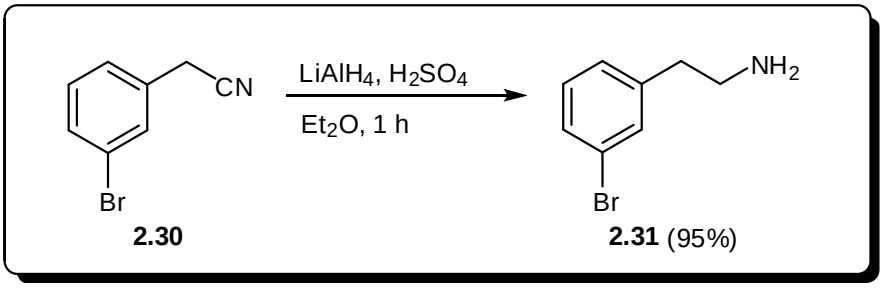
2.23 **2.29** (86%)

Scheme 2.13 Lithiation of **2.23** followed by reaction with iodoethane

To test the generality of the bromine–lithium exchange, it was of interest to see whether the conditions that were successful for Br–Li exchange of **2.23** would also apply for Br–Li exchange of compounds having the bromine at a different position on the ring. It was expected that *N*′-2-(4-bromophenyl)ethyl-*N*,*N*-dimethylurea would behave in a similar manner to the 2-bromo derivative **2.23**. Therefore, attention was turned instead to the synthesis of *N*′-2-(3-bromophenyl)ethyl-*N*,*N*-dimethylurea and investigation of its bromine–lithium exchange followed by reaction with an electrophile under similar condition to that used for **2.23**.

2.7 Synthesis of 2-(3-bromophenyl)ethylamine (2.31)

Compound **2.31** was synthesised based on a literature procedure.[25] Reaction of 2-(3-bromophenyl)acetonitrile[25] (**2.30**) with a mixture of lithium aluminium hydride (2.2 molar equivalents) and concentrated sulfuric acid (1.1 molar equivalents) in diethyl ether at 0 °C for 1 h was carried out (Scheme 2.14). The mixture was worked-up and washed with sodium hydroxide to give pure 2-(3-bromophenyl)ethylamine (**2.31**, Scheme 2.14) in 95% yield as an oil.

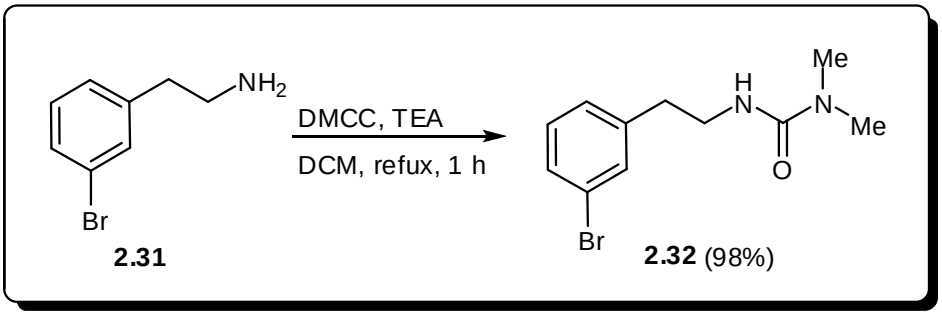


Scheme 2.14 Synthesis of 2-(3-bromophenyl)ethylamine (**2.31**)

Our attention was next turned to synthesis *N′*-(2-(3-bromophenyl)ethyl)-*N,N*-dimethylurea (**2.32**) from reaction of **2.31** with dimethylcarbamoyl chloride.

2.8 Synthesis of *N′*-(2-(3-bromophenyl)ethyl)-*N,N*-dimethylurea (2.32)

N′-(2-(3-Bromophenyl)ethyl)-*N,N*-dimethylurea (**2.32**) was obtained from the reaction of **2.31** with dimethylcarbamoyl chloride in 98% yield (Scheme 2.15) by the method[18] shown in Scheme 2.5 for the synthesis of **2.10**. The structure of **2.32** was confirmed by IR, NMR, MS and HRMS spectral data (see Section 2.14.7 for details).



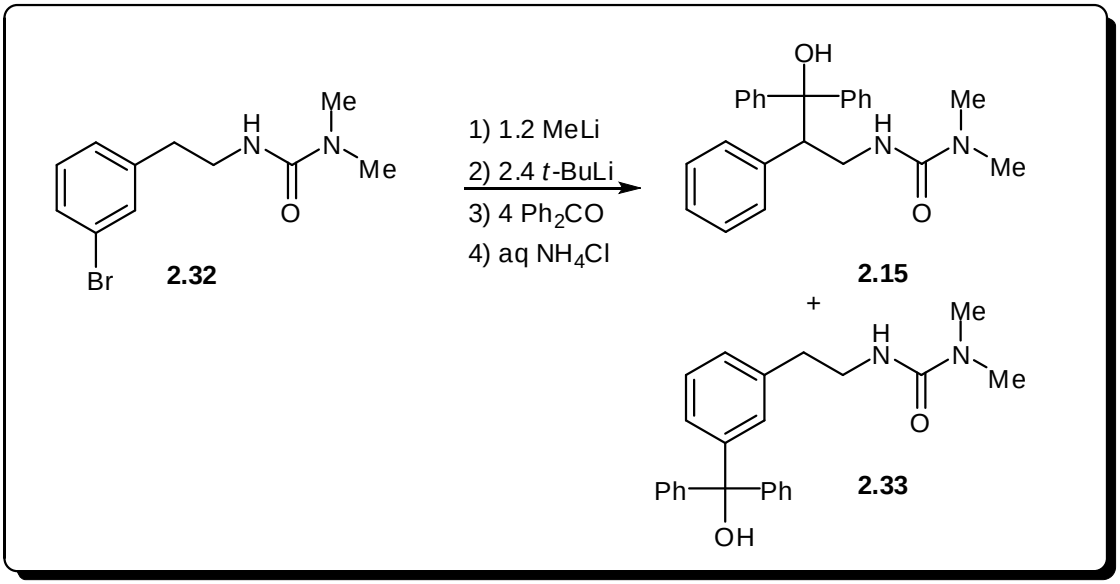
Scheme 2.15 Synthesis of *N′*-2-(3-bromophenyl)ethyl-*N,N*-dimethylurea (**2.32**)

Having successfully produced **2.32**, attention was turned to investigation of its bromine–lithium exchange under conditions similar to those used with **2.23**.

2.9 Bromine-lithium exchange and substitution of *N′*-(2-(3-bromophenyl)ethyl)-*N,N*-dimethylurea (2.32)

The Br–Li exchange of *N′*-2-(3-bromophenyl)ethyl-*N,N*-dimethylurea (**2.32**) was investigated by the use of MeLi (1.2 equivalents) followed by *t*-BuLi (2.4 equivalents) at –78 °C (Scheme 2.16). Reaction of the dilithium reagent produced *in situ*

with benzophenone (4.0 equivalents) gave a mixture of **2.15** and a new product, identified as **2.33** (Scheme 2.16) by its spectral characteristics, in 85 and 13% yields, respectively. Product **2.33** would be produced as a result of Br–Li exchange to give dilithium reagent **2.35** (Figure 2.2), produced *in situ* from **2.34**, followed by reaction with benzophenone at the *meta*-position.



Scheme 2.16 Bromine–lithium exchange and substitution of **2.32** followed by reaction with benzophenone

We assume that product **2.15** arose as a result of isomerisation of the 3-lithium derivative **2.35** (Figure 2.2) formed by the initial Br–Li exchange reaction into the α-lithium derivative **2.12** (Scheme 2.6), probably because the 3-lithium reagent acted as a base to remove a proton from the side-chain of another molecule.

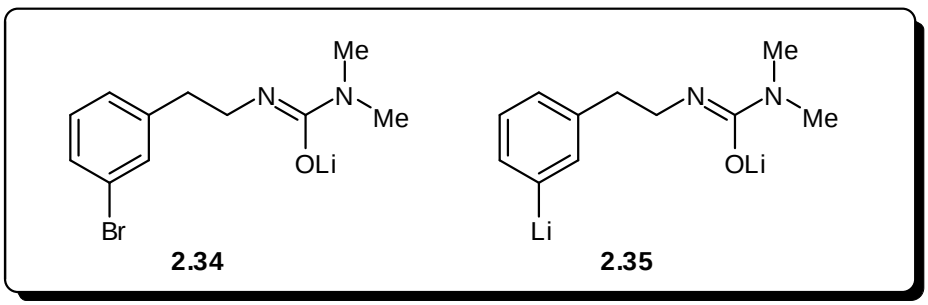


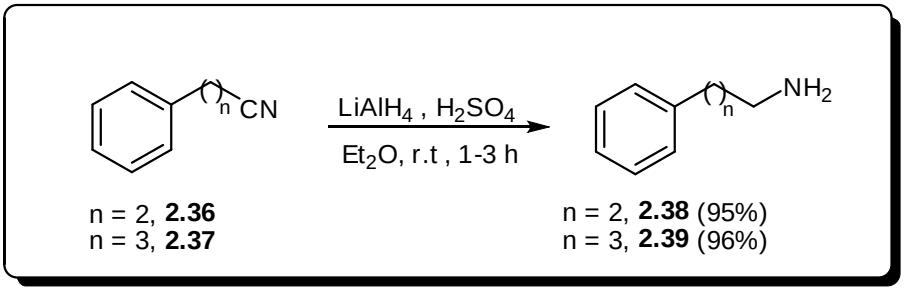
Figure 2.2 Structure of lithium intermediates **2.34** and **2.35**

In an attempt to improve the yield of **2.33** we shortened the reaction time with *tert*-butyllithium so as to reduce the opportunity for such isomerisation. Indeed, the yield of **2.33** was improved to 58% when the reaction time with *tert*-butyllithium was only 5 minutes, while the yield of **2.15** decreased to 13%. A significant quantity (22%) of unbrominated starting material **2.10** was also recovered, which supports the assumption that the initial Br–Li exchange product acts as a base.

It was also of interest to know whether lithiation of other *N*′-(ω-phenylalkyl)-*N*,*N*-dimethylureas, where extra methylene groups were present, would behave in the same way towards lithiation as the phenethyl derivative **2.10**, or whether the site of lithiation could be different. Therefore, we decided to synthesise *N*′-(3-phenylpropyl)-*N*,*N*-dimethylurea (three CH_2 groups) and *N*′-(4-phenylbutyl)-*N*,*N*-dimethylurea (four CH_2 groups) and then investigate their lithiation and substitution.

2.10 Synthesis of (ω-phenylalkyl)amines 2.38 and 2.39

3-Phenylpropylamine (**2.38**) and 4-phenylbutylamine (**2.39**) were synthesised in 95 and 96% yields, respectively by reduction of the corresponding nitrile derivatives **2.36** and **2.37** (Scheme 2.16) using a mixture of lithium aluminium hydride and sulfuric acid under identical conditions to those used for the synthesis of **2.31** (Scheme 2.14).



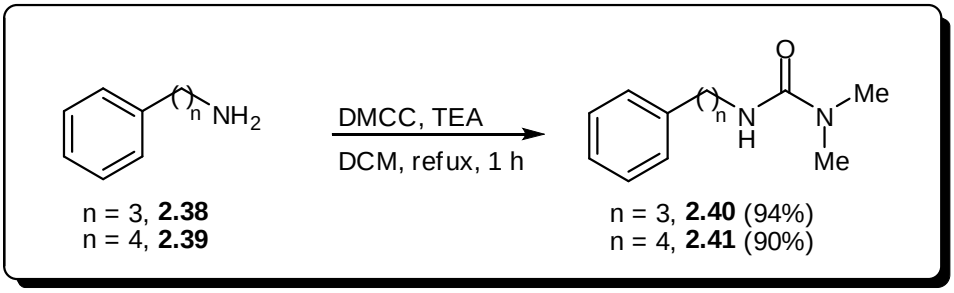
Scheme 2.17 Synthesis of (ω-phenylalkyl)amines **2.38** and **2.39**

Next, reactions of **2.38** and **2.39** with dimethylcarbamoyl chloride were attempted to produce the corresponding ureas.

2.11 Synthesis of *N*′-(ω-phenylalkyl)-*N*,*N*-dimethylureas 2.40 and 2.41

N′-(3-Phenylpropyl)-*N*,*N*-dimethylurea (**2.40**) and *N*′-(4-phenylbutyl)-*N*,*N*-dimethylurea (**2.41**) were synthesised in 94 and 90% yields, respectively (Scheme 2.18)

from the corresponding amino derivatives **2.38** and **2.39** on reactions with dimethylcarbamoyl chloride by the method[18] shown in Scheme 2.5 for the synthesis of **2.10**.

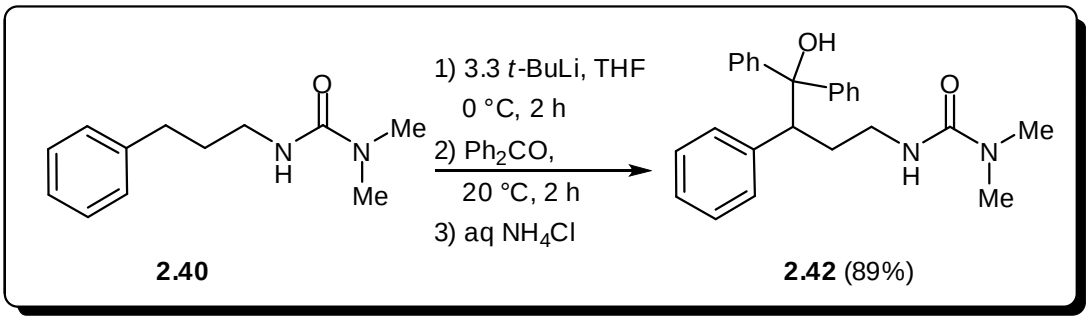


Scheme 2.18 Synthesis of *N′*-(ω-phenylalkyl)-*N*,*N*-dimethylureas **2.40** and **2.41**

Having successfully produced **2.34** and **2.35** attention was next turned to investigation of their lithiation and substitution to see what effect the extra CH_2 group(s) could have on the site of lithiation.

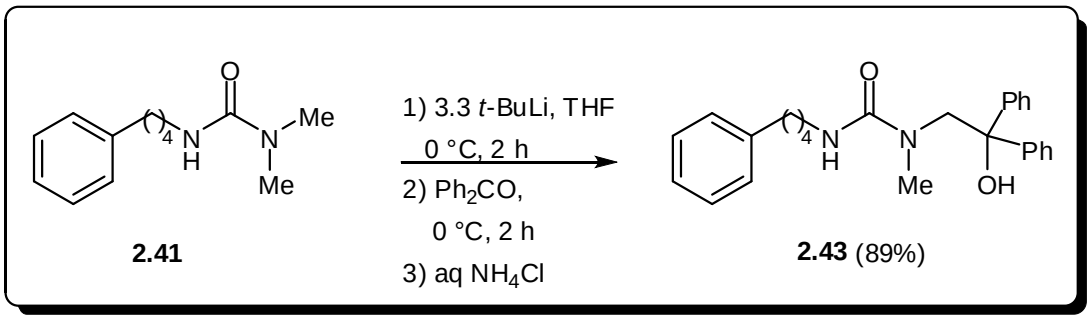
2.12 Lithiation and substitution of *N′*-(ω-phenylalkyl)-*N*,*N*-dimethylureas 2.40 and 2.41

Lithiation of **2.40** under the standard conditions that were used for **2.10** (Scheme 2.6) followed by reaction with benzophenone as a representative electrophile at –78 °C gave a new product, which was identified by various spectroscopic techniques as the corresponding α-substituted product **2.42** (Scheme 2.19), in 44% yield. The yield of **2.42** was improved to 85% when the whole reaction was carried out at 0 °C and to 89% when the lithiation was conducted at 0 °C and reaction with benzophenone was carried out at room temperature (Scheme 2.19).



Scheme 2.19 Lithiation and substitution of **2.40** followed by reaction with benzophenone

By contrast, lithiation of **2.41** followed by reaction with benzophenone at 0 °C gave a new product, which was identified by various spectroscopic techniques as **2.43**, in which lithiation and substitution had taken place on a methyl group of the urea (Scheme 2.20), in 89% yield. No product was obtained when the reaction was carried out at –78 °C.



2.41 **2.43** (89%)

Scheme 2.20 Lithiation and substitution of **2.41** followed by reaction with benzophenone

The contrast in the site of lithiation for compounds **2.40** and **2.41** could be due to the stability of the dilithium intermediates produced in each case. The dilithium intermediate **2.44** (Figure 2.3), produced *in situ* from side-chain lithiation of **2.40**, could be stabilised *via* chelation between oxygen and lithium atoms through a seven-membered ring (Figure 2.3) and on reaction with benzophenone would give **2.42**. However, lithiation at the *ortho*-position of the phenyl ring of **2.40** should involve formation of dilithium reagent **2.45** which is less able to be stabilised by chelation than **2.44** because chelation would require formation of a nine-membered ring (Figure 2.3). Also, the acidity of the proton at the α-position to the phenyl ring is higher than that of the *ortho*-protons of the phenyl ring as a result of the electron-withdrawing effect of the phenyl moiety.

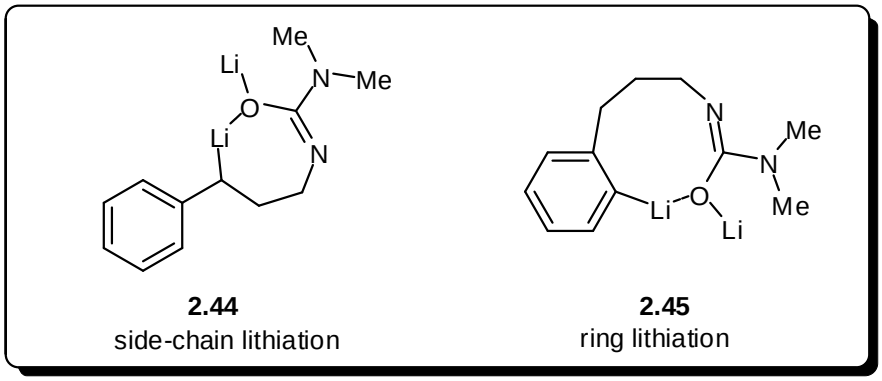


Figure 2.3 Possible chelated structures of lithium intermediates **2.44** and **2.45**

Product **2.43** was presumably obtained from reaction of dilithium reagent **2.46** (Figure 2.4), produced *in situ* from **2.41**, with benzophenone. This dilithium reagent could be highly stabilised *via* chelation through a five-membered ring. Neither ring nor α-lithiation were likely since they would receive little stabilisation from chelation, which would require formation of medium-ring dilithium intermediates **2.47** and **2.48** (Figure 2.4).

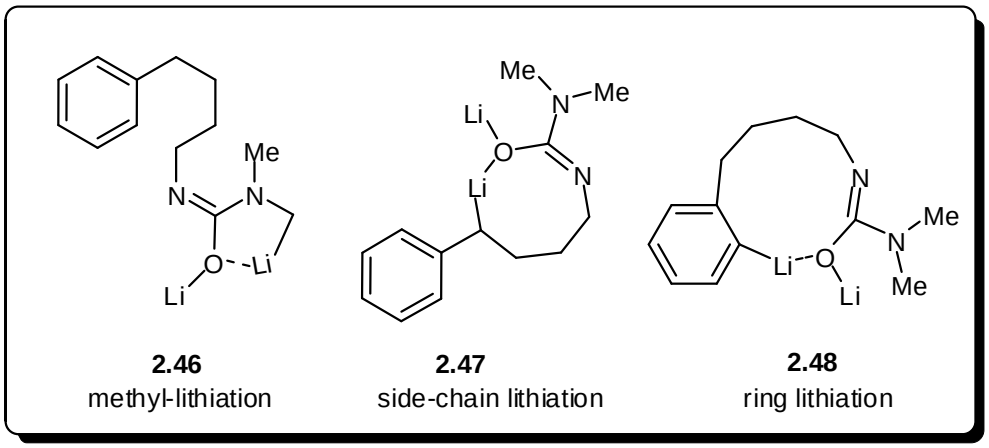


Figure 2.4 The structures of lithium intermediates **2.46–2.48**

2.13 Conclusions

Simple and efficient procedures that allow side-chain lithiation of *N*′-(phenylalkyl)-*N*,*N*-dimethylureas have been developed. Lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea took place at the CH_2 group next to the phenyl ring (α-lithiation) with three equivalents of *tert*-butyllithium in tetrahydrofuran at –78 °C. Ring substitution could be achieved via bromine–lithium exchange of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea using methyllithium followed by *tert*-butyllithium in tetrahydrofuran at -78 °C. Reactions of the dilithium reagents obtained with a variety of electrophiles gave the corresponding α- or 2-substituted derivatives in high yields. Similarly, lithiation of *N*-(3-phenylpropyl)-*N*,*N*-dimethylurea took place on the α-CH_2, although a higher temperature was required for a good yield. By contrast, lithiation of *N*′-(4-phenylbutyl)-*N*,*N*-dimethylurea took place on one of the methyl groups of the urea unit.

The results reported in this chapter illustrate how sensitive reactions of this nature are to subtle variations in structure, method of generation of lithium compound and reaction conditions. For the series of compounds $Ph(CH_2)_nNHCONMe_2$, with n = 0–4, direct lithiation at –20 °C gives side-chain substitution on a methyl group of the urea unit for n = 0,[7e] *ortho*-substitution at –78 °C for n = 1,[9] and α-substitution for n = 2 (this work) at –78 °C. Although α-substitution also prevails for n = 3, a higher temperature during the lithiation step is needed for a good yield, while no lithiation occurs at –78 °C for n = 4 and at 0 °C lithiation occurs on an *N*-methyl group. Similarly, conditions optimised for Br–Li exchange of (2-bromophenyl)ethyl derivative **2.23** produced only a low yield of the corresponding product from (3-bromophenyl)ethyl derivative **2.32**, although the yield could be improved substantially by varying the reaction conditions.

2.14 Experimental

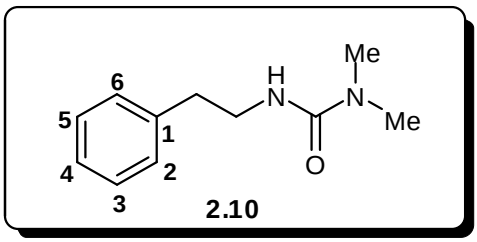
2.14.1 General Experimental

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C measurements. Chemical shifts δ are reported in parts per

million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, br. = broad, app. = apparent (*i.e.* appears as a signal with the specified multiplicity even though not all coupled protons are equivalent), exch. = exchangeable with D_2O. ^{13}C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns, and expected chemical shift values, and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra were recorded on a Waters GCT Premier spectrometer and high-resolution mass spectra were recorded on a Waters LCT Premier XE instrument. IR spectra were recorded on a Jasco FT/IR-660 plus instrument by dissolving the product in $CHCl_3$, applying droplets on a NaCl plate and allowing evaporation of the solvent. Column chromatography was carried out using Fischer Scientific silica 60A (35–70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[26] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl and other solvents were purified by standard procedures.[27,28] All reactions were performed under a nitrogen atmosphere. Glassware was oven dried, assembled hot and allowed to cool under a stream of nitrogen gas.

2.14.2 Synthesis of *N′*-Phenethyl-*N,N*-dimethylurea (2.10)[18]

A stirred mixture of **2.9** (10.40 g, 85.8 mmol), dimethylcarbamoyl chloride (DMCC, 11.08 g, 103.0 mmol) and Et_3N (13.03 g, 128.8 mmol) in DCM (100 mL) was heated under reflux for 1 h. The mixture was allowed to cool and the solid formed was collected by filtration and then washed with H_2O (2 × 25 mL). The solid was purified by crystallisation from a mixture of EtOAc and Et_2O (1:3 by volume) to give pure **2.10** (16.30 g, 84.9 mmol, 99%) as a colourless crystalline solid.



2.10

mp 88–90 °C (Lit.[18a] mp 81–82 °C, Lit.[18b] mp 98 °C).

IR (FT): ν_{max} = 3341, 2933, 1634, 1539, 1332 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H, C_6H_5), 4.38 (br., exch., 1 H, NH), 3.48 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.85 [s, 6 H, $N(CH_3)_2$], 2.82 (t, *J* = 7 Hz, 2 H, C*H*$_2C_6H_5$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 139.5 (s, C-1), 128.8 (d, C-3/C-5), 128.5 (d, C-2/C-6), 126.3 (d, C-4), 42.1 (t, CH_2NH), 36.5 (t, *C*$H_2C_6H_5$), 36.1 [q, $N(CH_3)_2$].

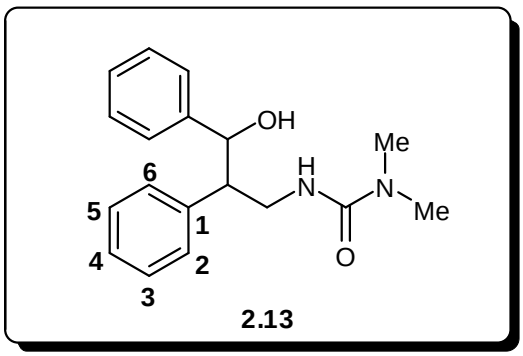
MS (EI): *m/z* (%) = 192 (29, $[M]^+$), 147 (8), 101 (42), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{16}N_2O$: 192.1263; found: 192.1260.

2.14.3 Lithiation and substitution of *N′*-phenethyl-*N*,*N*-dimethylurea 2.10: synthesis of substituted derivatives 2.13–2.19; general procedure

A solution of *t*-BuLi in pentane (4.51 mL, 1.9 M, 8.6 mmol) was added to a stirred solution of **2.10** (0.50 g, 2.6 mmol) at –78 °C in anhydrous THF (20 mL) under a N_2 atmosphere. The mixture was stirred at –78 °C for 2 h and a solution of the electrophile (2.9 mmol), in anhydrous THF (8 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at –78 °C, and then allowed to warm to r.t. The mixture was quenched with a sat. aq NH_4Cl (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **2.13**–**2.19**. The yields obtained were in the range of 86–99% (Table 2.2).

***N′*-(3-Hydroxy-2,3-diphenylpropyl)-*N*,*N*-dimethylurea (2.13)**



2.13

From benzaldehyde (0.30 g, 2.9 mmol); product **2.13** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.75 g (2.5 mmol, 97%); white solid; mp 180–184 °C.

IR (FT): ν_{max} = 3352, 2929, 1633, 1537, 1332 cm^{-1}.

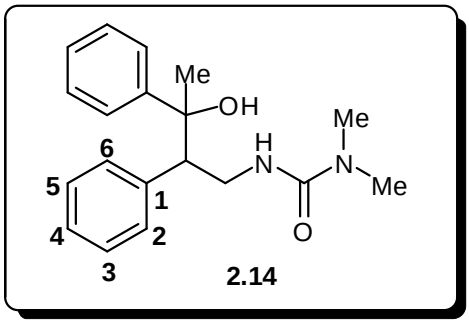
^1H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.11 (m, 20 H, 4 C_6H_5), 6.25 (t, exch., *J* = 7 Hz, 1 H, NH.), 6.00 (t, exch., *J* = 7 Hz, 1 H, NH), 5.72 (d, exch., *J* = 4 Hz, 1 H, OH), 5.53 (d, exch., *J* = 4 Hz, 1 H, OH), 4.94 (app. t, *J* = 4 Hz, 1 H, C*H*OH), 4.81 (dd, *J* = 4, 7 Hz, 1 H, C*H*OH), 3.58–3.49 (m, 2 H, 2 C*H*CH_2), 3.44 (dd, *J* = 7, 14 Hz, 1 H, CH_aH_b), 3.28 (m, 1 H, CH_aH_b), 3.18 (dd, *J* = 7, 14 Hz, 1 H, CH_aH_b), 3.13–3.09 (m, 1 H, CH_aH_b), 2.77 [s, 6 H, $N(CH_3)_2$], 2.71 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 158.8 (2 s, 2 C=O), 144.7, 144.6, 142.0, 140.7 (4 s, C-1 of 4 C_6H_5), 129.8, 129.3, 128.1, 127.9 (4 d, C-3/C-5 of 4 C_6H_5), 127.9, 127.8, 127.1, 126.7 (4 d, C-2/C-6 of 4 C_6H_5), 126.9, 126.6 (2 d, C-4 of 4 C_6H_5), 75.8, 73.0 (2 d, 2 CHOH), 53.34, 53.32 (2 d, 2 *C*HCH_2), 43.5, 42.7 (2 t, 2 CH_2), 36.3, 36.2 [2 q, 2 $N(CH_3)_2$].

MS (EI): *m/z* (%) = 298 (2, $[M]^+$), 280 (20), 208 (32), 180 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{22}N_2O_2$: 298.1681; found: 298.1677.

N′-(3-Hydroxy-2,3-diphenylbutyl)-N,N-dimethylurea (2.14)



2.14

From acetophenone (0.35 g, 2.9 mmol); product **2.14** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.78 g (2.5 mmol, 96%); white solid; mp 131–135 °C.

IR (FT): ν_{max} = 3365, 2928, 1625, 1537, 1367 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.13 (m, 20 H, 4 C_6H_5), 3.94 (br., exch., 1 H, NH,), 4.82 (br., exch., 1 H, NH), 4.77 (dd, *J* = 4, 7 Hz, 1 H, CH), 3.78 (m, 1 H, CH), 3.52 (m, 1 H, CH_aH_b), 3.40 (m, 1 H, CH_aH_b), 3.31 (dd, *J* = 7, 14 Hz, 1 H, CH_aH_b), 3.18

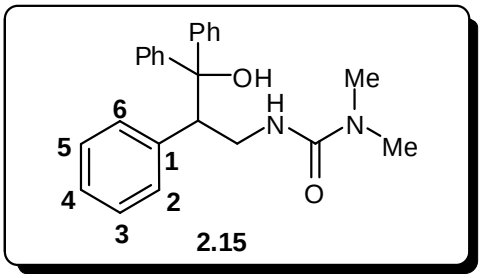
(dd, *J* = 7, 14 Hz, 1 H, CH_aH_b), 2.83 [s, 6 H, $N(CH_3)_2$], 2.42 [s, 6 H, $N(CH_3)_2$], 1.10 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9, 158.3 (2 s, 2 C=O), 149.0, 148.9, 140.5, 140.4 (4 s, C-1 of 4 C_6H_5), 129.7, 128.4, 128.35, 128.31 (4 d, C-3/C-5 of 4 C_6H_5), 127.89, 127.86, 127.5, 127.0 (4 d, C-2/C-6 of 4 C_6H_5), 126.2, 125.9, 124.67, 124.62 (4 d, C-4 of 4 C_6H_5), 75.3, 75.0 (2 s, 2 COH), 56.3, 49.2 (2 d, 2 CH), 42.1, 42.0 (2 t, 2 CH_2), 35.7, 36.3 [2 q, 2 $N(CH_3)_2$], 31.3, 31.1 (2 q, 2 CH_3).

MS (EI): *m/z* (%) = 294 (40, $[M - H_2O]^+$), 279 (3), 208 (32), 192 (100).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{19}H_{22}N_2O$: 294.1732; found: 294.1737.

N′-(3-Hydroxy-2,3,3-triphenylpropyl)-N,N-dimethylurea (2.15)



2.15

From benzophenone (0.53 g, 2.9 mmol); yield: 0.95 g (2.5 mmol, 98%); white solid; mp 202–205 °C.

IR (FT): ν_{max} =3239, 2920, 1629, 1531, 1360 cm^{-1}.

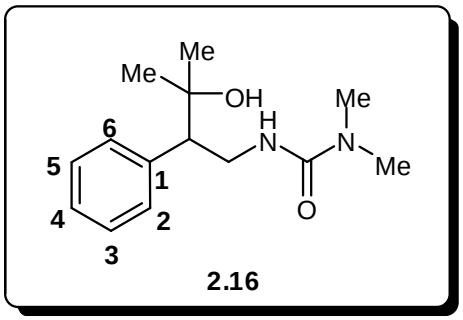
^1H NMR (500 MHz, $CDCl_3$): δ = 7.77–6.80 (m, 15 H, 3 C_6H_5), 6.38 (br. s, exch., 1 H, OH), 5.96 (t, exch., *J* = 6 Hz, 1 H, NH), 4.28 (app. t, *J* = 7 Hz, 1 H, CH), 3.62 (m, 1 H, CH_aH_b), 3.26 (m, 1 H, CH_aH_b), 2.43 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 148.2, 149.0, 141.6 (3 s, C-1 of 3 C_6H_5), 127.6, 127.9, 127.5 (3 d, C-3/C-5 of 3 C_6H_5), 126.2, 126.3, 126.0 (3 d, C-2/C-6 of 3 C_6H_5), 125.95, 125.92, 125.3 (3 d, C-4 of 3 C_6H_5), 79.0 (s, COH), 52.6 (d, CH), 43.6 (t, CH_2), 35.9 [q, $N(CH_3)_2$].

MS (EI): *m/z* (%) = 356 (40, $[M - H_2O]^+$), 311 (15), 256 (100), 192 (97).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{19}H_{22}N_2O$: 356.1889; found: 356.1883.

N′-(3-Hydroxy-3-methyl-2-phenylbutyl)-*N*,*N*-dimethylurea (2.16)



2.16

From acetone (0.17 g, 2.9 mmol); yield: 0.62 g (2.5 mmol, 98%); white solid; mp 148–151 °C.

IR (FT): ν_{max} = 3321, 2968, 1627, 1547, 1351 cm^{-1}.

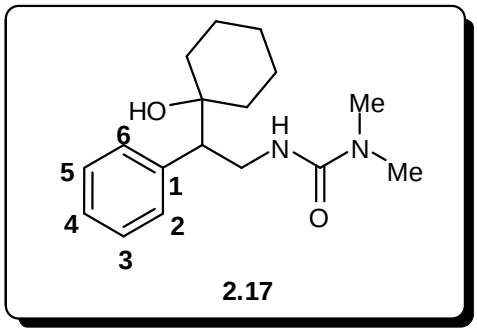
^1H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H, C_6H_5), 4.79 (br. s, exch., 1 H, OH), 4.41 (br., exch., 1 H, NH), 3.85 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 3.37 (dd, *J* = 9, 14 Hz, 1 H, CH_aH_b), 2.73 (dd, *J* = 6, 9 Hz, 1 H, CH), 2.72 [s, 6 H, $N(CH_3)_2$], 1.23 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 140.4 (s, C-1), 129.4 (d, C-3/C-5), 128.3 (d, C-2/C-6), 126.9 (d, C-4), 72.5 (s, COH), 56.5 (d, CH), 41.7 (t, CH_2), 35.9 [q, $N(CH_3)_2$], 29.1, 27.6 (2 q, 2 CH_3).

MS (EI): *m/z* (%) = 232 (25, $[M - H_2O]^+$), 217 (10), 192 (100).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{14}H_{20}N_2O$: 232.1576; found: 232.1570.

N′-[2-(1-Hydroxycyclohexyl)-2-phenylethyl]-*N*,*N*-dimethylurea (2.17)



2.17

From cyclohexanone (0.28 g, 2.9 mmol); yield: 0.74 g (2.6 mmol, 98%); white solid; mp 149–151 °C

IR (FT): ν_{max} = 3358, 2931, 1634, 1538, 1380 cm^{-1}.

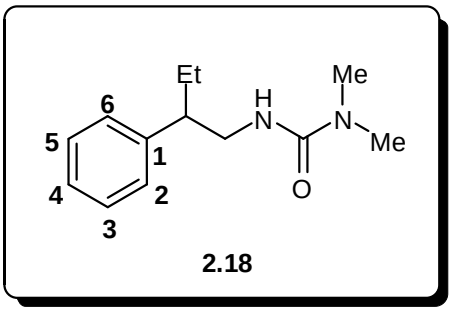
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 6 H, OH and C_6H_5), 4.29 (br., exch., 1 H, NH), 3.88 (dd, *J* = 5, 14 Hz, 1 H, C*H*$_a$H$_b$), 3.42 (dd, *J* = 9, 14 Hz, 1 H, CH$_a$*H*$_b$), 2.78 (dd, *J* = 5, 9 Hz, 1 H, CH), 2.64 [s, 6 H, $N(CH_3)_2$], 1.07–1.57 (m, 10 H, *c*-Hex).

^{13C} NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 140.1 (s, C-1), 129.7 (d, C-3/C-5), 128.3 (d, C-2/C-6), 126.8 (d, C-4), 72.9 (s, C-1 of *c*-Hex), 55.5 (d, CH), 40.9 (t, CH_2), 36.2, 36.0 (2 t, C-3/C-5 of *c*-Hex), 35.9 [q, $N(CH_3)_2$], 25.6 (t, C-4 of *c*-Hex), 21.9, 21.7 (2 t, C-2/C-6 of *c*-Hex).

MS (ES^+): *m/z* (%) = 581 (48, $[M + MH]^+$), 354 (55, $[M + MeCNNa]^+$), 313 (47, $[M + Na]^+$), 291 (100, $[MH]^+$), 272 (30).

HRMS (ES^+): *m/z* $[MH]^+$ calcd for $C_{17}H_{27}N_2O_2$: 291.2073; found: 291.2080.

N′-(2-Phenylbutyl)-*N*,*N*-dimethylurea (2.18)



2.18

From iodoethane (0.45 g, 2.9 mmol); yield: 0.50 g (2.3 mmol, 88%); yellow oil.

IR (FT): ν_{max} = 3346, 2928, 1635, 1540, 1377 cm^{-1}.

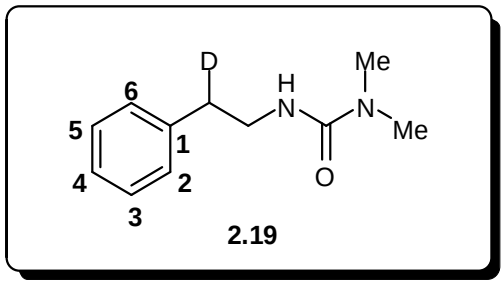
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.08 (m, 5 H, C_6H_5), 4.11 (br., exch., 1 H, NH), 3.62 (m, 1 H, C*H*$_a$H$_b$NH), 3.06 (m, 1 H, CH$_a$*H*$_b$NH), 2.67 [s, 6 H, $N(CH_3)_2$], 2.60 (m, 1 H, CH), 1.65 (m, 1 H, C*H*$_a$H$_b$CH$_3$), 1.50 (m, 1 H, CH$_a$*H*$_b$CH$_3$), 0.74 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3 (s, C=O), 143.1 (s, C-1), 128.6 (d, C-3/C-5), 127.8 (d, C-2/C-6), 126.5 (d, C-4), 48.0 (t, CH_2), 46.3 (d, CH), 35.9 [q, $N(CH_3)_2$], 26.5 (t, *C*H$_2$CH$_3$), 11.9 (q, CH_3).

MS (ES^+): *m/z* (%) = 463 (20, $[2 M + Na]^+$), 243 (100, $[M + Na]^+$), 221 (30, $[MH]^+$).

HRMS (ES^+): *m/z* $[MH]^+$ calcd for $C_{13}H_{21}N_2O$: 221.1646; found: 221.1654.

N′-(2-Deuterio-2-phenylethyl)-N,N-dimethylurea (2.19)



2.19

From D_2O (0.06 g, 2.9 mmol); yield: 0.50 g (2.6 mmol, 99%); white solid; mp 89–90 °C (undeuterated analogue mp: Lit.[18a] 81–82 °C; Lit.[18b] 98 °C).

IR (FT): ν_{max} = 3342, 2932, 1634, 1538, 1382 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.11 (m, 5 H, C_6H_5), 4.38 (br., exch., 1 H, NH,), 3.40–3.38 (m, 2 H, CH_2), 2.76 [s, 6 H, $N(CH_3)_2$], 2.72 (m, 1 H, CH).

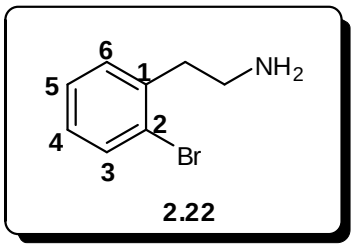
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 139.4 (s, C-1), 128.8 (d, C-3/C-5), 128.5 (d, C-2/C-6), 126.3 (d, C-4), 42.1 (t, CH_2), 36.1 [q, $N(CH_3)_2$], 36.2 (seen as three lines, 1:1:1, because of coupling to D, CH).

MS (EI): *m/z* (%) = 193 (48, $[M]^+$), 180 (8), 101 (55), 83 (89), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{15}DN_2O$: 193.1325; found: 193.1328.

2.14.4 Synthesis of 2-(2-bromophenyl)ethylamine (2.22)

A solution of $AlCl_3$ (7.55 g, 56.7 mmol) in anhydrous diethyl ether (50 mL) was added to lithium aluminium hydride (6.45 g, 170.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. A solution of (2-bromophenyl)acetonitrile (**2.21**; 15.10 g, 77.0 mmol) in anhydrous diethyl ether (30 mL) was added to the mixture. The reaction mixture was stirred for 3 h at room temperature. The mixture was diluted with diethyl ether (50 mL) and quenched with the dropwise addition of water (100 mL). The mixture was acidified with conc. sulfuric acid and then basified with sodium hydroxide (6.0 M). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford **2.22** (15.09 g, 75.5 mmol, 98%)[19] as a colourless oil.



2.22

IR (FT): ν_{max} = 3341, 3290, 2933, 1539, 1332, 677 cm^{-1}.

1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8 Hz, 1 H, H-3), 7.16–7.13 (m, 2 H, H-4/H-5), 6.97 (m, 1 H, H-6), 2.90 (m, 2 H, C*H*$_2$$NH_2$), 2.81 (m, 2 H, CH_2Ar), 1.80 (br., exch., 2 H, NH_2).

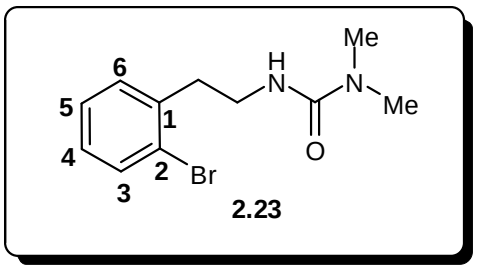
^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0 (s, C-1), 132.9 (d, C-3), 130.8 (d, C-6), 127.9 (d, C-4), 127.4 (d, C-5), 124.7 (s, C-2), 42.0 (t, CH_2NH_2), 40.2 (t, CH_2Ar).

MS (EI): *m/z* (%) = 578 (100), 410 (37), 202 (58, $M^{81}Br$), 200 (60, $M^{79}Br$), 184 (20).

HRMS (EI): *m/z* calc. for $C_8H_{10}N^{79}Br$ $[M]^+$, 200.0075; found, 200.0077.

2.14.5 Synthesis of *N′*-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (2.23)

The procedure was identical with that described for the synthesis of **2.10** in which a stirred mixture of **2.22** (8.00 g, 40.0 mmol), DMCC (5.16 g, 48.0 mmol) and Et_3N (6.07 g, 60.0 mmol) in DCM (60 mL) was heated under reflux for 1 h. Following workup, the crude product was purified by column chromatography (silica gel; Et_2O) to give pure **2.23** (10.73 g, 39.7 mmol, 99%) as a yellow oil.



2.23

IR (FT): ν_{max} = 3333, 2931, 1633, 1537, 1356 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8 Hz, 1 H, H-3), 7.16–7.19 (m 2 H, H-4/H-5), 7.01 (m, 1 H, H-6), 4.43 (br., exch., 1 H, NH), 3.41 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.90 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 138.9 (s, C-1), 132.7 (d, C-3), 131.0 (d, C-6), 128.0 (d, C-4), 127.5 (d, C-5), 124.5 (s, C-2), 40.7 (t, CH_2NH_2), 36.5 (t, *C*H_2Ar), 36.1 [q, $N(CH_3)_2$].

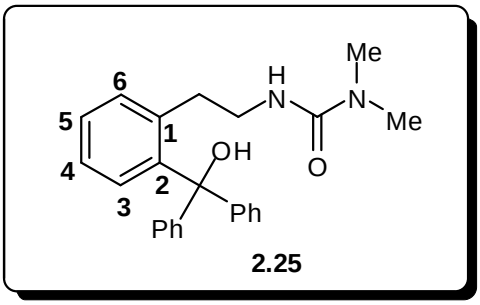
MS (EI): *m/z* (%) = 273 (4, $[M^{81}Br + H]^+$), 271 (4, $[M^{79}Br + H]^+$), 192 (100, $[M - {}^{79}Br]^+$), 171 (98), 146 (10), 101 (97).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{16}{}^{79}BrN_2O$: 271.0446; found: 271.0441.

2.14.6 Bromine-lithium exchange and substitution of *N′*-(2-(2-bromophenyl)ethyl)-*N*,*N*-dimethylurea: synthesis of *N′*-(2-(2-substituted phenyl)ethyl)-*N*,*N*-dimethylureas 2.25–2.29; general procedure

A solution of MeLi in Et_2O (1.38 mL, 1.60 M, 2.2 mmol) was added to a stirred solution of **2.23** (0.50 g, 1.8 mmol) at –78 °C in anhydrous THF (20 mL) under a N_2 atmosphere. The mixture was stirred for 10 min to give the monolithium reagent **2.24** after which a solution of *t*-BuLi in pentane (2.42 mL, 1.90 M, 4.6 mmol) was added. The mixture was stirred at –78 °C for 15 min to give the dilithium reagent **2.20** and a solution of the electrophile (7.4 mmol), in anhydrous THF (8 mL) if solid, neat otherwise, was added. The cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. The mixture was quenched with a saturated aqueous NH_4Cl (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **2.25**–**2.29**. The yields obtained were in the range of 86–98% (Table 2.3).

N′-[2-(Hydroxydiphenylmethyl)-2-phenyl]ethyl-*N*,*N*-dimethylurea (2.25)



2.25

From benzophenone (1.35 g, 7.4 mmol); yield: 0.65 g (1.7 mmol, 95%); white solid; mp 186–188 °C.

IR (FT): ν_{max} = 3348, 2925, 1624, 1541, 1334 cm^{-1}.

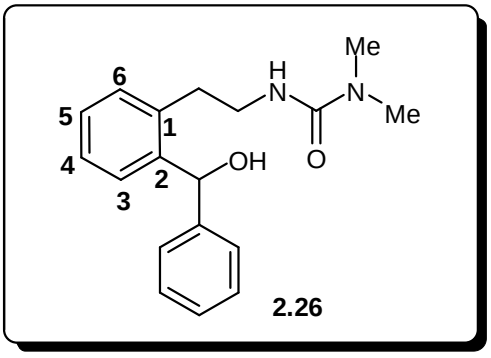
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 13 H, 2 C_6H_5, H-3, H-5 and OH), 7.02 (m, 1 H, H-4), 6.63 (d, *J* = 8 Hz, 1 H, H-6), 4.93 (br., exch., 1 H, NH), 3.37 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.81 [s, 6 H, N(CH_3)$_2$], 2.68 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 147.6 (s, C-1 of 2 C_6H_5), 145.4 (s, C-2), 139.2 (s, C-1), 131.8 (d, C-6), 130.0 (d, C-4), 127.81 (d, C-2/C-6 of 2 C_6H_5), 127.83 (d, C-3/C-5 of 2 C_6H_5), 127.6 (d, C-5), 127.0 (d, C-4 of 2 C_6H_5), 125.2 (d, C-3), 82.9 (s, COH), 42.5 (t, CH_2NH_2), 36.0 [q, N(CH_3)$_2$], 34.3 (t, *C*H$_2$Ar).

MS (EI): *m/z* (%) = 356 (90, [M – H_2O]$^+$), 312 (20), 279 (97), 255 (65), 191 (40), 178 (100), 165 (68), 105 (90).

HRMS (EI): *m/z* [M – H_2O]$^+$ calcd for $C_{24}H_{24}N_2O$: 356.1889; found: 356.1892.

N′-2-{2-[Hydroxy(phenyl)methyl]phenyl}ethyl-*N*,*N*-dimethylurea (2.26)



From benzaldehyde (0.78 g, 7.4 mmol); yield: 0.49 g (1.7 mmol, 90%); white solid; mp 145–148 °C.

IR (FT): ν_{max} = 3325, 2932, 1626, 1537, 1358 cm^{-1}.

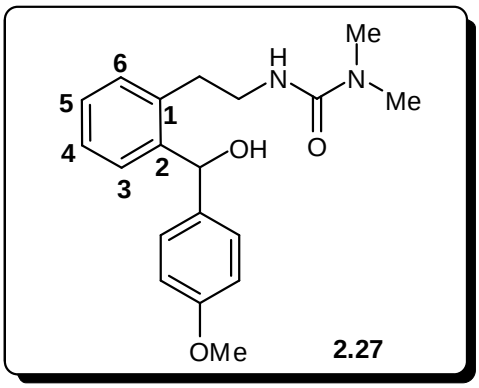
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.17 (m, 10 H, H-3, H-4, H- 5, H-6, C_6H_5 and OH), 6.17 (s, 1 H, C*H*OH), 4.66 (br., exch., 1 H, NH), 3.52–3.39 (m, 2 H, C*H*$_2$NH), 3.04 (m, 1 H, C*H*$_a$H$_b$Ar), 2.83 [s, 6 H, N(CH_3)$_2$], 2.79 (m, 1 H, CH$_a$*H*$_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 143.7 (s, C-1 of C_6H_5), 142.2 (s, C-1), 137.1 (s, C-2), 130.2 (d, C-6), 128.3 (d, C-3), 128.2 (d, C-3/C-5 of C_6H_5), 127.6 (d, C-4), 127.2 (d, C-4 of C_6H_5), 126.74 (d, C-5), 126.73 (d, C-2/C-6 of C_6H_5), 72.6 (d, CHOH), 42.0 (t, CH_2NH_2), 36.1 [q, N(CH_3)$_2$], 33.5 (t, *C*H$_2$Ar).

MS (ES$^-$): *m/z* (%) = 335 (40), 333 (100, [M + Cl]$^-$), 319 (1).

HRMS (ES$^-$): *m/z* [M + Cl]$^-$ calcd for $C_{18}H_{22}{}^{35}ClN_2O_2$: 333.1370; found: 333.1384.

_N′_-2-{2-[Hydroxy(4-methoxyphenyl)methyl]phenyl}ethyl-_N_,_N_dimethylurea (2.27)



From 4-methoxybenzaldehyde (1.00 g, 7.4 mmol); yield: 0.52 g (1.6 mmol, 87%); white solid; mp 149–151 °C.

IR (FT): ν_{max} = 3437, 2930, 1640, 1509, 1390 cm^{-1}.

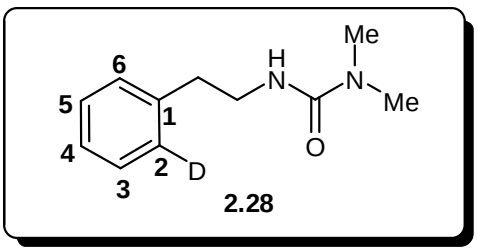
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 7 H, H-3, H-4, H-5, H-6, H-2/H-6 of 4-$CH_3OC_6H_4$ and OH), 6.87 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 6.11 (s, 1 H, C*H*OH), 4.63 (br., exch., 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.48–3.40 (m, 2 H, CH_2NH), 3.01 (m, 1 H, C$H_a$$H_b$Ar), 2.83 [s, 6 H, N$(CH_3)_2$], 2.79 (m, 1 H, $CH_a$$H_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8 (s, C-4 of 4-$CH_3OC_6H_4$), 158.6 (s, C=O), 142.3 (s, C-1), 137.0 (s, C-1 of 4-$CH_3OC_6H_4$), 135.9 (s, C-2), 130.2 (d, C-6), 128.0 (d, C-2/C-6 of 4-$CH_3OC_6H_4$), 127.9 (d, C-3), 127.5 (d, C-4), 126.6 (d, C-5), 113.7 (d, C-3/C-5 of 4-$CH_3OC_6H_4$), 72.3 (d, CHOH), 55.2 (q, OCH_3), 41.9 (t, CH_2NH_2), 36.1 [q, N$(CH_3)_2$], 33.3 (t, CH_2Ar).

MS (ES^-): *m/z* (%) = 365 (38), 363 (100, $[M + Cl]^-$), 349 (1).

HRMS (ES^-): *m/z* $[M + Cl]^-$ calcd for $C_{19}H_{24}{}^{35}ClN_2O_3$: 363.1475; found: 363.1480.

_N′_-(2-(2-Deuteriophenyl)ethyl)-_N_,_N_-dimethylurea (2.28)



From D_2O (0.15 g, 7.4 mmol); yield: 0.34 g (1.8 mmol, 98%); white solid; mp 89–91 °C (undeuterated analogue mp: Lit.[18a] 81–82 °C; Lit.[18b] 98 °C).

IR (FT): ν_{max} = 3337, 2929, 1634, 1539, 1357 cm^{-1}.

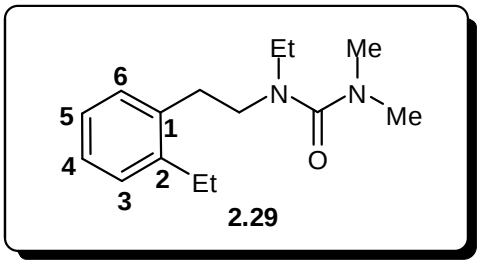
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 4 H, H-3, H-4, H-5 and H-6), 4.46 (br., exch., 1 H, NH), 3.49 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.85 [s, 6 H, N(C*H*$_3$)$_2$], 2.83 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 139.4 (s, C-1), 128.8 (d, C-5), 128.54 (d, C-3), 128.52 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.4 (d, C-6), 126.3 (d, C-4), 42.1 (t, CH_2NH), 36.4 (t, *C*H$_2$Ar), 36.0 [q, N(C*H*$_3$)$_2$].

MS (EI): *m/z* (%) = 193 (90, $[M]^+$), 148 (28), 101 (93), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{15}DN_2O$: 193.1325; found: 193.1329.

N′-Ethyl-N′-(2-(2-ethylphenyl)ethyl)-N,N-dimethylurea (2.29)



2.29

From iodoethane (1.15 g, 7.4 mmol); yield: 0.39 g (1.6 mmol, 86%); yellow oil.

IR (FT): ν_{max} = 2965, 1646, 1489, 1354 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12–7.02 (m, 4 H, H-3, H-4, H-5 and H-6), 3.20 (t, *J* = 7 Hz, 2 H, ArCH$_2$C*H*$_2$N), 3.13 (q, *J* = 7 Hz, 2 H, CH$_3$C*H*$_2$N), 2.77 (t, *J* = 7 Hz, 2 H, ArC*H*$_2$CH$_2$N), 2.73 [s, 6 H, N(C*H*$_3$)$_2$], 2.62 (q, *J* = 7 Hz, 2 H, ArC*H*$_2$CH$_3$), 1.16 (t, *J* = 7 Hz, 3 H, C*H*$_3$CH$_2$N), 1.04 (t, *J* = 7 Hz, 3 H, ArCH$_2$C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (s, C=O), 142.2 (s, C-1), 137.1 (s, C-2), 129.7 (d, C-6), 128.4 (d, C-3), 126.5 (d, C-4), 125.8 (d, C-5), 48.9 (t, ArCH$_2$*C*H$_2$N), 43.5 (t, CH$_3$*C*H$_2$N), 38.6 [q, N(CH$_3$)$_2$], 31.2 (t, Ar*C*H$_2$CH$_2$N), 25.4 (t, Ar*C*H$_2$CH$_3$), 15.5 (q, ArCH$_2$*C*H$_3$), 13.3 (q, *C*H$_3$CH$_2$N).

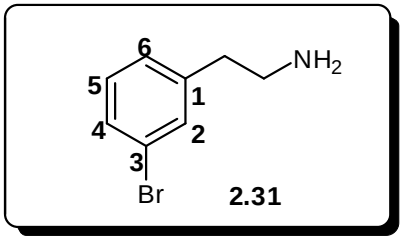
MS (ES): *m/z* (%) = 519 (100, $[2\ M + Na]^+$), 312 (50, $[M + MeCNNa]^+$), 287 (5, $[M + K]^+$), 271 (23, $[M + Na]^+$), 249 (15, $[MH]^+$).

HRMS (ES): *m/z* $[MH]^+$ calcd for $C_{15}H_{25}N_2O$: 249.1967; found: 249.1959.

2.14.7 Synthesis of 2-(3-bromophenyl)ethylamine (2.31)[24]

Compound **2.31** was synthesised based on a literature procedure[19] and the reaction was carried out with caution in an open flask. A solution of lithium aluminium hydride (27.20 ml, 56.3 mmol, 2.4 M) in anhydrous Et_2O (30 mL) was cooled at 0 °C.

Concentrated sulfuric acid (1.60 ml, 28.2 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at 0 °C. A solution of 2-(3-bromophenyl)acetonitrile (**2.30**; 5.00 g, 25.6 mmol) in anhydrous Et_2O (10 mL) was added dropwise and the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The mixture was cooled back to 0 °C and quenched with the dropwise addition of water (25 mL) followed by a solution of sodium hydroxide (3.0 M, 18 mL). The mixture was filtered through celite and the solid was washed with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford pure **2.31** (5.00 g, 25.1 mmol, 98%) as an oil.[24]



FT–IR: ν_{max} = 3371, 3283, 2933, 1492, 1335, 671 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.26 (m, 2 H, H-2/H-4), 7.11–7.04 (m, 2 H, H-5/H-6), 2.88 (t, *J* = 7 Hz, 2 H, C*H*$_2$$NH_2$), 2.64 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 1.33 (br., exch., 2 H, NH_2).

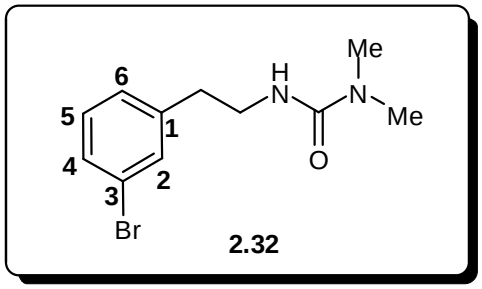
^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.2 (s, C-1), 132.0 (d, C-2), 129.9 (d, C-4), 129.3 (d, C-6), 127.4 (d, C-5), 122.5 (s, C-3), 43.3 (t, *C*$H_2$$NH_2$), 39.7 (t, *C*$H_2$Ar).

MS (ES^+): *m/z* (%) = 201 ([$M^{81}Br$] $^+$, 35), 199 ([$M^{79}Br$] $^+$, 41), 186 (30), 184 (34), 171 (55), 169 (57), 86 (100), 84 (98).

HRMS (ES^+): *m/z* calc. for $C_8H_{10}N^{79}Br$ (M^+), 198.9997; found, 198.9991.

2.14.8 Synthesis of *N′*-(2-(3-bromophenyl)ethyl)-*N*,*N*-dimethylurea (2.32)

The procedure was identical to that described for the synthesis of **2.10** except that it involved stirring a mixture of **2.31** (5.00 g, 25.1 mmol), DMCC (3.24 g, 30.1 mmol), and Et_3N (3.81 g, 37.7 mmol) in DCM (30 mL) under reflux for 1 h. Following workup, the crude product was purified by crystallisation from a mixture of hexane and Et_2O (3:1 by volume) to give pure **2.32** (6.65 g, 24.6 mmol, 98%) as a white crystalline solid.



2.32

mp 62–64 °C.

IR (FT): ν_{max} = 3337 2928, 1635, 1538, 1356, 676 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 2 H, H-2/H-4), 7.20–7.13 (m, 2 H, H-5/H-6), 4.42 (br., exch., 1 H, NH), 3.47 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.88 [s, 6 H, $N(CH_3)_2$], 2.80 (t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2 (s, C=O), 141.9 (s, C-1), 131.9 (d, C-2), 130.1 (d, C-4), 129.4 (d, C-6), 127.5 (d, C-5), 122.5 (s, C-3), 41.9 (t, CH_2NH), 36.2 [q, $N(CH_3)_2$], 36.1 (t, CH_2Ar).

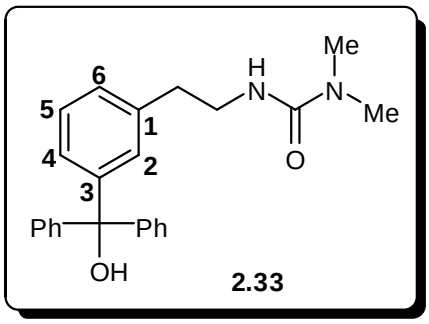
MS (ES^+): *m/z* (%) = 272 ($[M^{81}Br]^+$, 100), 270 ($[M^{79}Br]^+$, 98), 227 (12), 225 (14).

HRMS (ES^+): *m/z* $[M]^+$ calcd for $C_{11}H_{15}{}^{79}BrN_2O$: 270.0368; found: 270.0359.

2.14.9 Bromine–lithium exchange and substitution of *N′*-(2-(3-bromophenyl)ethyl)-*N*,*N*-dimethylurea (2.32)

The procedure was identical with that described for the bromine–lithium exchange of **2.23** except that it involved **2.32** (0.36 g, 1.3 mmol). Following workup the crude product was purified by column chromatography (silica gel; Et_2O) to give the pure products **2.15** (85%) and **2.33** (13%). Product **2.15** was consistent in all respect with the one produced by direct lithiation of **2.10** followed by reaction with benzophenone. The yield of product **2.33** was improved to 58% after purification by column chromatography when a shorter reaction time (5 minutes) was applied to the lithiation step.

N′-(2-[3-(Hydroxydiphenylmethyl)phenyl]ethyl)-*N*,*N*-dimethylurea (2.33)



2.33

Yield: 0.065–0.29 g (0.17–0.77 mmol, 13–58%); white solid; mp 174–176 °C.

IR (FT): ν_{max} = 3348, 2930, 1634, 1532, 1357, 1032 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.13 (m, 12 H, 2 C_6H_5, H-5 and OH), 7.12 (s, 1 H, H-2), 7.01–6.99 (m, 2 H, H-4/H-6), 4.20 (br., exch., 1 H, NH), 3.35 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.69 [s, 6 H, N(CH_3)$_2$], 2.68 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 147.2 (s, C-3), 146.9 (s, C-1 of 2 C_6H_5), 139.2 (s, C-1), 128.2 (d, C-5), 128.0 (d, C- 2), 127.95 (d, C-3/C-5 of 2 C_6H_5), 127.90 (d, C-2/C-6 of 2 C_6H_5), 127.4 (d, C-4), 127.3 (d, C-4 of 2 C_6H_5), 126.2 (d, C-6), 81.9 (s, COH), 42.0 (t, CH_2NH), 36.5 (t, CH_2Ar), 36.0 [q, N(CH_3)$_2$].

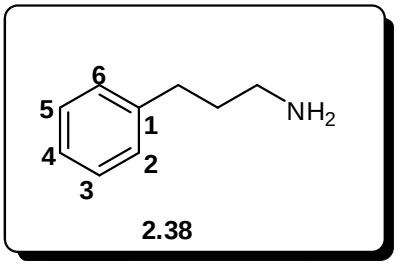
MS (ES^+): *m/z* (%) = 375 ($[M + H]^+$, 4), 357 ($[M – OH]^+$, 80), 193 (100), 142 (10), 104 (18).

HRMS (ES^+): *m/z* calcd for $C_{24}H_{25}N_2O$ ($[M – OH]^+$), 357.1967; found, 357.1978.

2.14.10 Synthesis of (ω-phenylalkyl)amines 2.38 and 2.39

The procedure was identical with that described for the synthesis of **2.31** except that a stirred mixture of **2.36** (10.0 g, 76.3 mmol) or **2.37** (10.0 g, 68.9 mmol) with a mixture of lithium aluminium hydride and sulfuric acid at room temperature for 3 h and 1 h, respectively. Following work-up the crude product was purified by column chromatography (silica gel; Et_2O) to give pure products.

_N′_-(3-phenylpropyl)amine (2.38)



2.38

Yield: 9.80 g (72.5 mmol, 95%) white crystals; mp 69–73 °C.

FT–IR: ν_{max} = 3295, 2930, 1495, 1386 cm^{-1}.

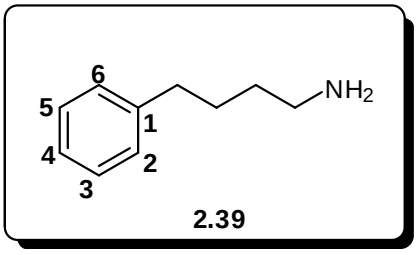
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.19 (m, 2 H, H-3/H-5), 7.12–7.10 (m, 3 H, H-2/H-6 and H-4), 2.66 (t, *J* = 7 Hz, 2 H, C*H*$_2$$NH_2$), 2.59 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 1.71 (pentet, *J* = 7 Hz, 2 H, C*H*$_2$$CH_2NH_2$), 1.45 (br., exch., 2 H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.1 (s, C-1), 128.39 (d, C-3/C-5), 128.36 (d, C-2/C-6), 125.8 (d, C-4), 41.7 (t, CH_2NH_2), 35.3 (t, *C*$H_2C_6H_5$), 33.2 (t, *C*$H_2CH_2NH_2$).

MS (EI): *m/z* (%) = 135 ($[M]^+$, 14), 118 (100), 103 (19), 91 (85), 83 (58), 77 (28), 65 (21).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_{13}N$: 135.1048; found: 135.1052.

_N′_-(4-Phenyl)butyl amine (2.39)



2.39

Yield: 9.85 g (66.1 mmol, 96%); colourless oil

FT–IR: ν_{max} = 3283, 2929, 1495, 1388 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.17 (m, 2 H, H-3/H-5), 7.10–7.07 (m, 3 H, H-2/H-6 and H-4), 2.62 (t, *J* = 7 Hz, 2 H, C*H*$_2$$NH_2$), 2.54 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 1.66 (br., exch., 2 H, NH_2), 1.60–1.53 (m, 2 H, C*H*$_2$$CH_2$Ar), 1.44–1.35 (m, 2 H, C*H*$_2$$CH_2NH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.4 (s, C-1), 128.4 (d, C-3/C-5), 128.3 (d, C-2/C-6), 125.7 (d, C-4), 42.0 (t, *C*H_2NH_2), 35.8 (t, *C*$H_2C_6H_5$), 33.2 (t, *C*$H_2CH_2NH_2$), 28.7 (t, *C*$H_2CH_2C_6H_5$).

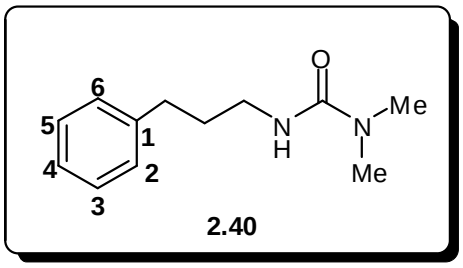
MS (EI): *m/z* (%) = 149 ([M]$^+$, 45), 132 (15), 117 (19), 104 (33), 91 (54), 86 (95), 83 (100), 77 (13), 65 (17).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{10}H_{15}N$: 149.1204; found: 149.1201.

2.14.11 Synthesis of *N′*-(ω-phenylalkyl)-*N*,*N*-dimethylureas 2.40 and 2.41

The procedure was identical with that described for the synthesis of **2.10** except that a stirred mixture of **2.38** or **2.39** (63.7 mmol), DMCC (8.22 g, 76.5 mmol) and Et_3N (9.67 g, 95.6 mmol) in DCM (50 mL) was heated under reflux for 1 h. Following work-up the crude product was purified by column chromatography (silica gel; Et_2O) to give pure products.

_N′_-(3-Phenylpropyl)-_N_,_N_-dimethylurea (2.40)



2.40

Yield: 12.36 g (60.0 mmol, 94%); white crystals; mp 72–74 °C.

IR (FT): ν_{max} = 3374, 2934, 1630, 1496, 1379 cm^{-1}.

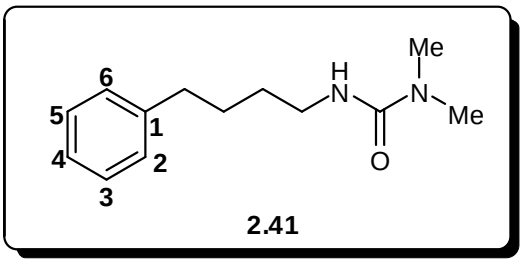
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.14 (m, 2 H, H-3/H-5), 7.0–7.05 (m, 3 H, H-2,/H-6 and H-4), 4.61 (br., exch., 1 H, NH), 3.15 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.71 [s, 6 H, N(CH$_3$)$_2$], 2.54 (t, *J* = 7 Hz, 2 H, C*H*$_2$C$_6$H$_5$), 1.74 (app. pentet, *J* = 7 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5 (s, C=O), 141.9 (s, C-1), 128.38 (d, C-3/C-5), 128.36 (d, C-2/C-6), 125.8 (d, C-4), 40.7 (t, *C*H$_2$NH$_2$), 36.0 [q, N(CH$_3$)$_2$], 33.5 (t, *C*H$_2$C$_6$H$_5$), 31.9 (t, CH$_2$*C*H$_2$CH$_2$).

MS (EI): *m/z* (%) = 206 ([M]$^+$, 47), 162 (49), 117 (49), 102 (47), 91 (69), 72 (100).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{12}H_{18}N_2O$: 206.1419; found: 206.1418.

***N′*-(4-Phenylbutyl)-*N*,*N*-dimethylurea (2.41)**



2.41

Yield: 12.63 g (57.4 mmol, 90%); yellow oil.

IR (FT): ν_{max} = 3340, 2931, 1627, 1453, 1377 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.13 (m, 2 H, H-3/H-5), 7.06–7.03 (m, 3 H, H-2/H-6 and H-4), 4.72 (br., exch., 1 H, NH,), 3.10 (app. q, *J* = 8 Hz, 2 H, C*H*$_2$NH), 2.74 [s, 6 H, N(CH_3)$_2$], 2.51 (t, *J* = 8 Hz, 2 H, C*H*$_2$$C_6H_5$), 1.53 (m, 2 H, C*H*$_2$$CH_2C_6H_5$), 1.42 (m, 2 H, C*H*$_2$$CH_2NH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 142.3 (s, C-1), 128.3 (d, C-3/C-5), 128.2 (d, C-2/C-6), 125.7 (d, C-4), 40.7 (t, *C*H_2NH_2), 36.1 [q, N(CH_3)$_2$], 35.6 (t, *C*$H_2C_6H_5$), 33.0 (t, *C*$H_2CH_2NH_2$), 28.7 (t, *C*$H_2CH_2C_6H_5$).

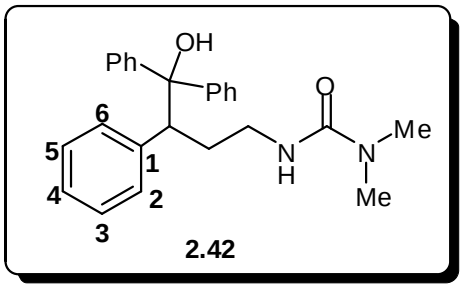
MS (EI): *m/z* (%) = 220 ($[M]^+$, 54), 175 (54), 146 (15), 130 (35), 116 (94), 104 (90), 91 (100), 72 (97).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1580.

2.14.12 Lithiation and substitution of *N′*-(ω-phenylalkyl)-*N*,*N*-dimethylureas 2.40 and 2.41

The procedure was identical with that described for lithiation and substitution of **2.10** except involving **2.40** or **2.41** (2.6 mmol) with benzophenone (0.52 g, 2.9 mmol) as the electrophile and carried out at 0 or 20 °C (See Section **2.12** for temperature details). Following work-up, the crude product was purified by column chromatography (silica gel; Et_2O) to give the pure products **2.42** or **2.43**.

N′-(4-Hydroxy-3,4,4-triphenylbutyl)-*N*,*N*-dimethylurea (2.42)



2.42

Yield: 0.86–0.89 g (2.2–2.3 mmol, 85–89%); white solid; mp 229–231 °C.

IR (FT): ν_{max} = 3349, 2928, 1636, 1492, 1360 cm^{-1}.

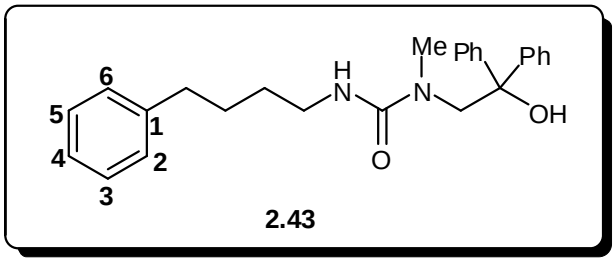
^1H NMR (500 MHz, $CDCl_3$): δ = 7.53–6.91 (m, 16 H, 3 C_6H_5 and OH), 4.00 (br., exch., 1 H, NH), 3.73 (dd, *J* = 3, 11 Hz, 1 H, CH), 3.14 (m, 1 H, C$H_a$$H_b$NH), 3.03 (m, 1 H, $CH_a$$H_b$NH), 2.61 [s, 6 H, $N(CH_3)_2$], 2.06–1.92 (m, 2 H, CH_2CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C=O), 145.9, 145.8 (2 s, C-1 of 2 C_6H_5), 140.0 (s, C-1), 130.5, 128.4 (2 d, C-3/C-5 of 2 C_6H_5), 128.0, 127.7 (2 d, C-2/C-6 of 2 C_6H_5), 126.9 (d, C-3/C-5), 126.7 (d, C-2/C-6), 126.2 (d, C-4 and C-4 of one C_6H_5), 125.7 (d, C-4 of other C_6H_5), 81.0 (s, C–OH), 52.6 (d, CH), 40.2 (t, *C*H_2NH), 36.0 [q, $N(CH_3)_2$], 31.1 (t, *C*H_2CH).

MS (EI): *m/z* (%) = 370 (5, $[M - H_2O]^+$), 325 (28), 269 (30), 207 (53), 194 (90), 182 (93), 152 (46), 105 (100), 77 (97).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O$: 370.2045; found: 370.2034.

N′-(2-Hydroxy-2,2-diphenylethyl)-*N′*-methyl-*N*-(4-phenylbutyl)urea (2.43)



2.43

Yield: 0.93 g (2.3 mmol, 89%); yellow oil.

IR (FT): ν_{max} = 3348, 2934, 1621, 1543, 1318 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 1, 8 Hz, 4 H, H-2/H-6 of 2 C_6H_5), 7.18–7.03 (m, 11 H, H-2, H-3, H-4, H-5, H-6 and H-3/H-5 and H-4 of 2 C_6H_5), 6.05 (s, exch., 1 H, OH,), 4.34 (br., exch., 1 H, NH), 3.98 (s, 2 H, CH_2COH), 3.11 (app. q, *J* = 8 Hz, 2

H, C*H*$_2$NH), 2.51 (t, *J* = 8 Hz, 2 H, C*H*$_2$C$_6$H$_5$), 2.17 (s, 3 H, NCH$_3$), 1.51 (m, 2 H, C*H*$_2$CH$_2$C$_6$H$_5$), 1.39 (m, 2 H, C*H*$_2$CH$_2$NH).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.7 (s, C=O), 145.8 (s, C-1 of 2 C$_6$H$_5$), 142.2 (s, C-1), 128.4 (d, C-3/C-5), 128.3 (d, C-2/C-6), 128.0 (d, C-3/C-5 of 2 C$_6$H$_5$), 126.9 (d, C-4 of 2 C$_6$H$_5$), 126.6 (d, C-2/C-6 of 2 C$_6$H$_5$), 125.8 (d, C-4), 78.6 (s, COH), 61.0 (t, *C*H$_2$COH), 40.9 (t, CH$_2$NH), 36.9 (t, *C*H$_2$C$_6$H$_5$), 35.5 (q, NCH$_3$), 29.8 (t, *C*H$_2$CH$_2$NH$_2$), 28.5 (t, *C*H$_2$CH$_2$C$_6$H$_5$).

MS (EI): *m/z* (%) = 403 ([M + H]$^+$, 100), 385 (98), 305 (25), 234 (25), 210 (59), 191 (68).

HRMS (EI): *m/z* [M]$^+$ calcd for C$_{26}$H$_{31}$N$_2$O$_2$: 403.2386; found: 403.2402.

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Chapter Three

Lithiation of 2-(2-Methylphenyl)ethanamine Derivatives

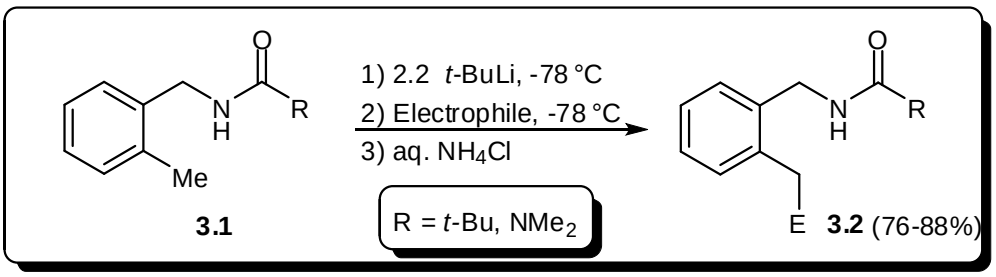
Chapter Three

Lithiation of 2-(2-Methylphenyl)ethanamine Derivatives

3.1 Introduction

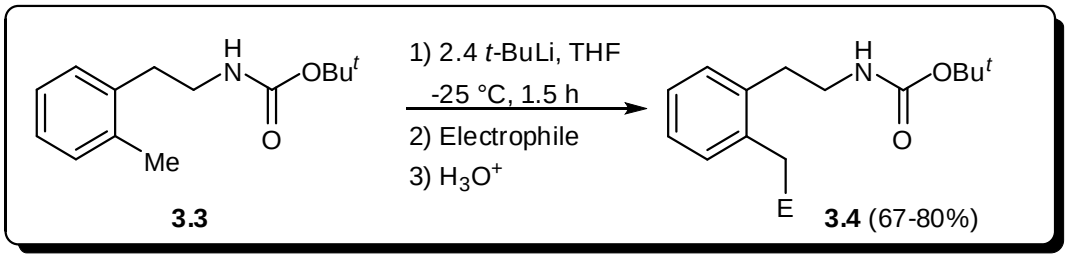
As indicated in Chapter 2, organolithium reagents produced *in situ* in lithiation reactions play a reliable and efficient role in functionalizing a broad-range of aromatic and/or heterocyclic systems regioselectively.[1–4] Lateral (benzylic) lithiation of alkyl groups that are *ortho*- to a directing metalating group (DMG) is a well-known example of such methodology in organic synthesis.[1,5] Such lateral lithiation of benzenoid systems is encouraged by a stabilizing group capable of delocalizing a negative charge, stabilizing the organolithium by coordination, or acidifying the benzylic proton by an electron-withdrawing inductive effect.[1,5] For example, lateral lithiation of *N*-(2-methylphenyl)pivalamide was achieved by the use of *n*-butyllithium (*n*-BuLi; 2.0 molar equivalents) at 0 °C in THF and reactions of the dilithium reagents produced *in situ* with electrophiles gave the corresponding substituted derivatives in high yields.[6] However, lateral lithiation of *N'*-(2-methylphenyl)-*N*,*N*-dimethylurea has never been reported.

The Smith research group has studied lateral lithiation and substitution of several simple substituted aromatics and heterocycles.[7,8] For example, lateral lithiations of *N*-(2-methylbenzyl)pivalamide and *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea **3.1** were achieved by the use of *tert*-butyllithium (*t*-BuLi; 2.2 equivalents) at −78 °C to provide the corresponding dilithium reagents, which on reaction with various electrophiles gave the corresponding 2-substituted derivatives **3.2** in high yields (Scheme 3.1).[8]



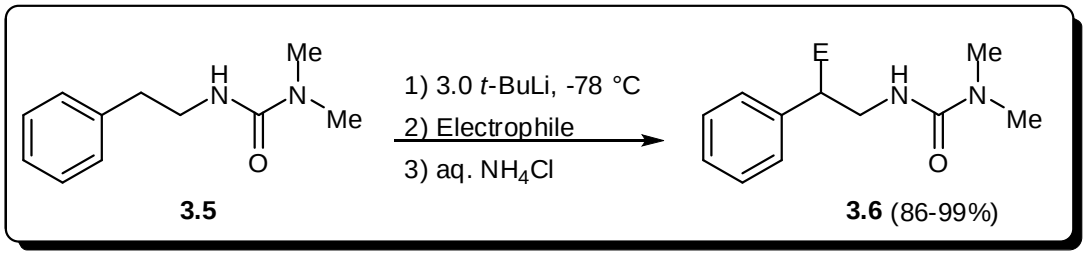
Scheme 3.1 Lateral lithiation and substitution of 2-methylbenzyl derivatives **3.1**

Lateral lithiation of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**3.3**) with *t*-BuLi (2.4 equivalents) at –60 °C has been reported by Clark.[9] The dilithium reagent obtained was allowed to react with iodomethane and carbon dioxide (in the presence of CH_2N_2) as electrophiles at *ca*. –25 to –30 °C to give the corresponding substituted products **3.4** (Scheme 3.2) in 80 and 67% yields, respectively.[9] However, there are no reports of lithiation and substitution of *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea or *N*-(2-(2-methylphenyl)ethyl)pivalamide.



Scheme 3.2 Lateral lithiation of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**3.3**)

In Chapter Two, we showed that lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea (**3.5**), with three equivalents of *t*-BuLi in anhydrous THF at –78 °C took place on the nitrogen and on the CH_2 next to the phenyl ring (Scheme 3.3). Reactions of the dilithium reagent produced *in situ* with various electrophiles gave the corresponding substituted derivatives **3.6** in excellent yields (Scheme 3.3). However, ring lithiation was achieved *via* bromine lithium exchange of bromo derivatives. Such work has been published.[10]



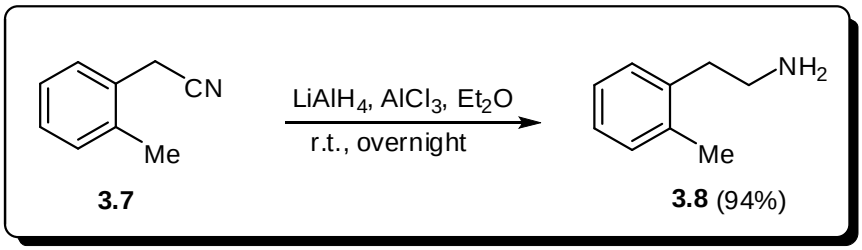
Scheme 3.3 Lithiation and substitution of *N*′-phenethyl-*N*,*N*-dimethylurea (**3.5**)

The aim of the work presented in this chapter was to synthesise *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**) and *N*-(2-(2-methylphenyl)ethyl)-pivalamide (**3.18**) and investigate their lithiation reactions to see what effect the extra

CH_2 could have on the site of lithiation compared with **3.1** (Scheme 3.1) and also, to compare between the lithiation results of these substrates with the early results produced by Clark[9] for lithiation and substitution of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**3.3**; Scheme 3.2).

3.2 Synthesis of 2-(2-methylphenyl)ethylamine (3.8)

The first task was to synthesis 2-(2-methylphenyl)ethylamine (**3.8**) from the corresponding nitrile **3.7** based on the literature procedure used in Chapter Two for an analogous compound (Section 2.4).[11] Reduction of 2-(2-methylphenyl)acetonitrile (**3.7**) was carried out with lithium aluminium hydride (2.2 equivalents) in presence of aluminium chloride (0.75 equivalents) in diethyl ether at room temperature overnight. Following work-up, essentially pure **3.8** was obtained in 94% yield (Scheme 3.4). No purification was necessary for the crude product.



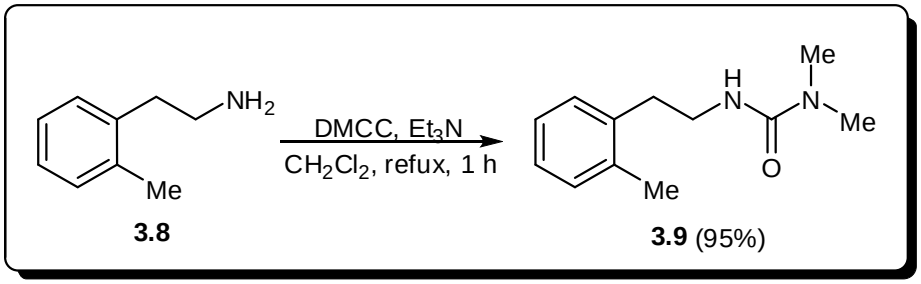
Scheme 3.4 Synthesis of 2-(2-methylphenyl)ethylamine **(3.8)**

The structure of compound **3.8** was confirmed by various spectroscopic techniques (see Section 3.10.2). Our attention was next turned to synthesis of the corresponding urea derivative **3.9**.

3.3 Synthesis of *N'*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (3.9)

N'-(2-(2-Methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**) was synthesized using a literature procedure for analogous compounds.[8,10] Reaction of 2-(2-methylphenyl)ethanamine (**3.8**) with dimethylcarbamoyl chloride (DMCC) in dichloromethane (DCM) in the presence of triethylamine (TEA) as base was carried out under reflux for 1 h. The crude product obtained after work-up was recrystallized from a

mixture of ethyl acetate and diethyl ether (1:3 by volume) to give pure **3.9** in 95% yield (Scheme 3.5).



3.8 **3.9** (95%)

Scheme 3.5 Synthesis of *N′*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**)

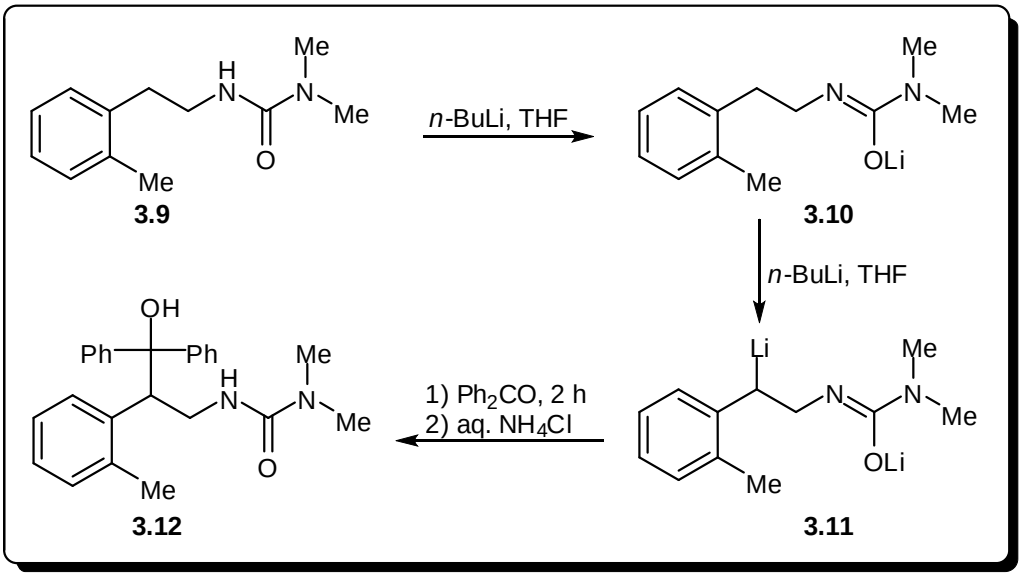
The electron–impact mass spectrum of **3.9** showed an intense molecular ion peak at *m/z* = 206 and the high resolution mass analysis of this peak confirmed the formula as $C_{12}H_{18}N_2O$ (M). Also, the structure of **3.9** was confirmed by its NMR spectral data (see Section 3.10.3 for details).

Having successfully produced **3.9** our attention was next turned to attempt its lithiation and substitution under various reaction conditions.

3.4 Lithiation and substitution of *N′*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (3.9)

Initially the reaction of **3.9** with *n*-BuLi (2.2 equivalents) was carried out in anhydrous THF under a nitrogen atmosphere at –78 °C. Initial addition of *n*-BuLi provided a pale yellow solution, presumably because of formation of the monolithium reagent **3.10** (Scheme 3.6), until approximately one equivalent had been added, then gave a deep yellow solution as the remaining *n*-BuLi was added, presumably because of formation of a dilithium reagent. The mixture was stirred for 2 h at –78 °C. Benzophenone (1.2 equivalents) was added and the mixture was stirred for another 2 h at -78 °C and then quenched by the addition of aqueous ammonium chloride solution. Following work-up the crude product was tested by TLC and showed the formation of a new product along with the starting material **3.9**. The crude mixture was purified by column chromatography to give the starting material **3.9** in 80% yield along with a new product. The new product was subjected to NMR and mass spectral analysis. The ^{1}H NMR spectrum of the new compound showed the presence of fourteen aromatic

protons, indicating that lithiation followed by substitution with benzophenone had taken place. Also, it showed the presence of two exchangeable protons, a six proton signal for the methyl groups of the urea unit, a three proton methyl group and three other aliphatic CH signals. Clearly, lithiation followed by substitution had taken place on one of the CH_2 groups (side-chain lithiation), since all the original aromatic protons were still present, as were the three protons of the methyl group attached to the aromatic ring, whereas one of the protons of the side-chain had been lost. The ^{13}C NMR spectrum, in connection with DEPT spectra, indicated the presence of a CH carbon, which resonated at 48 ppm, and a CH_2 carbon, which resonated at 42.6 ppm. ChemDraw calculations for the two isomeric structures involving substitution at the CH_2 group next to the aromatic ring or next to the NH group suggested that lithiation has taken place on the CH_2 next to the 2-methylphenyl ring (ChemDraw prediction that CH should resonate at 52 ppm and CH_2 at 38 ppm) rather than the one next to NH (ChemDraw prediction that CH next to NH should resonate in the region of 68 ppm and the CH_2 group around 30 pm). It was clear that lithiation had taken place on the CH_2 next to the 2-methylphenyl ring (α-lithiation). The new compound was therefore identified to be **3.12**, which would of course be present as a racemic mixture, and was produced in 12% yield after purification by column chromatography (silica gel; Et_2O) (Table 3.1; Entry 1). The structure of **3.12** was further confirmed by electron–impact mass spectrum that showed a peak at *m/z* = 307 and the high resolution mass of this peak confirmed the formula as $C_{25}H_{26}N_2O$ (M – H_2O). Clearly, monolithium reagent **3.10** and dilithium reagent **3.11** were produced *in situ*. Reaction of **3.11** with benzophenone gave the corresponding substituted derivative **3.12** (Scheme 3.6).



Scheme 3.6 Lithiation and substitution of **3.9** followed by reaction with benzophenone

The ^{13}C NMR signals of the two phenyl groups originating in benzophenone appeared separately, verifying that they were diastereotopic. The diastereotopicity arises from creation of a stereogenic carbon during lithiation at the side-chain followed by reaction with benzophenone.

Both the CH_2 next to the nitrogen and that next to the aryl ring are somewhat acidic because they can form anions stabilized by the urea moiety or ring conjugation, respectively. However, the dilithium reagent **3.11** produced *via* α-lithiation can be further stabilised through chelation, which is more difficult for the one produced *via* lithiation on the CH_2 next to the NH group (**3.13**; Figure 3.1).

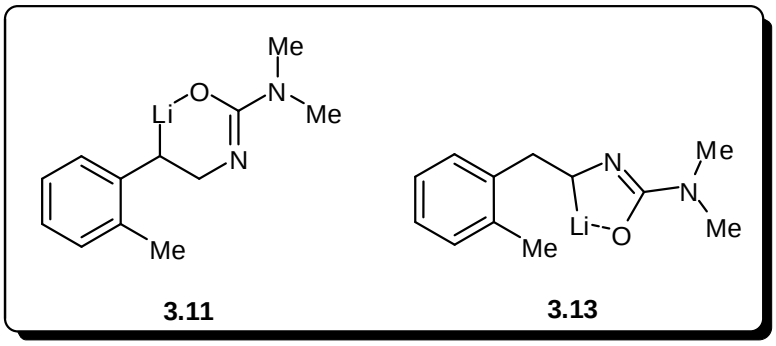


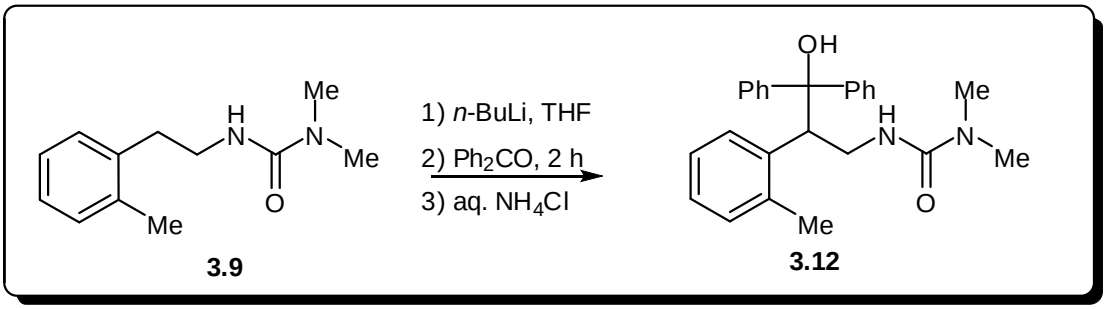
Figure 3.1 Chelation of dilithium reagents **3.11** and **3.12**

Several experiments were conducted to see what effect the conditions (temperature and molar equivalents of lithium reagent and benzophenone) could have on the yield of **3.12**. Use of MeLi (1.1 equivalents) to remove the NH proton, followed by *n*-BuLi (1.1 equivalents), since such combination was found to be more efficient in lithiation of simple aromatic compounds, [12] at –78 °C under similar reaction conditions also provided a very low yield of **3.12** (5%). The yield of **3.12** was improved, but to only 30%, when MeLi (1.1 equivalents) followed by *n*-BuLi (2.2 equivalents) was used at –78 °C under similar reaction conditions. Since use of two different lithiating agents did not seem to produce any significant benefit, further experiments concentrated on use of just a single lithiating agent.

Raising the temperature of lithiation to 0 °C, to increase the reaction rate and also to reduce the aggregation state of BuLi, had a much greater effect on the yield of product, giving **3.12** in 65% yield after a lithiation period of just 30 minutes (Table 3.1; Entry 4). On the other hand, use of *t*-BuLi or *sec*-butyllithium (*s*-BuLi) at 0 °C gave **3.12** in lower yields, 35 and 2%, respectively, along with starting material **3.9**, which was recovered in 20% and 60% yields, respectively following column chromatography. Also, a polar dark material was adsorbed at the top of the chromatography column in both cases. No product was obtained when the less nucleophilic lithium reagent, lithium diisopropylamide (LDA), was used as the lithium reagent at 0 °C.

The results obtained so far indicated that low temperature (–78 °C) for the lithiation step was not efficient to produce the dilithium reagent **3.11** quantitatively, possibly because of the high aggregation state of *n*-BuLi at such a low temperature. In none of these reactions was any product of lateral lithiation isolated. The crude products were purified by column chromatography (silica gel; Et_2O) and the yields of **3.12** obtained are summarized in Table 3.1.

Table 3.1: Yield of **3.12** obtained from lithiation of **3.9** followed by reaction with benzophenone (1.2 equivalents) under reaction conditions



3.9 **3.12**

Entry	RLi (mole equiv)	T (h)	Temp. (°C)	Yield of **3.12** (%)
1	*n*-BuLi (2.2)	2	–78	12
2	MeLi (1.1), *n*-BuLi (1.1)	2	–78	5
3	MeLi (1.2), *n*-BuLi (2.2)	2	–78	30
4	*n*-BuLi (2.2)	0.5	0	65
5	*t*-BuLi (2.2)	0.5	0	35
6	*sec*-BuLi (2.2)	0.5	0	2
7	LDA (2.2)	0.5	0	—

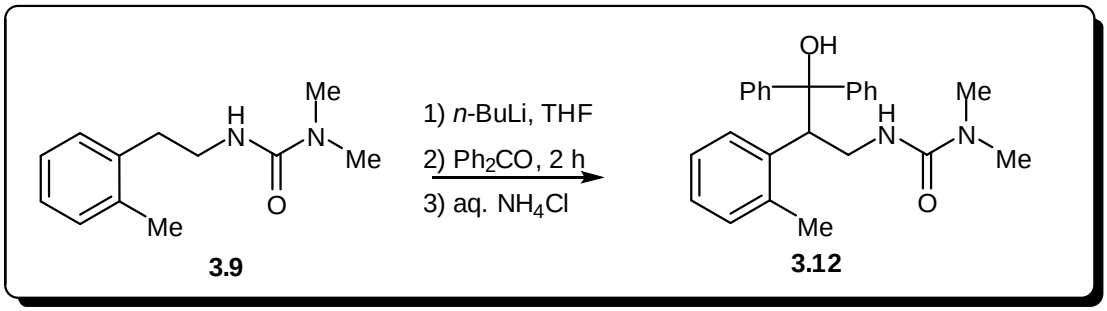
Use of *n*-BuLi at 0 °C was selected for further study and several experiments were conducted to try to improve the yield of **3.12** or to find conditions under which lateral lithiation could be achieved instead. The crude products were purified by column chromatography or analysed by ^{1}H NMR spectroscopy and the approximate yields of **3.12** obtained are summarized in Table 3.2.

However, it was found that use of excess benzophenone could have only a small effect on the yield of the product. For example, the yield of **3.12** was 69% when the reaction time was 30 minutes and 2.2 mole equivalents of benzophenone were used (Table 3.2; Entry 1), just a 4% increase over the comparable reaction with 1.2 mole equivalents, which is barely significant. The yield of **3.12** was increased more (to 78%) when the lithiation reaction time was increased to 1 h (Table 3.2; Entry 2). A comparable yield (76%) was obtained when the reaction time was increased to 2 h with only 1.2 mole equivalents of benzophenone (Table 3.2; Table 3). Use of 2.2 mole equivalents of *n*-BuLi for 2 h during the lithiation step with larger excesses (2.2 or 3.3 mole equivalents) of benzophenone again provided only a modest improvement (to

83%) in yield of **3.12** (Table 3.2; Entries 4 and 5). It was clear that a longer reaction and only 1.2 molar equivalents of benzophenone could be optimised to provide a high yield of the product.

We therefore investigated the effect of the use of excess *n*-BuLi (3.3 mole equivalents) and only a small excess of benzophenone (1.2 mole equivalents) on the yield of **3.12** over different lithiation reaction times. It was found that the yield of **3.12** after purification by column chromatography was 80% after a lithiation time of only 30 minutes (Table 3.2; Entry 6), and increased to 83 and 93% when the reaction time was 1 and 2 h, respectively (Table 3.2; Entries 7 and 8).

Table 3.2 Synthesis of **3.12** under various reaction conditions according to Scheme 3.6



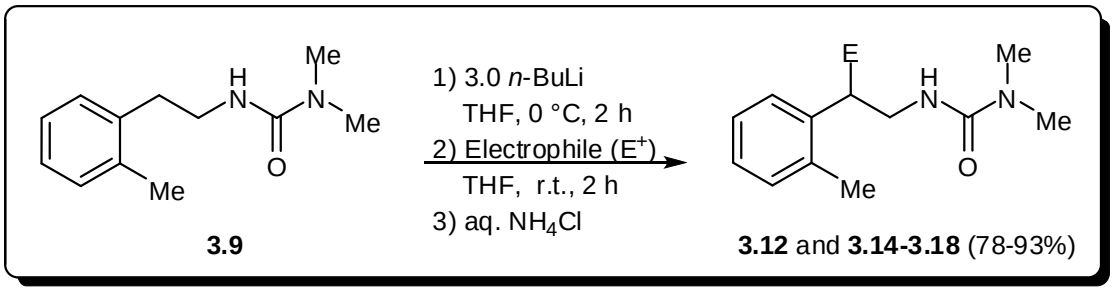
3.9 **3.12**

Entry	*n*-BuLi		Temp (°C)	Ph_2CO (mole equiv.)	Yield of **3.12** (%)[a]
	mole equiv.	T (h)			
1	2.2	0.5	0	2.2	69[b,c]
2	2.2	1	0	2.2	78[b,c]
3	2.2	2	0	1.2	76[b,c]
4	2.2	2	0	2.2	83
5	2.2	2	0	3.3	83
6	3.0	0.5	0	1.2	80
7	3.0	1	0	1.2	83
8	3.0	2	0	1.2	93

[a] Yield of **3.12** after purification by column chromatography unless otherwise indicated.
[b] Starting material **3.9** was recovered in significant quantities.
[c] Yield by ^{1}H NMR.

In cases where excess *n*-BuLi and benzophenone were used, a side product was obtained due to the addition of *n*-BuLi to benzophenone. It was obvious that no lateral lithiation had taken place under the conditions tried and in all cases **3.12** was the only new product isolated. Clearly, α-lithiation had taken place rather than lateral lithiation on the methyl group at the 2-position, which was unexpected.

Having established conditions under which the lithium intermediate **3.11** could be produced almost quantitatively, it was of interest to see if its reactions with other electrophiles would be useful and general. Consequently, reactions of **3.11**, prepared *in situ* from compound **3.9**, with other electrophiles (4-methoxyacetophenone, cyclohexanone, dimethyl formamide, benzaldehyde and 4-anisaldehyde) were carried out. Each reaction was conducted under identical conditions and then quenched by the addition of aq. NH_4Cl. Afterwards, the crude products were purified by column chromatography (silica gel; Et_2O) to give the corresponding pure substituted derivatives **3.14–3.18** (Scheme 3.7) in high yields (Table 3.3).



Scheme 3.7 Lithiation and substitution of *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**)

The structures of the new products **3.14–3.18** were confirmed by various spectroscopic techniques including IR, NMR and mass spectra (See Section 3.10.4). ^1H NMR spectra of all compounds showed that the signals of the two hydrogens of the CH_2 group were diastereotopic. The diastereotopicity arises from creation of a stereogenic carbon during lithiation at the side-chain followed by reaction with electrophile. The NMR spectra of compounds **3.14**, **3.17** and **3.18** showed the presence of two racemic diastereoisomers in approximately equal proportions.

Table 3.3 Synthesis of substituted *N'*-(2-methylphenyl)ethyl)-*N*,*N*-dimethylureas **3.12** and **3.14–3.18** according to Scheme 3.7

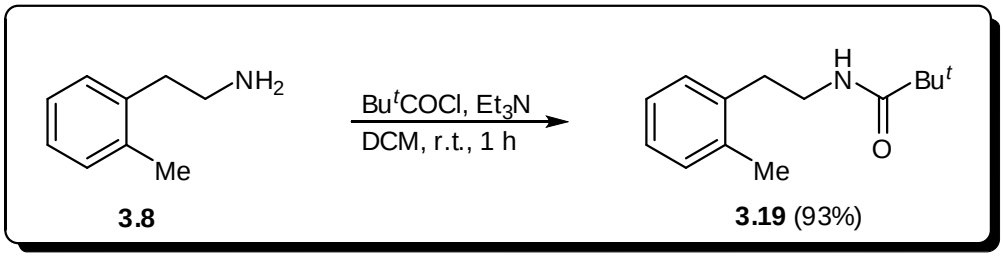
Products	Electrophile	E	Yield (%)[a]
3.12	Ph_2CO	$Ph_2C(OH)$	93[b]
3.14	4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)Me$	82[c]
3.15	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	90[d]
3.16	Me_2NCHO	CHO	84
3.17	PhCHO	PhCH(OH)	82[c]
3.18	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78[c]

[a] Yield of the pure product.
[b] The ^{13}C NMR spectrum showed that the carbons of the two phenyl groups appeared as separated signals, verifying that they are diastereotopic.
[c] The NMR spectra showed a mixture of two racemic diastereoisomers in approximately equal proportions.
[d] The ^{13}C NMR spectrum showed that the two sides of the cyclohexane ring appeared as separated signals, verifying that they are diastereotopic.

Clearly, lithiation and substitution of **3.9** took place on the α-position of the side-chain in all cases. It was of interest to know whether lithiation of *N*-(2-(2-methylphenyl)ethyl)pivalamide would behave in the same way as the urea derivative **3.9**. Therefore, our attention was next turned to the synthesis of *N*-(2-(2-methylphenyl)-ethyl)pivalamide (**3.19**) using a literature procedure that has been reported for analogous compounds (Scheme 3.5).[8]

3.5 Synthesis of *N*-(2-(2-methylphenyl)ethyl)pivalamide (3.19)

N-(2-(2-Methylphenyl)ethyl)pivalamide (**3.19**) was synthesized from the reaction of 2-(2-methylphenyl)ethanamine (**3.8**) with pivaloyl chloride (Bu^tCOCl; 1.2 equivalents) in dichloromethane (DCM) in the presence of triethylamine (TEA) for one hour at room temperature (Scheme 3.8). Following work-up, the crude product obtained was recrystallized from a mixture of diethyl ether and hexane (1:3 by volume) to give pure **3.19** in 93% yield as a colourless crystalline solid. The structure of compound **3.18** was confirmed by various spectroscopic techniques (see Section 3.10.5).



3.8 **3.19** (93%)

Scheme 3.8 Synthesis of *N*-(2-(2-methylphenyl)ethyl)pivalamide (**3.19**)

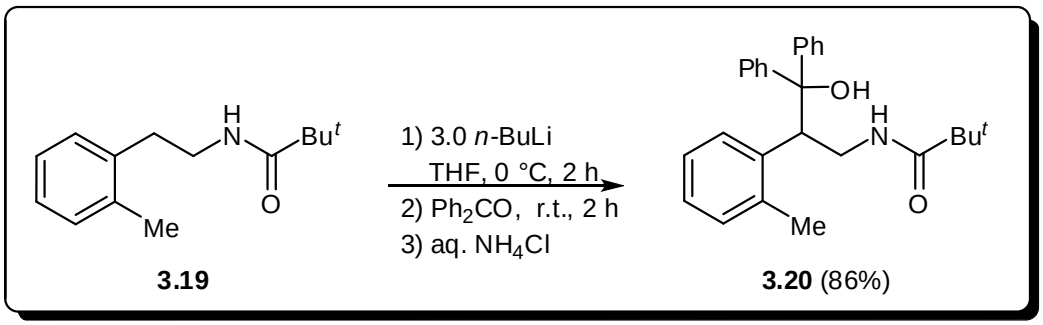
Our attention was next turned to investigation of lithiation of **3.19** with *n*-BuLi at 0 °C followed by reactions with a representative electrophile under conditions similar to those used in Scheme 3.7, to see if the different substituent (the pivalamide-containing group) at the 1-position has any effect on the site of lithiation.

3.6 Lithiation and substitution of *N*-(2-(2-methylphenyl)ethyl)pivalamide (3.19)

Lithiation of **3.19** was carried out at 0 °C under the standard conditions that were used for **3.9** (Scheme 3.7), followed by reaction with benzophenone as a representative electrophile. Following work-up, the reaction mixture was checked by TLC and showed the formation of a new product. The crude product was purified by column chromatography (silica gel; hexane–Et_2O, 2:1 by volume). The new solid product was subjected to NMR, MS and IR spectral analysis (See Section 3.10.6 for details).

The ^{1}H NMR spectra of the new compound showed the presence of fourteen aromatic protons, the *tert*-butyl group, an intact methyl group, two exchangeable protons and three other aliphatic protons. Clearly, lithiation followed by substitution had taken place on one of the CH_2 groups of the side-chain. That the position of substitution was next to the 2-methylphenyl ring (α-lithiation) was shown by calculating the ^{13}C chemical shifts of the CH and CH_2 groups of the two possible isomers, and recognising that they were consistent only with this isomer. The ^{13}C NMR spectrum also showed that the carbons of the two phenyl groups appeared as separated signals, verifying that they are diastereotopic. The structure was further confirmed by electron–impact mass spectrometry, which showed a peak at *m/z* = 383, the high resolution mass of which confirmed the formula as $C_{27}H_{29}NO$ (M − H_2O). The new compound was therefore

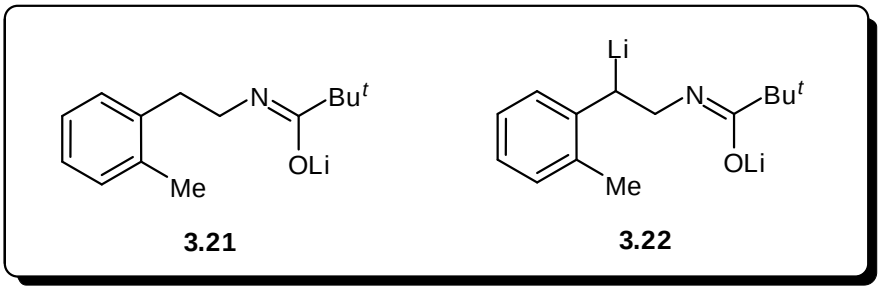
identified to be **3.20** which would of course be present as a racemic mixture and was produced in 86% yield (Scheme 3.9) after purification by column chromatography.



3.19 **3.20** (86%)

Scheme 3.9 Lithiation and substitution of **3.19** followed by reaction with benzophenone

Again no product due to lateral lithiation and substitution was isolated. Clearly, monolithium reagent **3.21** and dilithium reagent **3.22** (Figure 3.2) were produced *in situ* from reaction of **3.19** with *n*-BuLi.



3.21 **3.22**

Figure 3.2 The structures of lithium reagents **3.21** and **3.22**

The high selectivity for α-lithiation, with no evidence for lateral lithiation on the methyl group, shown by both *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**) and *N*-(2-(2-methylphenyl)ethyl)pivalamide (**3.19**) were completely at odds with the lateral lithiation of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate reported by Clark,[9] albeit that Clark's conditions were somewhat different (lithiation with *t*-BuLi at –60 °C, 1.5 h).

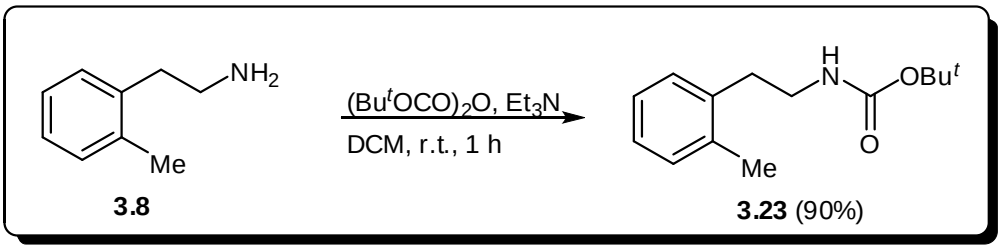
Therefore, we became interested to investigate lithiation of both **3.9** and **3.19** under the conditions used by Clark[9] for the carbmate derivative to see what effect the conditions could have on the site of lithiation.

Lithiations of **3.9** and **3.19** were attempted under Clark's conditions [9] followed by reactions with benzophenone in each case. The corresponding α-substituted products **3.12** and **3.20** were produced in 63 and 52% yields, respectively, after column chromatography, along with significant quantities of starting materials (31–43%). No products due to lateral lithiation and substitution were isolated.

Our attention was therefore turned to synthesis of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (**3.23**) and investigation of its lithiation.

3.7 Synthesis of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (3.23)

tert-Butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (**3.23**) was synthesized from the reaction of 2-(2-methylphenyl)ethanamine **(3.8)** with di-*tert*-butyl dicarbonate ($(Bu^tOCO)_2O$; Scheme 3.10) under conditions similar to those used for the synthesis of pivalamide derivative **3.19** (Scheme 3.8). Following work-up, the crude product obtained was recrystallized from hexane to give pure **3.23** in 90% yield (Scheme 3.10) as a white solid.



Scheme 3.10 Synthesis of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (**3.23**)

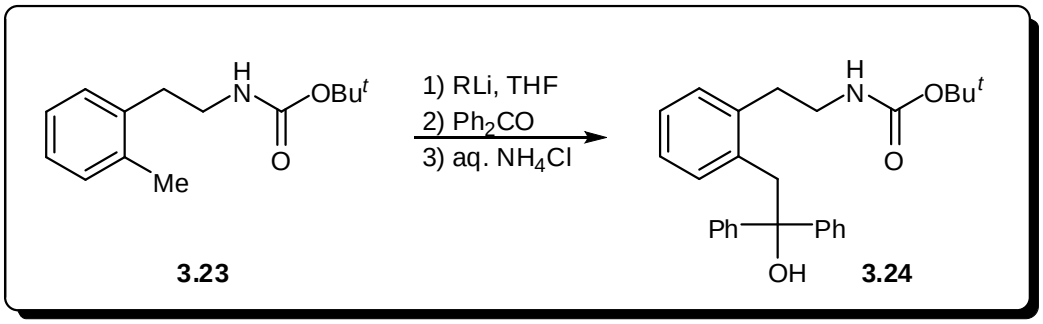
Next we attempted lithiation of **3.23** under the conditions used with **3.9** and **3.19** and under Clark lateral lithiation conditions[9] to see what effect the conditions could have on the site of lithiation.

3.8 Lithiation and substitution of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)-carbamate (3.23)

Lithiation of **3.23** was attempted under the standard conditions that were used for **3.9** using three equivalents of *n*-BuLi at 0 °C, followed by reaction with benzophenone (1.2 equivalents) as a representative electrophile. Following work-up, the TLC showed the presence of a new product along with starting material **3.23**. The crude

product mixture was purified by column chromatography to give the starting material **3.23** in 80% yield, along with a pure sample of the new product.

The ^{1}H NMR spectrum of the new product showed the presence of fourteen aromatic protons and three CH_2 groups (See Section 3.10.8 for more details). Clearly, lateral lithiation on the CH_3 followed by reaction with benzophenone had taken place to give the new product. The new product was identified as the laterally-substituted product **3.24** (Scheme 3.11) and was obtained in 13% yield as the only observable product. The structure of **3.24** was also confirmed by low and high resolution mass spectra. The electron–impact mass of **3.24** showed a peak at *m/z* = 399 and the high resolution mass spectrum of this peak confirmed its formula as $C_{27}H_{29}NO_2$ (M – H_2O).



3.23 **3.24**

Scheme 3.11 Lithiation and substitution of **3.23** followed by reaction with benzophenone

Several experiments were carried out in order to find conditions under which the yield of **3.24** could be improved. It was found that the yield of **3.24** was slightly higher (16%) when *t*-BuLi (3.0 equivalents) was used instead of *n*-BuLi, and slightly higher again (20%) when three equivalents of benzophenone were used with *t*-BuLi. Significant quantities of **3.23** (*ca*. 70–80%) were recovered under all the above conditions. There was no evidence for the formation of the α-substitution product in any of the reactions. When the reaction was carried out under Clark's conditions (–60 to –25 °C) with 1.5 equivalents of benzophenone the yield of **3.24** was good (80%) and this was improved further to 88% when excess benzophenone (2.4 equivalents) was used.

There are several possible explanations for the low yields of **3.24** (13–20%) obtained at higher temperature (0 °C). It is unlikely that lateral lithiation is slow at 0 °C, since lithiation occurs readily enough at –60 to –25 °C. It was thought to be possible that the dilithium intermediate **3.26** (Figure 3.3), produced *in situ* from reaction of **3.25**

(Figure 3.3) and benzophenone, may be unstable, dissociating back to benzophenone and lateral-lithiated species **3.25** and that the proportion of **3.26** in the equilibrium mixture would be lower at higher temperature. This possibility was tested by treating **3.24** with *t*-BuLi (2.4 equivalents) in dry THF at 0 °C for 2 h. However, following work up **3.24** was recovered quantitatively (98%). The most likely explanation is therefore that at 0 °C the lateral-lithiated species **3.25** is reactive enough to deprotonate THF, leading to the mono-lithiated derivative of the starting material **3.23**, which cannot react with benzophenone.

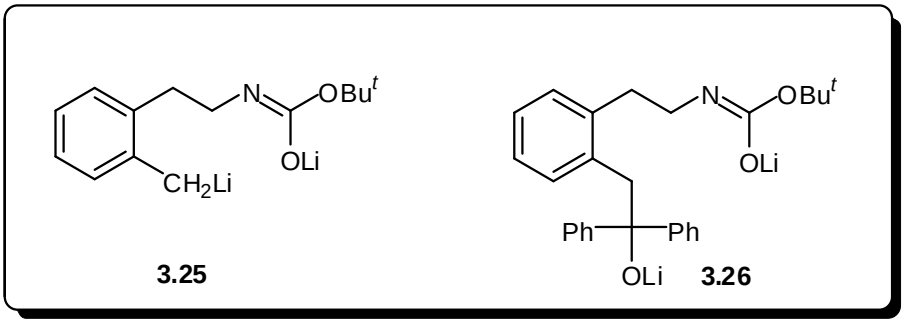


Figure 3.3 The structures of lithium intermediates **3.25** and **3.26**

The clear distinction between the carbamate **3.23** on the one hand and the urea **3.9** and pivalamide **3.19** derivatives of 2-(-methylphenyl)ethylamine on other hand, with **3.23** leading to clean lateral lithiation on the methyl group while the other derivatives lead to clean α-lithiation, is surprising. Based on the C=O stretching frequencies of the three derivatives, the carbamate would probably be the poorest at coordinating the organolithium reagent and therefore least likely to effect proximity-directed lithiation. This would imply that directed lithiation in the case of **3.9** and **3.19** favours α-lithiation, which would involve a smaller ring-size of interaction between the coordinated organolithium and the α-protons than between the coordinated organolithium and the protons of the methyl group. It would further imply that when coordination is insufficiently strong to direct lithiation, so that the intrinsic reactivity of the relevant protons becomes the dominant influence over the site of lithiation, the methyl protons in mono-deprotonated **3.23** are more reactive than the α-protons in that species. However, whatever the precise explanation, it is clear that by varying the acyl substituent on nitrogen, it is possible to select either α-lithiation or lateral lithiation of a 2-(2-methylphenyl)ethylamine derivative, which must have significant benefit for organic synthesis.

3.9 Conclusions

Unexpected side-chain lithiation of *N'*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (**3.9**) took place at the CH_2 group next to the phenyl ring (α-lithiation) with three equivalents of *n*-BuLi in THF at 0 °C. Reactions of the dilithium reagents obtained with a variety of electrophiles gave the corresponding α-substituted derivatives in high yields.

Similarly, lithiation of *N*-(2-(2-methylphenyl)ethyl)pivalamide (**3.19**) followed by reaction with benzophenone as a representative electrophile gave the corresponding α-substituted product in high yield. No products due to lateral lithiation and substitution were obtained under the conditions tried, which is in sharp contrast with the results obtained with *tert*-butyl 2-(2-methylphenyl)ethylcarbamate (**3.23**). The process is simple, general, efficient and high yielding to provide a range of substituted urea derivatives that would be more difficult to prepare by other means. The results of this study have been published.[13]

3.10 Experimental

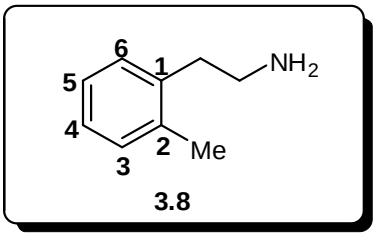
3.10.1 General Experimental

A general experimental section outlining the instrumentation and reagents used is included in Chapter Two (Section 2.14.1). The term "Ar" is used to represent the NMR spectra data for "2-methylphenyl" in this experimental section. For mixtures of two diastereoisomers, pairs of NMR signals that cannot be attributed to specific diastereoisomers are simply designated as 2 of a particular kind of signal (*e.g.* 2 C=O for the carbonyl carbon atoms of the two diastereoisomers).

3.10.2 Synthesis of 2-(2-methylphenyl)ethylamine (3.8)

A solution of $AlCl_3$ (7.45 g, 55.9 mmol) in anhydrous diethyl ether (70 mL) was added to lithium aluminum hydride (6.36 g, 167.6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. A solution of (2-methylphenyl)acetonitrile (10.00 g, 76.2 mmol) in anhydrous diethyl ether (30 mL) was added to the mixture at 0 °C. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (50 mL) and quenched with water (100 mL). After the solution was acidified with conc. sulfuric acid, it was basified with sodium hydroxide (6 M). The

layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford pure **3.8** (9.67 g, 71.6 mmol, 94%) as an oil.



3.8

IR (FT): ν_{max} = 3361, 3277, 2933, 1491, 1312 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.07–7.02 (m, 4 H, Ar), 2.84 (t, *J* = 7 Hz, 2 H, C*H*$_2$$NH_2$), 2.67 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.24 (s, 3 H, CH_3), 1.39 (br., exch., 2 H, NH_2).

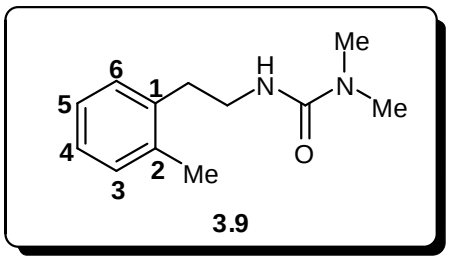
^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9 (s, C-1), 136.2 (s, C-2), 130.3 (d, C-3), 129.3 (d, C-6), 126.3 (d, C-4), 125.9 (d, C-5), 42.4 (t, CH_2NH_2), 37.5 (t, CH_2Ar), 19.4 (q, CH_3).

MS (ES^+): *m/z* (%) = 135 (48, $[M]^+$), 132 (55), 118 (97), 105 (100), 91 (90), 77 (65).

HRMS (ES^+): *m/z* $[M]^+$, calcd for $C_9H_{13}N$: 135.1048; found: 135.1048.

3.10.3 Synthesis of *N*′-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (3.9)

A stirred mixture of **3.9** (9.67 g, 71.6 mmol), dimethylcarbamoyl chloride (9.24 g, 85.9 mmol) and Et_3N (10.86 g, 107.4 mmol) in DCM (100 mL) was heated under reflux for 1 h. The mixture was allowed to cool and the solid formed was collected by filtration and then washed with H_2O (2 × 25 mL). The solid was purified by crystallization from a mixture of EtOAc and Et_2O (1:3 by volume) to give pure **3.9** (14.00 g, 67.9 mmol, 95%) as a white solid.



3.9

mp 74–76 °C.

IR (FT): ν_{max} =3333, 2931, 1635, 1540, 1356 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 4 H, Ar), 4.48 (br., exch., 1 H, NH), 3.46 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.88 [s, 6 H, N(CH_3)$_2$], 2.86 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.37 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 137.5 (s, C-1), 136.5 (s, C-2), 130.4 (d, C-3), 129.4 (d, C-6), 126.5 (d, C-4), 125.9 (d, C-5), 41.0 (t, CH_2NH), 36.1 [q, N(CH_3)$_2$], 33.9 (t, CH_2Ar), 19.3 (q, CH_3).

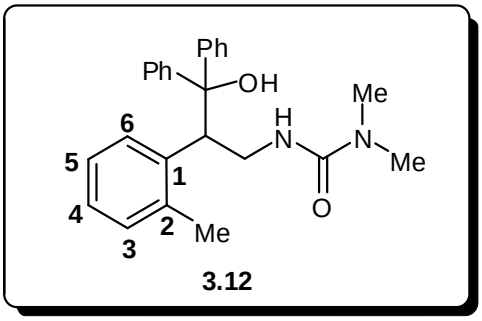
MS (EI): *m/z* (%) = 206 (65, $[M]^+$), 161 (15), 105 (50), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{18}N_2O$: 206.1419; found: 206.1414.

3.10.4 Lithiation and substitution of *N′*-(2-(2-methylphenyl)ethyl)-*N*,*N*-dimethylurea (3.9): Synthesis of substituted derivatives 3.12–3.17; general procedure

A solution of *n*-BuLi in hexane (1.88 ml, 1.60 M, 3.0 mmol) was added to a stirred solution of **3.9** (0.20 g, 0.97 mmol) at 0 °C in anhydrous THF (15 mL) under a N_2 atmosphere. The mixture was stirred at 0 °C for 2 h and the electrophile (1.2 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O) to give the pure products. The yields obtained of products **3.12** and **3.14–3.17** were in the range of 74–93% based on the starting material **3.9** (Table 3.3).

_N′_-[3-Hydroxy-2-(2-methylphenyl)-3,3-diphenylpropyl]-_N_,_N_-dimethylurea (3.12)



3.12

From benzophenone (0.22 g, 1.2 mmol); 0.35 g (0.90 mmol, 93%); white solid; mp 163–166 °C.

IR (FT): ν_{max} = 3266, 2926, 1642, 1537, 1308, cm^{-1}.

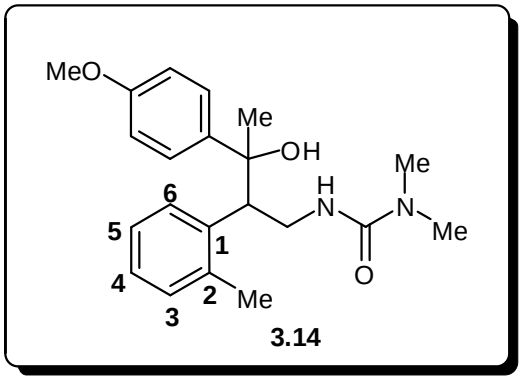
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8 Hz, 1 H, H-3), 7.70 (dd, *J* = 1, 8 Hz, 2 H, H-2/H-6 of C_6H_5), 7.24 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of C_6H_5), 7.17 (dd, *J* = 1, 8 Hz, 2 H, H-2/H-6 of other C_6H_5), 7.10 (app. t, *J* = 8 Hz, 1 H, H-4 of C_6H_5), 6.95 (app. dt, *J* = 1, 8 Hz, 1 H, H-4), 6.90–6.86 (m, 4 H, H-5 and H-6 of Ar and H-3/H-5 of other C_6H_5), 6.79 (app. t, *J* = 8 Hz, 1 H, H-4 of other C_6H_5), 5.53 (br., exch., 1 H, OH), 4.40 (dd, *J* = 5, 8 Hz, 1 H, CH), 4.03–3.92 (m, 2 H, NH and C$H_a$$H_b$), 3.20 (m, 1 H, CH_aH_b), 2.43 [s, 6 H, $N(CH_3)_2$], 2.22 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 148.6, 146.7 (2 s, C-1 of 2 C_6H_5), 138.6 (s, C-1), 135.9 (s, C-2), 129.7 (d, C-3), 129.5 (d, C-4), 127.9, 127.2 (2 d, C-2/C-6 of 2 C_6H_5), 126.22, 126.20 (2 d, C-4 of 2 C_6H_5), 125.8 (d, C-5), 125.8, 125.6 (2 d, C-3/C-5 of 2 C_6H_5), 125.5 (d, C-6), 79.2 (s, C-OH), 48.0 (d, CH), 42.6 (t, CH_2), 35.8 [q, $N(CH_3)_2$], 20.2 (q, CH_3).

MS (EI): *m/z* (%) = 370 (20, $[M - H_2O]^+$), 270 (100), 255 (80), 206 (100), 183 (88), 165 (50), 105 (100), 72 (100).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O$: 370.2045; found: 370.2040.

_N′_-[3-Hydroxy-2-(2-methylphenyl)-3-(4-methoxyphenyl)butyl]-_N_,_N_-dimethylurea (3.14)



3.14

From 4-methoxyacetophenone (0.18 g, 1.2 mmol); product **3.14** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.28 g (0.79 mmol, 82%); yellow oil.

IR (FT): ν_{max} = 3392, 2924, 1639, 1538, 1364 cm^{-1}.

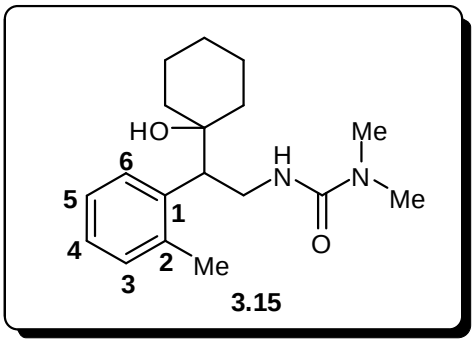
^1H NMR (500 MHz, $CDCl_3$): δ = 7.66 (br. d, *J* = 8 Hz, 1 H, H-3 of one diastereoisomer), 7.43 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$CH_3OC_6H_4$ of one diastereoisomer), 7.26–6.97 (m, 11 H, H-2/H-6 of 4-$CH_3OC_6H_4$, H-3 of other diastereoisomer, H-4, H-5, H-6 of 2 Ar and 2 OH), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 6.78 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 4.34 (br., exch., 1 H, NH),, 4.04 (br., exch., 1 H, NH), 3.87 (m, 1 H, CH of one diastereoisomer), 3.83 (s, 3 H, OCH_3 of one diastereoisomer), 3.79 (m, 1 H, CH of other diastereoisomer), 3.74 (s, 3 H, OCH_3 of other diastereoisomer), 3.75 (m, 1 H, CH_aH$_b$ of one diastereoisomer), 3.39–3.29 (m, 2 H, CH_aH_b), 3.20 (m, 1 H, CH$_a$$H_b$ of one diastereoisomer), 2.79 [s, 6 H, $N(CH_3)_2$ of one diastereoisomer],, 2.57 [s, 6 H, $N(CH_3)_2$ of other diastereoisomer], 2.39 (s, 3 H, CH_3C–OH of one diastereoisomer), 2.28 (s, 3 H, CH_3C–OH of other diastereoisomer), 1.61 (s, 3 H, CH_3 of one diastereoisomer), 1.21 (s, 3 H, CH_3 of other diastereoisomer).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6, 158.5 (2 s, C-4 of 2 × 4-$CH_3OC_6H_4$),158.3, 158.1 (2 s, 2 C=O), 141.2, 139.0 (2 s, 2 C-2), 138.9, 137.5 (2 s, 2 C-1), 137.0, 136.5 (2 s, C-1 of 2 × 4-$CH_3OC_6H_4$), 130.4, 130.3 (2 d, 2 C-3), 129.5, 128.3 (2 d, 2 C-4), 127.1, 126.6 (2 d, 2 C-6), 126.7, 126.2 (2 d, 2 C-5), 126.3, 125.8 (2 d, C-2/C-6 of 2 × 4-$CH_3OC_6H_4$), 113.2, 113.0 (2 d, C-3/C-5 of 2 × 4-$CH_3OC_6H_4$), 75.6, 74.6 (2 s, 2 C–OH), 55.3, 55.2 (2 q, 2 OCH_3), 49.8, 46.3 (2 d, 2 CH), 42.1, 41.0 (2 t, 2 CH_2), 36.1, 35.8 [2 q, 2 $N(CH_3)_2$], 30.4, 29.8 (2 q, 2 CH_3), 20.4, 19.3 (2 q, 2 *C*H_3C-OH).

MS (EI): *m/z* (%) = 356 (1), 355 (3), 338 (47, $[M - H_2O]^+$), 250 (83), 238 (97), 206 (100), 151 (80), 101 (98), 72 (99).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{21}H_{26}N_2O_2$ 338.1994; found: 338.1997.

_N′_-[2-(1-Hydroxycyclohexyl)-2-(2-methylphenyl)ethyl]-_N_,_N_-dimethylurea (3.15)



3.15

From cyclohexanone (0.19 g, 1.2 mmol); yield: 0.26 g (0.87 mmol, 90%); white solid; mp 164–166 °C.

IR (FT): ν_{max} = 3365, 2931, 1635, 1531, 1318 cm^{-1}.

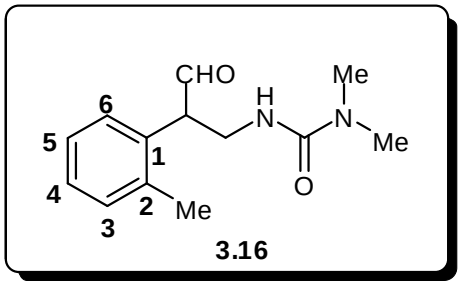
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8 Hz, 1 H, H-3), 7.13–7.03 (m, 3 H, H-4, H-5 and H-6), 4.22 (dd, *J* = 5, 6 Hz, exch., 1 H, NH), 3.87 (m, 1 H, CH), 3.35 (m, 1 H, CH_aH$_b$), 3.15 (m, 1 H, CH$_a$$H_b$), 2.63 [s, 6 H, $NCH_3)_2$], 2.23 (s, 3 H, CH_3), 1.57–1.01 (m, 10 H, *c*-Hex).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 138.9 (s, C-1), 137.9 (s, C-2), 130.4 (d, C-3), 128.0 (d, C-4), 126.3 (d, C-5), 126.0 (d, C-6), 73.5 (s, C-1 of *c*-Hex), 49.7 (d, CH), 41.4 (t, CH_2), 36.3, 35.5 (2 t, C-3/C-5 of *c*-Hex), 35.9 [q, $N(CH_3)_2$], 25.7 (t, C-4 of *c*-hex), 21.8, 21.6 (2 t, C-2/C-6 of *c*-Hex), 20.6 (q, CH_3).

MS (EI): *m/z* (%) = 304 (15, $[M]^+$, 15), 286 (93, $[M - H_2O]^+$), 207 (100), 186 (97), 143 (93), 117 (96), 89 (95), 72 (92).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{28}N_2O_2$: 304.2151; found: 304.2145.

_N′_-[3-Oxo-2-(2-methylphenyl)propyl]-_N_,_N_-dimethylurea (3.16)



3.16

From dimethylformamide (0.09 g, 1.2 mmol); yield: 0.19 g (0.82 mmol, 84%); yellow oil.

IR (FT): ν_{max} = 3344, 2931, 1721, 1638, 1533, 1354 cm^{-1}.

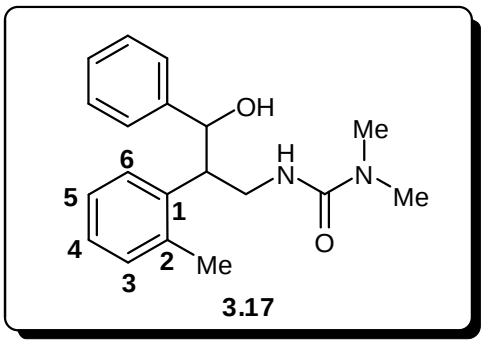
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.64 (br., 1 H, CHO), 7.20–7.04 (m, 3 H, H-3, H-4 and H-5), 6.83 (dd, *J* = 1, 7 Hz, 1 H, H-6), 4.91 (app. t, *J* = 5 Hz, exch., 1 H, NH), 4.15 (dd, *J* = 5, 9 Hz, 1 H, CH), 3.54 (m, 1 H, C$H_a$$H_b$), 3.45 (m, 1 H, C$H_a$$H_b$), 2.79 [s, 6 H, $N(CH_3)_2$], 2.41 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.4 (d, CHO), 158.2 (s, C=O), 137.8 (s, C-2), 132.4 (s, C-1), 131.3 (d, C-3), 128.0 (d, C-4 and C-5), 126.5 (d, C-6), 55.7 (d, CH), 41.1 (t, CH_2), 36.1 [q, $N(CH_3)_2$], 19.6 (q, CH_3).

MS (EI): *m/z* (%) = 234 (70, $[M]^+$), 206 (89), 134 (100), 105 (95), 91 (98), 72 (94).

HRMS (EI): *m/z* [M^+] calcd for $C_{13}H_{18}N_2O_2$: 234.1368; found: 234.1372.

_N′_-[3-(Hydroxy)-3-(phenyl)-2-(2-methylphenyl)propyl]-_N_,_N_-dimethylurea (3.17)



3.17

From benzaldehyde (0.13 g, 1.2 mmol); product **3.17** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.24 g (0.79 mmol, 82%); yellow oil.

IR (FT): ν_{max} = 3349, 2932, 1634, 1536, 1358 cm^{-1}.

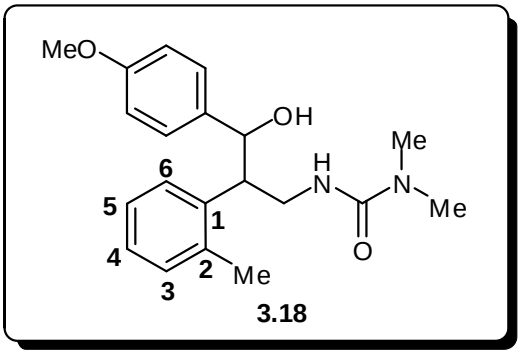
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–6.92 (m, 18 H, 2 C_6H_5 and 2 Ar), 4.94 (br. s, exch., 2 H, 2 OH), 4.90 (d, *J* = 6 Hz, 1 H, C*H*OH), 4.82 (d, *J* = 6 Hz, 1 H, C*H*OH), 4.58 (app. t, exch., *J* = 6 Hz, 1 H, NH), 4.38 (app. t, exch., *J* = 6 Hz, 1 H, NH), 3.93 (m, 1 H, C*H*CH_2), 3.57 (m, 1 H, C*H*CH_2), 3.37–3.30 (m, 4 H, 2 CH_2), 2.77 [s, 6 H, $N(CH_3)_2$], 2.70 [s, 6 H, $N(CH_3)_2$], 1.99 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.18, 159.15 (2 s, 2 C=O), 142.96, 142.94 (2 s, 2 C-1), 139.12, 139.11 (2 s, C-1 of 2 C_6H_5), 136.31, 136.30 (2 s, 2 C-2), 130.54, 153.53 (2 d, 2 C-3), 127.98, 127.82 (2 d, C-3/C-5 of 2 C_6H_5), 127.35, 127.34 (2 d, C-4 of 2 C_6H_5), 127.03, 127.00 (2 d, 2 C-4), 126.6, 126.5 (2 d, C-2/C-6 of 2 C_6H_5), 126.35, 126.34 (2 d, 2 C-5), 125.73, 125.72 (2 d, 2 C-6), 75.1, 74.6 (2 d, 2 CHOH), 49.4, 48.8 (2 d, 2 C*H*CH_2), 43.0, 42.3 (2 t, 2 CH_2), 36.2, 36.1 [2 q, 2 $N(CH_3)_2$], 19.72, 19.70 (2 q, 2 CH_3).

MS (EI): *m/z* (%) = 295 (100, $[M - OH]^+$), 205 (3), 146 (5).

HRMS (EI): *m/z* ($[M - OH]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1810; found: 295.1798.

_N′_-[3-(Hydroxy)-3-(4-methoxyphenyl)-2-(2-methylphenyl)propyl]-_N_,_N_-dimethylurea (3.18)



3.18

From 4-methoxybenzaldehyde (0.16 g, 1.2 mmol); product **3.18** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.26 g (0.76 mmol, 78%); yellow oil.

IR (FT): ν_{max} = 3355, 2931, 1637, 1537, 1350 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (br. d, *J* = 8 Hz, 2 H, H-3 of 2 Ar), 7.32 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$CH_3OC_6H_4$ of one diastereoisomer), 7.13 (br. t, *J* = 8 Hz, 2 H, H-4 of 2 Ar), 7.06–6.98 (m, 6 H, H-5, H-6 of 2 Ar and H-2/H-6 of 4-$CH_3OC_6H_4$ of other diastereoisomer), 6.83 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 6.69 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 4.84 (d, *J* = 6 Hz, 2 H, 2 C*H*OH), 4.30 (app. t, *J* = 6 Hz, exch., 2 H, 2 NH) 3.68 (s, 6 H, 2 OCH_3), 3.32–3.28 (m, 4 H, 2 C*H*CH_2 and 2 OH),

3.17–3.12 (m, 2 H, 2 CH_aH$_b$), 2.98 (br. s, 2 H, 2 CH$_a$$H_b$), 2.70 [s, 12 H, 2 N(CH$_3$)$_2$], 1.98 (s, 6 H, 2 CH$_3$).

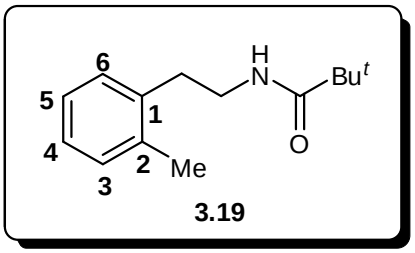
^{13}C NMR (125 MHz, CDCl$_3$): δ = 158.98, 158.95 (2 s, 2 C=O), 158.83, 158.81 (2 s, C-4 of 2 × 4-CH$_3$OC$_6$H$_4$), 137.7, 137.6 (2 s, 2 C-1), 134.5, 134.4 (2 s, C-1 of 2 × 4-CH$_3$OC$_6$H$_4$), 132.5, 132.4 (2 s, 2 C-2), 130.25, 130.21 (2 d, 2 C-3), 129.12, 129.09 (2 d, 2 C-4), 127.77, 127.74 (2 d, C-2/C-6 of 2 × 4-CH$_3$OC$_6$H$_4$), 126.64, 126.61 (2 d, 2 C-5), 126.12, 126.09 (2 d, 2 C-6), 113.57, 113.51 (2 d, C-3/C-5 of 2 × 4-CH$_3$OC$_6$H$_4$), 74.87, 74.85 (2 d, 2 CHOH), 55.3, 55.2 (2 q, 2 OCH$_3$), 48.55, 48.52 (2 d, 2 *C*HCH$_2$), 43.12, 43.14 (2 t, 2 CH$_2$), 36.12, 36.10 [2 q, 2 N(CH$_3$)$_2$], 19.9, 19.8 (2 q, 2 CH$_3$).

MS (EI): *m/z* (%) = 325 (100, [M – OH]$^+$), 237 (70), 208 (40).

HRMS (EI): *m/z* [M – OH]$^+$ calcd for C$_{20}$H$_{25}$N$_2$O$_2$: 325.1916; found: 325.1912.

3.10.5 Synthesis of *N*-(2-(2-methylphenyl)ethyl)pivalamide (3.19)

To a cooled solution (0 °C) of **3.8** (6.50 g, 48.1 mmol) and Et$_3$N (7.30 g, 72.1 mmol) in DCM (50 mL) pivaloyl chloride (6.96 g, 57.7 mmol) was slowly added in a dropwise manner over 30 min. The reaction mixture was stirred at room temperature for 1 h. The mixture was poured onto H$_2$O (50 mL) and the organic layer was separated, washed with H$_2$O (2 × 50 mL) and dried (MgSO$_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from Et$_2$O–hexane (1:1 by volume) to give pure **3.19** (9.80 g, 44.7 mmol, 93%) as a white solid.



3.19

mp 85–88 °C.

IR (FT): ν$_{max}$ = 3354, 2969, 1641, 1530, 1358, 1012 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.20–7.12 (m, 4 H, Ar), 5.69 (br., exch., 1 H, NH), 3.49 (app. q, *J* = 7 Hz, 2 H, CH_2NH), 2.85 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.38 (s, 3 H, CH$_3$), 1.18 [s, 9 H, C(CH$_3$)$_3$].

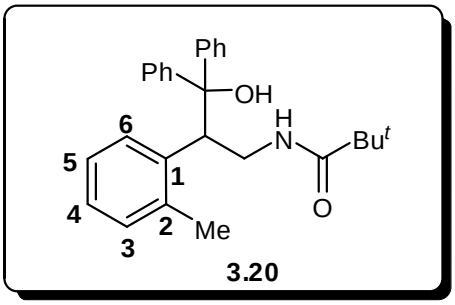
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3 (s, C=O), 137.0 (s, C-1), 136.4 (s, C-2), 130.5 (d, C-3), 129.4 (d, C-6), 126.6 (d, C-4), 126.0 (d, C-5), 39.4 (t, CH_2NH), 38.7 [s, $C(CH_3)_3$], 33.1 (t, CH_2Ar), 27.5 [q, $C(CH_3)_3$], 19.3 (q, CH_3).

MS (EI): *m/z* (%) = 219 (35, $[M]^+$), 118 (100), 105 (15), 85 (34), 57 (50).

HRMS (EI): *m/z* [M^+] calcd for $C_{14}H_{21}NO$: 219.1623; found: 219.1623.

3.10.6 Lithiation and substitution of *N*-(2-(2-methylphenyl)ethyl)pivalamide: synthesis of *N*-[3-hydroxy-3,3-diphenyl-2-(2-methylphenyl)propyl]pivalamide (3.20)

The procedure was identical with that described for lithiation and substitution of **3.9** except that it involved **3.19** (0.20 g, 0.91 mmol), with benzophenone (0.20 g, 1.1 mmol) as the electrophile, and was carried out at 0 °C. Following work-up, the crude product was purified by column chromatography (silica gel; Et_2O) to give pure **3.20** (0.31 g, 0.78 mmol, 86%) as a white solid.



3.20

mp 95–98 °C.

IR (FT): ν_{max} = 3359, 2964, 1643, 1524, 1303 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 1, 8 Hz, 2 H, H-2/H-6 of one C_6H_5), 7.58 (d, *J* = 8 Hz, 1 H, H-3), 7.26 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of one C_6H_5), 7.13–7.09 (m, 1 H, H-4 of one C_6H_5), 6.99 (dd, *J* = 1, 8 Hz, 2 H, H-2/H-6 of other C_6H_5), 6.96 (t, *J* = 8 Hz, 1 H, H-4 of other C_6H_5), 6.86 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of other C_6H_5), 6.89–6.80 (m, 3 H, H-4, H-5 and H-6), 5.32 (t, *J* = 6 Hz, exch., 1 H, NH), 4.37 (app. t, *J* = 7 Hz, 1 H, CH), 3.94 (br. s, exch., 1 H, OH), 3.83 (m, 1 H, CH_aH_b), 3.26 (m, 1 H, CH_aH_b), 1.97 (s, 3 H, CH_3), 0.78 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.4 (s, C=O), 146.8 (s, C-1), 146.3 (s, C-1 of one C_6H_5), 137.6 (s, C-1 of other C_6H_5), 137.1 (s, C-2), 130.0 (d, C-3), 129.1 (d, C-4 of one C_6H_5), 128.3 (d, C-3/C-5 of one C_6H_5), 127.3 (d, C-3/C-5 of other C_6H_5), 126.9 (d, C-4

of other C_6H_5), 126.4 (d, C-4), 126.3 (d, C-2/C-6 of one C_6H_5), 126.0 (d, C-5), 125.9 (d, C-2/C-6 of other C_6H_5), 125.7 (d, C-6), 79.8 (s, C-OH), 46.3 (d, CH), 41.2 (t, CH_2), 38.4 [s, $C(CH_3)_3$], 27.2 [q, $C(CH_3)_3$], 20.0 (q, CH_3).

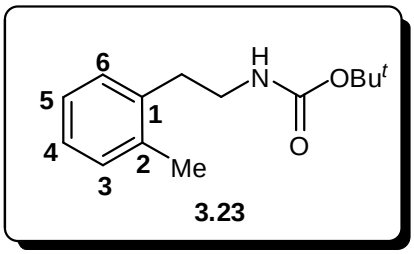
MS (EI): *m/z* (%) = 383 (5, $[M - H_2O]^+$), 282 (12), 219 (33), 182 (97), 133 (12), 118 (82), 105 (100), 72 (94).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{27}H_{29}NO$: 383.2253; found: 383.2249.

3.10.7 Synthesis of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (3.23)[9]

Compound **3.23** was synthesised based on a modified literature procedure.[14] However, the literature procedure was reported to give an oil and its ^{1}H NMR spectral data appeared to be wrong. No ^{13}C NMR spectral data were reported, and moreover, the purity was less than 93% and no yield was reported.[9]

To a cooled solution (0 °C) of **3.8** (2.00 g, 14.8 mmol) and Et_3N (2.24 g, 22.2 mmol) in DCM (20 ml) di-*tert*-butyl dicarbonate (3.87 g, 17.7 mmol) was slowly added in a dropwise manner. The cooling bath was removed and the reaction mixture was stirred under reflux for 1 h. The mixture was allowed to cool to room temperature and poured onto H_2O (50 mL). The organic layer was separated, washed with H_2O (2 × 50 mL) and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from hexane to give pure **3.23** (3.13 g, 13.3 mmol, 90%); white solid.



3.23

mp 56–59 °C (Lit.[9] oil).

IR (FT): ν_{max} = 3354, 2979, 1698, 1511, 1365, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08–7.04 (m, 4 H, Ar), 4.51 (br., exch., 1 H, NH), 3.26 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.73 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 2.26 (s, 3 H, CH_3), 1.37 [s, 9 H, $C(CH_3)_3$].

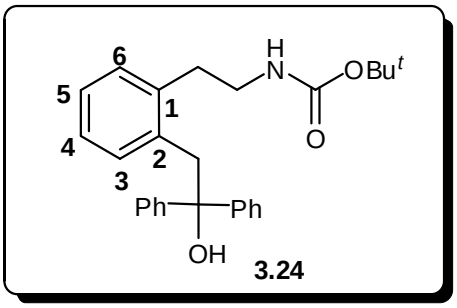
^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9 (s, C=O), 137.1 (s, C-1), 136.4 (s, C-2), 130.4 (d, C-3), 129.4 (d, C-6), 126.5 (d, C-4), 126.0 (d, C-5), 79.2 [s, *C*$(CH_3)_3$], 40.7 (t, CH_2NH), 33.6 (t, CH_2Ar), 28.4 [q, C(*C*$H_3)_3$], 19.3 (q, CH_3).

MS (EI): *m/z* (%) = 235 (3, $[M]^+$), 218 (2), 179 (98), 161 (97), 132 (73), 118 (100), 79 (98), 59 (96).

HRMS (EI): *m/z* [M^+] calcd for $C_{14}H_{21}NO_2$: 235.1572; found: 235.1572.

3.10.8 Lithiation and substitution of *tert*-butyl *N*-(2-(2-methylphenyl)ethyl)carbamate (3.23): synthesis of *tert*-butyl *N*-(2-(2-(2-hydroxy-2,2-diphenylethyl)phenyl)ethyl)carbamate (3.24)

A solution of *t*-BuLi in pentane (1.07 ml, 1.90 M, 2.0 mmol) was added to a stirred solution of **3.23** (0.20 g, 0.85 mmol) at –60 °C in anhydrous THF (15 mL) under a N_2 atmosphere. The mixture was stirred at *ca*. –30 to –25 °C for 1.5 h. A solution of benzophenone (0.36 g, 2.0 mmol) in anhydrous THF (5 mL) was added at –60 °C and the reaction mixture was allowed to warm up to 0 °C and stirred for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and diluted with Et_2O (20 ml). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; Et_2O) to give pure **3.24** (0.31 g, 0.75 mmol, 88%) as a colourless oil.



3.24

IR (FT): ν_{max} = 3366, 2976, 1698, 1508, 1366, 1031 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 C_6H_5), 7.18 (app. t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 C_6H_5), 7.12 (t, *J* = 8 Hz, 2 H, H-4 of 2 C_6H_5), 7.03–6.99 (m, 2 H, H-3 and H-5), 6.82 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 6.54 (d, *J* = 8 Hz, 1 H, H-6), 4.56 (br., exch., 1 H, NH), 4.27 (br., exch., 1 H, OH), 3.62 (s, 2 H, C*H*$_2$COH), 3.16 (br., 2 H, C*H*$_2$Ar), 2.55 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 1.30 [s, 9 H, C$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 147.1 (s, C-1 of 2 C_6H_5), 139.1 (s, C-2), 134.5 (s, C-1), 131.9 (d, C-6), 129.5 (d, C-5), 128.7 (d, C-4), 128.0 (d, C-3/C-5 of 2 C_6H_5), 126.9 (d, C-4 of 2 C_6H_5), 126.5 (d, C-2/C-6 of 2 C_6H_5), 125.7 (d, C-3), 79.3 [s, $C(CH_3)_3$], 77.3 (s, C–OH), 43.7 (t, CH_2C–OH), 41.4 (t, CH_2NH), 33.0 (t, CH_2Ar), 28.4 [q, C(CH_3)$_3$].

MS (EI): *m/z* (%) = 399 (14, $[M - H_2O]^+$), 343 (36), 325 (16), 299 (24), 282 (32), 183 (88), 167 (100), 132 (88), 105 (73), 91 (32), 77 (42).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{27}H_{29}NO_2$: 399.2198; found: 399.2210.

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Chapter Four

Directed Lithiation of 2-(4-Methoxyphenyl)ethanamine Derivatives

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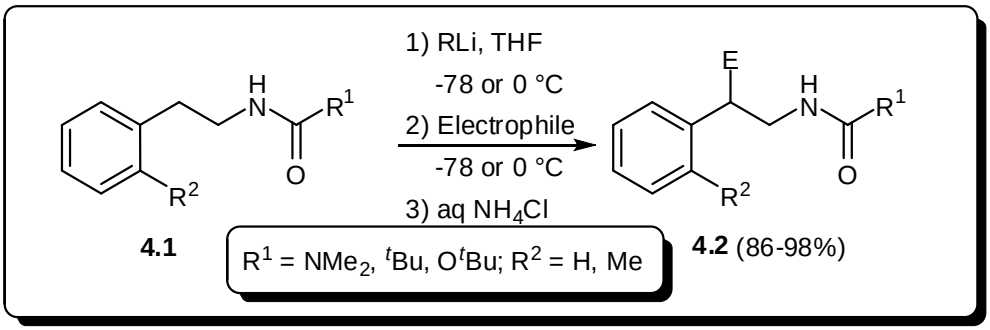
4.1 Introduction

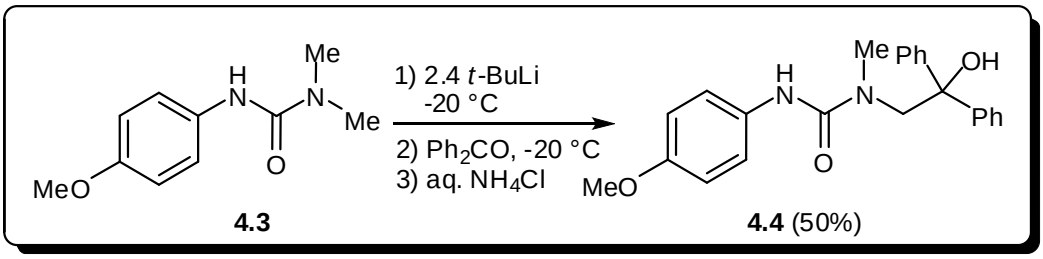
Phenylethylamine derivatives, especially ones containing oxygen substituents on the phenyl ring (which includes many biologically active compounds such as dopamine, adrenaline and mescaline), represent a hugely important class of chemicals of interest to both industry and academe, and selective methods for their synthesis are of considerable interest. Organolithium reagents play an important role in the development of clean and environmentally friendly processes for the regioselective production of specific products.[1,2] For example, lithiation of aromatic compounds often takes place proximal to a directing metalating group (DMG), which typically possess an oxygen or nitrogen atom.[3] Use of such DMGs to facilitate lithiation, followed by reactions of the organolithium intermediates obtained *in situ* with electrophiles, has found wide application in a variety of synthetic transformations to produce substituted aromatics or heterocycles.[4,5] This approach is one of the most efficient for synthesis of substituted and/or modified derivatives, which sometimes might be difficult to produce by other routes.[4,5]

Previously, in Chapters Two and Three, we have shown that the lithiation of *N′*-phenethyl-*N*,*N*-dimethylurea, and other *N*-(2-(2-methylphenyl)ethyl)amine derivatives **4.1** with an alkyllithium (RLi) in THF at -78 or 0 °C takes place on the nitrogen and on the CH_2 next to the phenyl or 2-methylphenyl ring (α-lithiation). Reactions of the lithium reagents produced *in situ* with various electrophiles produced a series of α-substituted derivatives **4.2** in high yields (Scheme 4.1). Some of the results have already been published.[6,7]



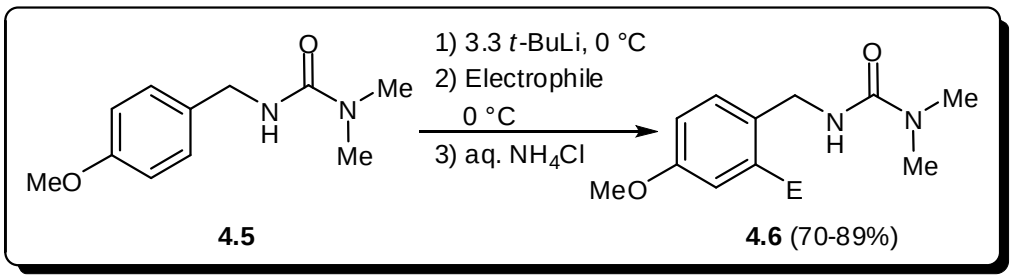
Scheme 4.1 Side–chain lithiation and substitution of substituted phenylethylamines **4.1**

In connection with other work on the use of lithium reagents in organic synthesis,[7] the Smith research group has recently reported a detailed study of the regioselective lithiation and substitution of various substituted phenylamines.[8,9] Sometimes different products were formed, depending on the nature of the lithium reagent used, the nature of the directing group and/or the reaction conditions. For example, lithiation of *N*′-(4-methoxyphenyl)-*N*,*N*-dimethylurea (**4.3**), using *tert*-butyllithium (*t*-BuLi; 2.4 equivalents) at –20 °C followed by reaction with benzophenone gave the corresponding substituted urea **4.4** as the main product, indicating that lithiation and substitution took place on one of the methyl groups of the urea moiety (Scheme 4.2).[8] Similarly, lithiation and substitution of *N*′-phenyl- and *N*′-(4-methylphenyl)-*N*,*N*-dimethylureas with *t*-BuLi at –20 °C followed by reaction with electrophiles gave the corresponding substituted products where lithiation and substitution took place on one of the methyl groups of the urea moiety exclusivly.[8] On the other hand, electron-withdrawing groups (*e.g.* Cl, F, CF_3) on the phenyl ring of the urea induced ring substitution to provide substituted derivatives in high yields.[8]



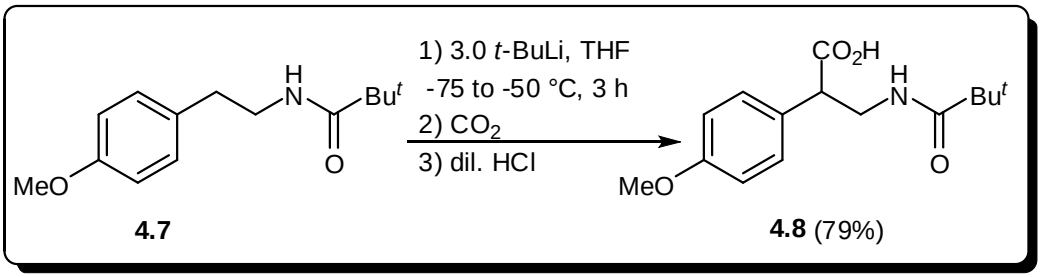
Scheme 4.2 Lithiation of *N*′-(4-methoxyphenyl)-*N*,*N*-dimethylurea (**4.3**) followed by reaction with benzophenone

Also, lithiation and substitution of *N*′-(4-methoxybenzyl)-*N*,*N*-dimethylurea (**4.5**) have been reported by Smith's group.[9a] Lithiation with *t*-BuLi (3.3 equivalents) at 0 °C for 6 h took place exclusively on the ring next to the urea-containing group (Scheme 4.3).[9a]



Scheme 4.3 Ring lithiation and substitution of *N*′-(4-methoxybenzyl)-*N*,*N*-dimethylurea (**4.5**)

The literature revealed that lithiation of *N*-2-((4-methoxyphenyl)-ethyl)pivalamide using *t*-BuLi at −75 to −50 °C, followed by treatment with carbon dioxide, resulted in carboxylation at the CH_2 next to the 4-methoxyphenyl ring (α-lithiation) to give the corresponding acid **4.8** in 79% yield (Scheme 4.4).[10]

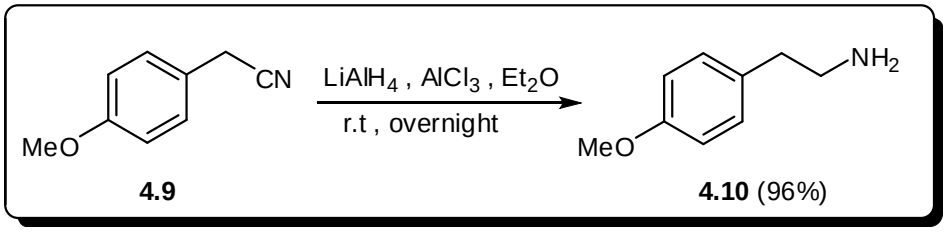


Scheme 4.4 Lithiation of **4.7** followed by reaction with CO_2 as reported by Schlosser[10]

There was no report of the lithiation and substitution of *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea at the outset of this work, and since the pivalamide and urea derivatives do not necessarily behave in a similar manner we became interested to study the lithiation of *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea. Four possible sites of lithiation are available; side-chain lithiation either on the CH_2 group next to the aromatic ring (α-lithiation) or on one of the methyl groups of the urea moiety, or ring lithiation (*ortho*-lithiation) either next to the urea-containing group or the methoxy group. In this chapter we report lithiation of *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea as well as the pivalamide and carbamate analogues. Some of the work represented in this chapter has been published while other is in preparation for publication.[11] The first task was to synthesise the urea derivative and investigate its lithiation under various reaction conditions.

4.2 Synthesis of 2-(4-methoxyphenyl)ethanamine (4.10)

2-(4-Methoxyphenyl)ethanamine (**4.10**) was synthesized from the corresponding nitrile **4.9** based on a literature procedure.[12] Reduction of 2-(4-methoxyphenyl)acetonitrile (**4.9**) with lithium aluminium hydride (2.2 equivalents) in presence of aluminium chloride (0.75 equivalents) in diethyl ether at room temperature overnight provided pure **4.9** in 96% yield without further purification (Scheme 4.5).

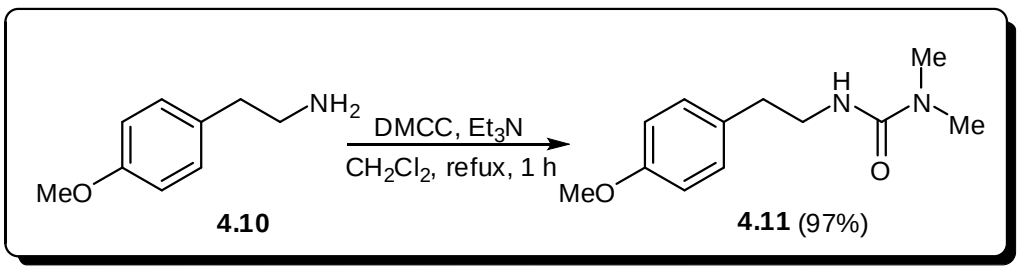


Scheme 4.5 Synthesis of 2-(4-methoxyphenyl)ethanamine (**4.10**)

The structure of compound **4.10** was confirmed by various spectroscopic techniques (see Section 4.10.2). The conversion of **4.10** into the corresponding urea derivative was next attempted.

4.3 Synthesis of *N′*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (4.11)

N′-(2-(4-Methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.11**) was synthesized based on a literature procedure for analogous compounds.[6,9e] Reaction of 2-(4-methoxyphenyl)ethanamine (**4.10**) with dimethylcarbamoyl chloride (DMCC) in dichloromethane (DCM) in the presence of triethylamine (TEA) as a base was carried out under reflux for 1 h. The crude product obtained after work-up was recrystallized from a mixture of hexane and Et_2O (1:1 by volume) to give pure **4.11** in 97% yield (Scheme 4.6).



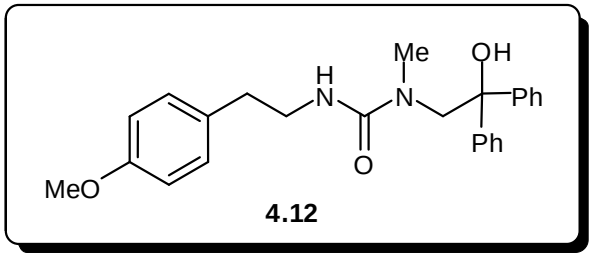
Scheme 4.6 Synthesis of *N′*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.11**)

The electron–impact (EI) mass spectrum of **4.11** showed a very intense molecular ion peak at *m/z* = 222 and the high resolution mass of this peak confirmed the formula as $C_{12}H_{18}N_2O_2$ (M). The structure of **4.11** was confirmed by its NMR spectral data (See Section 4.10.3 for details).

Having successfully produced **4.11**, our attention was next turned to investigation of its lithiation and substitution under various reaction conditions.

4.4 Lithiation and substitution of *N′*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (4.11)

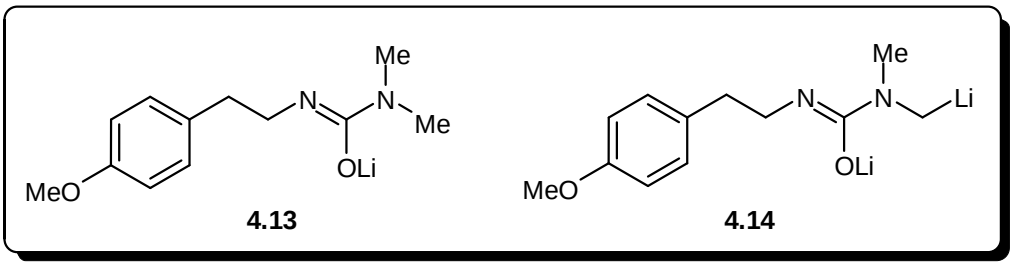
Reaction of **4.11** with *n*-BuLi (3.3 equivalents) was carried out in anhydrous THF under a nitrogen atmosphere at –78 °C for 2 h, then benzophenone (1.4 mole equivalents) was added. Following work-up the starting material was recovered quantitatively, indicating that no *C*-lithiation had taken place under such conditions. The reaction was repeated with *t*-BuLi under identical conditions and the TLC showed the presence of a new product along with recovered **4.11**. The crude reaction mixture was separated by column chromatography (silica gel; hexane–Et_2O in 1:1 by volume) to give unreacted starting material **4.11** (89%) along with the new product. The mass and NMR spectra of the new product were collected. Its ^{1}H NMR spectrum showed signals for three CH_2 groups, one of which resonated as a singlet at lower field (~4 ppm), fourteen aromatic protons, a methoxy group, and one methyl group. Its ^{13}C NMR confirmed the presence of three CH_2 carbons and one of them resonated at 61 ppm. Clearly, *C*-lithiation followed by substitution had taken place at one of the methyl groups of the urea unit. The electron–impact mass spectrum of the new product showed an intense peak at *m/z* = 386 and the high resolution mass of this peak confirmed the formula as $C_{25}H_{26}N_2O_2$. Such a formula corresponds to the loss of a molecule of water from the molecular ion expected from reaction of a dilithium reagent produced from **4.11** with benzophenone. Therefore, the structure of the new product was identified as *N*-(2-hydroxy-2,2-diphenylethyl)-*N′*-(2-(4-methoxyphenyl)ethyl)-*N*-methylurea (**4.12**; Figure 4.1).



4.12

Figure 4.1 The structure of product **4.12**

Clearly, lithiation of **4.11** produced monolithium reagent **4.13** due to lithiation on NH, when one mole equivalent of *t*-BuLi was added, followed by lithiation on one of the methyl groups to give the dilithium reagent **4.14** (Figure 4.2) when the second mole equivalent of *t*-BuLi was added. Reaction of **4.14** with benzophenone gave **4.12** (Figure 4.1), which was produced in 5% yield.



4.13 **4.14**

Figure 4.2 The structures of lithium intermediates **4.13** and **4.14**

In an attempt to improve the yield of **4.12** the reaction was repeated with *n*-BuLi (2.4 equivalents) at a higher temperature (–30 to –20 °C). Following work up the TLC showed the presence of two products along with the starting material. The crude product was purified by column chromatography (silica gel; hexane–Et_2O 1:1 by volume) to give the starting material **4.11** (61%), the methyl substituted product **4.12** (13%) and another new product. Product **4.12** was consistent in all respects with the one produced previously when *t*-BuLi was used at –78 °C.

The ^{1}H NMR spectrum of the second new product showed signals for two CH_2 groups, a dimethylamino group, a methoxy group, two exchangeable protons and thirteen aromatic protons. This indicated that the lithiation followed by reaction of benzophenone had taken place on the ring either next to either the methoxy group or the urea-containing group. Also, the ^{13}C NMR spectrum of the second product confirmed

that ring substitution had taken place. The chemical shifts for the carbon atoms of the two possible ring substitution products were predicted by ChemDraw and were compared with the ones recorded for the second product. After careful inspection it was clear that the carbon chemical shifts of the second new product matched the ones predicted for the C-2 substitution product (next to the urea-containing group) better than the ones predicted for C-3 substitution. For example, the new aromatic singlet resonated at 146.8 ppm and C-2 for the 2-substituted was predicted to resonate at 145.0 ppm, while, C-3 for the 3-substituted product was predicted to resonate at 118.9 ppm.

The electron–impact mass spectrum of the second product showed an intense peak at *m/z* = 386 and the high resolution mass analysis of this peak confirmed its formula as $C_{25}H_{26}N_2O_2$, which could be attributed to the elimination of water from the molecular ion. Therefore, the structure of the second product was identified as *N*′-(2-(2-(hydroxydiphenylmethyl)-4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.15**; Figure 4.3) and was produced in 22% yield. Product **4.15** was produced from reaction of the dilithium reagent **4.16** (Figure 4.3), produced *in situ* from **4.13**.

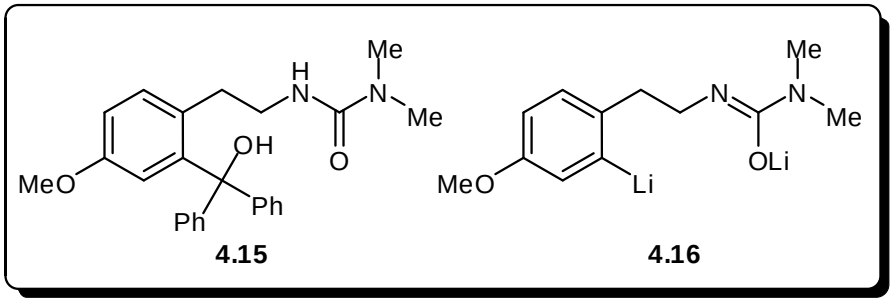


Figure 4.3 The structures of product **4.15** and its dilithium intermediate **4.16**

The structure of **4.15** was confirmed further by X-ray crystallography (Figure 4.4).

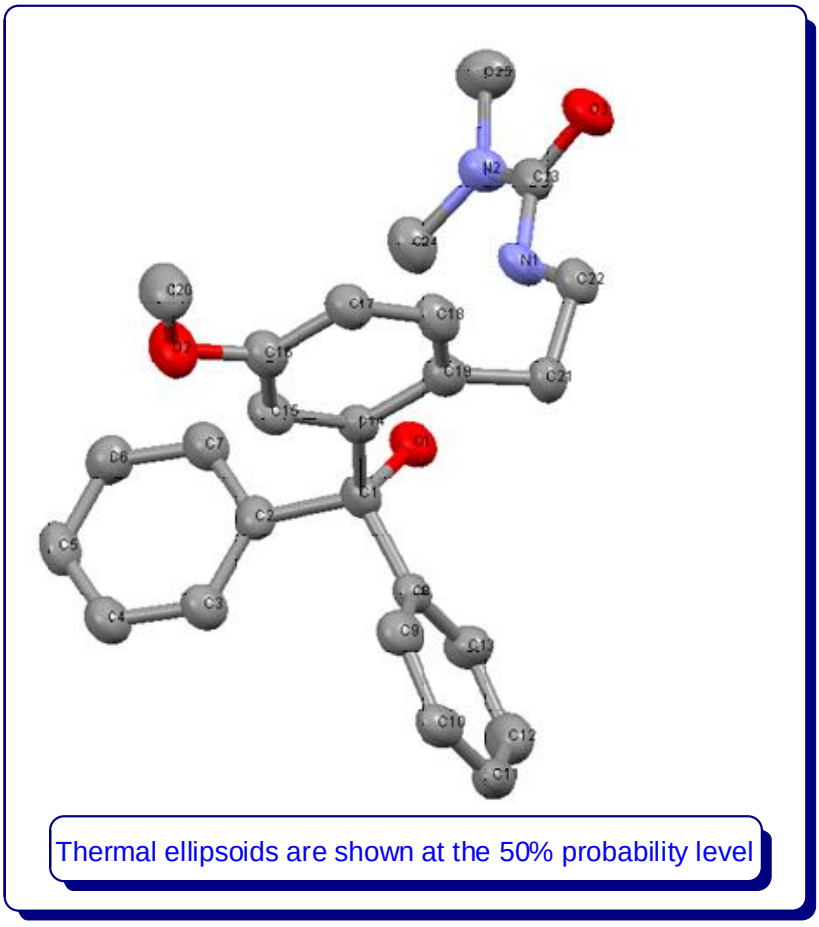


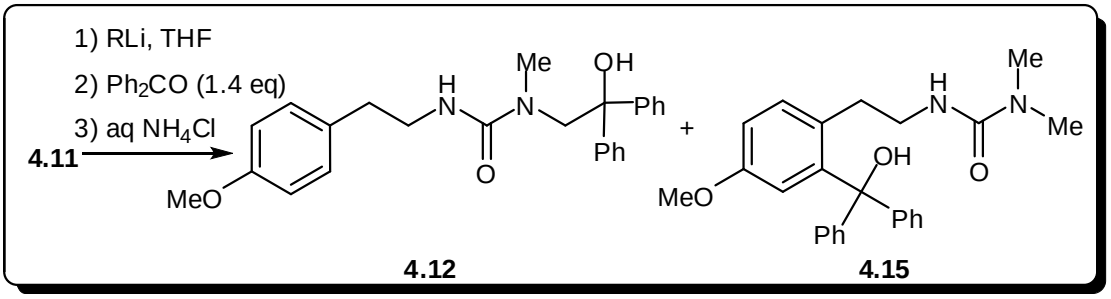
Figure 4.4 X-ray crystal structure of compound **4.15**

Several experiments were conducted in order to find conditions under which the lithiation could be more selective toward the ring position to provide **4.15** in high yield. Double lithiation of **4.11** with 2.4 equivalents of *t*-BuLi at the reaction temperature used with *n*-BuLi (–30 to –20 °C) followed by reaction with benzophenone gave a mixture of **4.12** (16%) and **4.15** (20%) (Table 4.1, Entry 4), suggesting that the regioselectivity was somewhat less favourable for formation of **4.15** than when *n*-BuLi was used (Table 4.1; Entry 3).

Higher combined yields of the substitution products **4.12** and **4.15** (75% with *n*-BuLi and 68% with *t*-BuLi) were obtained when 3.3 equivalents of lithiating agent were used (Table 4.1; Entries 5 and 6). It was clear that the regioselectivity for formation of the ring-substituted product was again better in the case of *n*-BuLi (**4.12**/**4.15** was 18/57) compared with using *t*-BuLi (**4.12**/**4.15** was 22/46). Having

successfully produced a high overall yield of products (75%) using *n*-BuLi (Table 4.1; Entry 5), we next investigated the effect of temperature on the regioselectivity and yields of **4.12** and **4.15**.

Table 4.1 Lithiation of **4.11** followed by reaction with benzophenone under various reaction conditions



Entry	RLi		T (°C)	Yield (%)[a]	
	Mol. equiv	Time (h)		**4.12**	**4.15**
1	*n*-BuLi (3.3)	2	–78	—	—[b]
2	*t*-BuLi (3.3)	2	–78	5	—[b]
3	*n*-BuLi (2.4)	2	–30 to –20[c]	13	22
4	*t*-BuLi (2.4)	2	–30 to –20[c]	16	20
5	*n*-BuLi (3.3)	2	–30 to –20[c]	18	57
6	*t*-BuLi (3.3)	2	–30 to –20[c]	22	46
7	*n*-BuLi (3.3)	2	–20 to 0	7	85
8	*t*-BuLi (3.3)	2	–20 to 0	27	55
9	*n*-BuLi (2.4)	2	0	9	38
10	*t*-BuLi (2.4)	2	0	16	28
11	*t*-BuLi (3.3)	1	0	21	62
13	*n*-BuLi (3.3)	0.25	0	10	40
14	*n*-BuLi (3.3)	1	0	12	69
15	*n*-BuLi (3.3)	2	0	15	83
16	*t*-BuLi (3.3)	2	0	23	75

[a] Isolated yield after purification by column chromatography.
[b] Starting material **4.11** was recovered (90–96%).
[c] Initial addition of BuLi was at –60 °C.

Better yields and selectivity for formation of **4.15** were obtained when the reaction was attempted at a higher temperature (−20 to 0 °C) with *n*-BuLi as the lithium reagent. Under these conditions compound **4.12** was produced in only 7% yield along with **4.15** as the major product, produced in 85% yield (Table 4.1; Entry 7). Poorer results in terms of overall yield and selectivity were obtained when *t*-BuLi was used under identical conditions (Table 4.1; Entry 8). Various attempts were made in order to find conditions under which **4.15** could be produced as the only product by varying the molar equivalents and type of lithium reagent and reaction time at a higher temperature (0 °C). Excellent overall yields of up to 98% could be produced, but with lower regioselectvities (Table 4.1; Entries 9–16). The yields of pure **4.12** and **4.15** obtained are summarized in Table 4.1.

Some general trends can be deduced from the results in Table 4.1. At low temperature (-78 °C), no lithiation takes place with *n*-BuLi and only a low yield of lithiation-substitution product (specifically **4.12**) is obtained after 2 hours with the more reactive *t*-BuLi. At -30 to -20 °C, both reagents bring about lithiation, but the reaction appears to be slow, yielding about 35% of products after a 2 hour lithiation period with just a small excess of lithiating agent (2.4 equivalents instead of the theoretical 2.0). Both reagents show a small preference for lithiation on the ring (ratio **4.15**/**4.12** = 1.7 with *n*-BuLi and 1.3 with *t*-BuLi). Use of a larger excess of lithiating agent (3.3 equivalents) understandably results in higher levels of lithiation (around 70% after 2 hours), but also in greater selectivity for ring-lithiation (ratio **4.15**/**4.12** = 3.2 with *n*-BuLi and 2.1 with *t*-BuLi), which is less easy to understand. Perhaps use of the larger quantity of reagent resulted in a quicker temperature rise, so that more of the reaction occurred at the higher end of the temperature range, at which the selectivity for **4.15** appears to be greater. Alternatively, perhaps the rate equation for ring lithiation involves a higher order in lithiating agent than the rate equation for *N*-methyl lithiation, so that it would be favoured to a greater extent at higher concentration of organolithium. At -20 to 0 °C the yields were better still and the selectivity was greater too (ratio **4.15**/**4.12** = 12.1) with *n*-BuLi. The best yields were achieved at 0 °C, and at that temperature the higher selectivity was also recognizable with *t*-BuLi. Thus, it is clear that the general trend is that the yields and selectivity for formation of **4.15** increase as the temperature increases and with larger quantities of alkyllithium. In terms of selectivity for formation of **4.15**, *n*-BuLi is better than *t*-BuLi. From experiments conducted under similar

conditions for different periods of time the evidence for equilibration of the intermediate organolithium species is not strong, but if it is occurring it appears that **4.15** is the more favoured species at 0 °C.

The results in Table 4.1 indicated that **4.15** was the major product at higher temperature (0°C) while **4.12** was the only product at lower temperature (–78 °C). It appeared that the lithiation of **4.11** at low temperature was under kinetic control to form the intermediate **4.14** with a strong lithium reagent (*t*-BuLi), possibly as a result of chelation (Figure 4.5). At higher temperature, the intermediate **4.16** was thermodynamically stable, possibly due to chelation (Figure 4.5) and the inductive effect of the methoxy group.

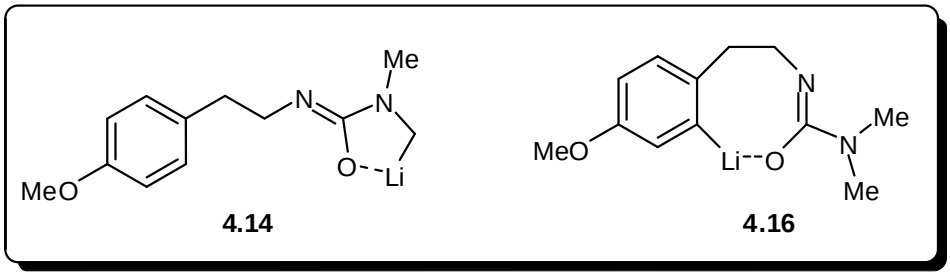
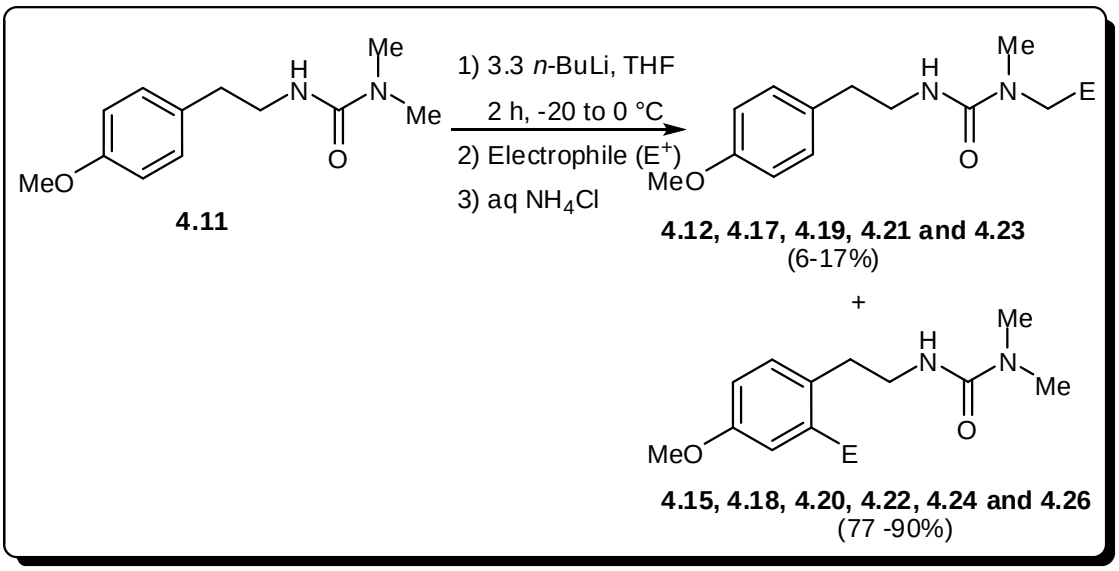


Figure 4.5 Stabilization of dilithium intermediates **4.14** and **4.16**

The results clearly indicated that no conditions were found under which only one product could be obtained. However, product **4.15** could be produced as the major product under conditions where the yield of **4.12** was low. The best conditions were found to involve use of *n*-BuLi (3.3 equivalents) as the lithium reagent at –20 to 0 °C for at least 2 hours (Table 4.1, Entry 7).

It was of interest to see if the reaction with other electrophiles would be useful and general. Consequently, reactions of **4.11** under the conditions described above (Table 4.1; Entry 7), with various other electrophiles (benzophenone, 4-methoxyacetophenone, cyclohexanone, 4-dimethylaminobenzaldehyde, benzaldehyde, iodoethane and dimethylformamide) were carried out (Scheme 4.7).



Scheme 4.7 Lithiation and substitution of *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.11**)

Each reaction was conducted under identical conditions. The crude products were purified by column chromatography (silica gel; Et_2O–hexane 1:1 by volume), to give the corresponding substituted derivatives **4.17**–**4.26** in high overall yields (Table 4.2).

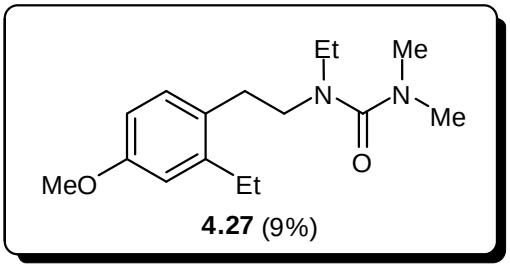
Table 4.2 Synthesis of substituted *N*′-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylureas **4.12, 4.15** and **4.17–4.26** according to Scheme 4.8

Electrophile	E	Product (%)[a]	
		Side-chain	*ortho*-
Ph_2CO	$Ph_2C(OH)$	**4.12** (7)	**4.15** (85)
4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)(Me)$	**4.17** (12)	**4.18** (82)
$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**4.19** (17)	**4.20** (77)
4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	**4.21** (10)	**4.22** (80)
PhCHO	PhCH(OH)	**4.23** (6)	**4.24** (82)
EtI	Et	—	**4.25** (86)[b]
Me_2NCHO	CHO	—	**4.26** (90)

[a] Yield of the isolated pure product after column chromatography.
[b] Diethyl derivative **4.27** (Figure 4.5) was produced in 9% yield.

As can be seen from Table 4.2 it was clear that lithiation and substitution of **4.11** gave a mixture of two products in which ring substitution products were the major ones. It appears that directed lithiation and substitution of *N′*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.11**) were achieved under the conditions tried in high yields (77–90%) along with side-products due to methyl substitution but in low yields (0 to 17%). The structures of the products were confirmed by various spectroscopic techniques including IR, NMR and mass spectra (see Section 4.10.4 for details).

When iodoethane and dimethylformamide were used as electrophiles no *N*-methyl substitution products were obtained. Furthermore, in the case of iodoethane as an electrophile a side-product was obtained. Its NMR spectra showed the presence of two ethyl groups. Also, its ^{1}H NMR spectrum showed no exchangeable signals, indicating that further ethylation had taken place on the NH nitrogen. The structure of the side-chain product was identified as diethyl derivative **4.27** (Figure 4.6) and was obtained in 9% yield. The structure of **4.27** was confirmed further by low and high resolution mass spectra (see Section 4.10.4).



4.27 (9%)

Figure 4.6 The structure of compound **4.27**

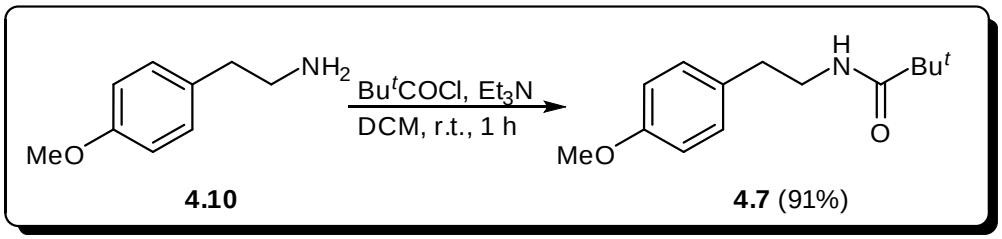
When the yields of **4.25** and **4.27** are added together, the total isolated yield of ring-substitution products is seen to be 95%. Also, when DMF was used as electrophile the isolated yield of ring-substitution product was 90%. On the other hand, 17% of *N*-methyl substitution product was isolated from the reaction with cyclohexanone, so that the maximum quantity of ring-substitution product formed in that case, even allowing for any losses, could have been no higher than 83%. These differences appear to be too great to be explained by accidental differences in experimental conditions and cannot be explained simply by failure to isolate all of one or other of the products, so the most likely explanation is that there is equilibration between the two intermediate

organolithium species **4.14** and **4.16**. The equilibrium position would favour **4.16** and a highly reactive electrophile such as cyclohexanone might trap the equilibrium mixture sufficiently rapidly to produce more-or-less the proportions of products that reflect the two lithium species in the equilibrium mixture. However, a relatively unreactive electrophile that reacted more rapidly with **4.16** than with **4.14** would remove **4.16** from the mixture, thereby allowing the equilibrium to shift by conversion of **4.14** into more **4.16**, resulting ultimately in the production of a significantly higher yield of ring-substitution product. This would explain the 95% production of ring-substitution products in the case of iodoethane as electrophile.

The results obtained are in sharp contrast with the early results reported by Schlosser[11] for the α–lithiation for *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**4.7**) using three molar equivalents of *t*-BuLi at −75 to −50 °C (Scheme 4.4). It was therefore of interest to test lithiation of **4.7** under the conditions optimised for the ring lithiation for **4.11** (Scheme 4.7) to see if its ring lithiation could be achieved. Therefore, we decided to study the lithiation of **4.7**. The first task was the synthesis of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**4.28**) from the corresponding amine.

4.5 Synthesis of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (4.7)

N-(2-(4-Methoxyphenyl)ethyl)pivalamide (**4.7**) was synthesized from reaction of 2-(4-methoxyphenyl)ethanamine (**4.10**) with pivaloyl chloride (1.2 equivalents) in DCM in the presence of triethylamine (TEA) for one hour at room temperature (Scheme 4.9). Following work-up the crude product was recrystallized from a mixture of Et_2O–hexane (1:5 by volume) to give pure **4.7** in 91% yield (Scheme 4.8) as a colourless crystalline solid. The structure of compound **4.7** was confirmed by various spectroscopic techniques (see Section 4.10.5).



Scheme 4.8 Synthesis of *N*-(2-(2-methylphenyl)ethyl)pivalamide (**4.7**)

Our attention was next turned to investigation of lithiation of **4.7** with *t*-BuLi under Schlosser conditions[11] and with *n*-BuLi at −75 to −50 °C, followed by reaction with benzophenone as a representative electrophile.

4.6 Lithiation and substitution of *N*-(2-(4-methoxyphenyl)ethyl)-pivalamide (4.7)

First, we attempted to regenerate the result reported by Schlosser (Scheme 4.4)[11] for the side-chain substitution of **4.7**. It was found that lithiation of **4.7** with *t*-BuLi (three molar equivalents) followed by reaction with carbon dioxide under the Schlosser conditions gave the corresponding acid **4.8** in 72% yield, similar to the result found by Schlosser (Scheme 4.4).[11]

It was of interest to test the lithiation reaction of **4.7** with other electrophiles since carbon dioxide was the only electrophile used previously.[11] Therefore, the reaction of **4.7** was repeated under identical conditions but with benzophenone (1.4 molar equivalents) as the electrophile. Following work-up the reaction mixture was checked by TLC and showed the formation of a new product along with **4.7**. The crude product was purified by column chromatography to give residual starting material **4.7** (30% yield) and the new product. The new product was identified as the expected side-chain substitution product **4.28** (Figure 4.7) and was obtained in 58% yield. Compound **4.28** was clearly obtained *via* the intermediacy of dilithium intermediate **4.29** (Figure 4.7), which was consistent with the early result reported by Schlosser in terms of the site of lithiation.[11] The structure of **4.28** was confirmed by X-ray crystallography (Figure 4.8).

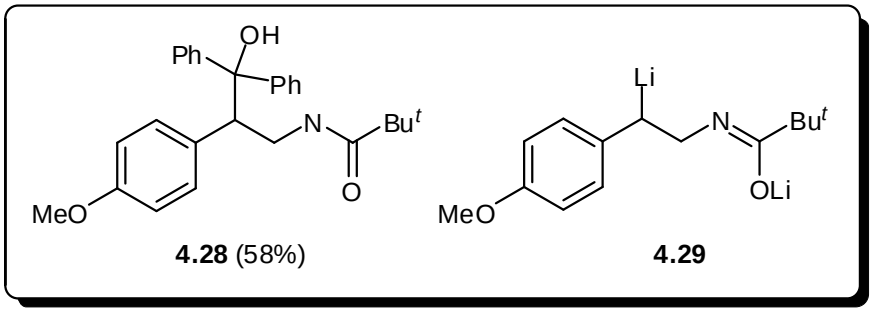


Figure 4.7 Structures of compound **4.28** and its dilithium intermediate **4.29**

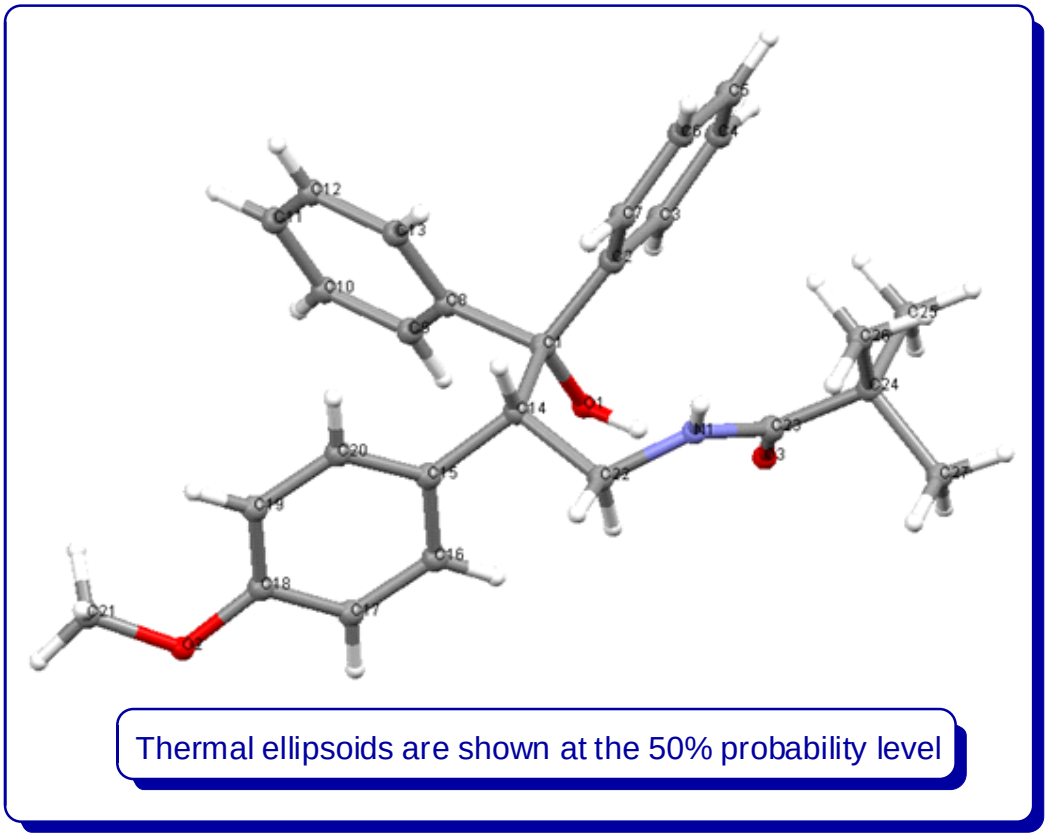


Figure 4.8 X-ray crystal structure of compound **4.28**

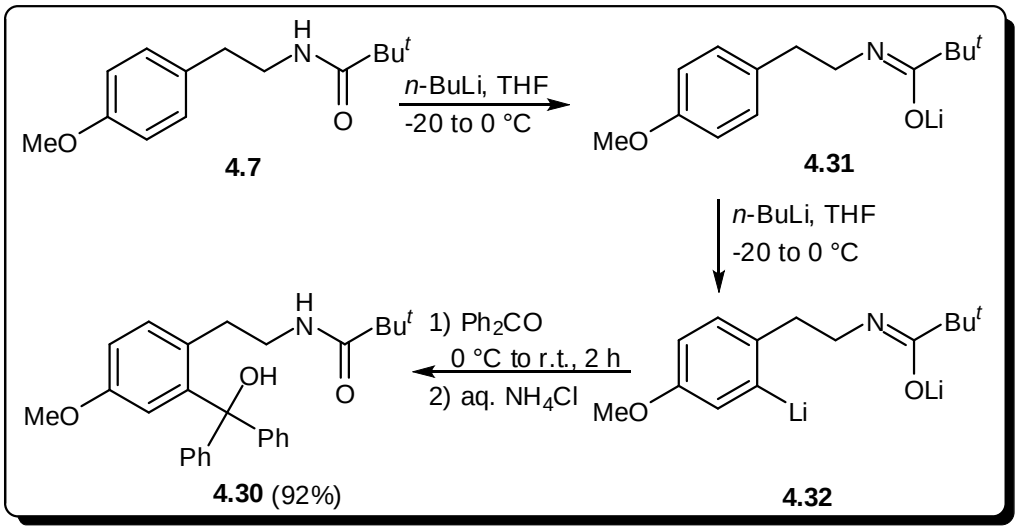
The ^{1}H NMR spectrum of **4.28** indicated that the two hydrogens of the CH_2 group were diastereotopic and appeared as separated signals. Also, in the ^{13}C NMR spectrum the carbons of the two phenyl groups appeared as separated signals, verifying that they were diastereotopic.

Next, we turned our attention to attempt lithiation of **4.7** under the conditions used for the ring lithiation of the urea derivative **4.11** (Scheme 4.7) to see what effect the conditions could have on the site of lithiation and/or the yield of product. Lithiation of **4.7** with *n*-BuLi (3.0 molar equivalents) at −20 to 0 °C for 2 h was attempted. A solution of benzophenone (1.4 molar equivalents) in THF was added to the reaction mixture at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h. Following work-up the crude product was purified by column chromatography to provide a new product.

The ^{1}H NMR spectrum of the new product showed signals for four protons due to two CH_2 groups, the nine protons of the *tert*-butyl group and thirteen aromatic protons. This indicated that the lithiation followed by reaction with benzophenone had

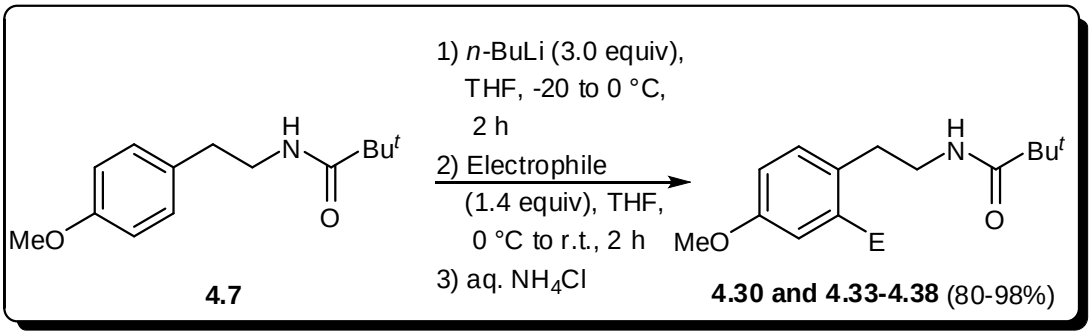
taken place on the ring next to either the methoxy or the urea counting group. The ^{13}C NMR spectrum of the new product showed signals that were consistent with ones predicted by ChemDraw for the substitution product due to lithiation at the 2-position (next to the pivaloyl-containing group). The new product was identified as *N*-(2-(hydroxydiphenylmethyl)-4-methoxyphenethyl)pivalamide (**4.30**; Scheme 4.9) and was obtained in 92% yield. The electron–impact mass spectrum of **4.30** showed a high intensity peak at *m/z* = 399 and the high resolution mass analysis of this peak confirmed its formula as $C_{27}H_{29}NO_2$, which could be attributed to the elimination of water from the molecular ion.

It is clear that the lithiation of **4.7** produced the monolithium reagent **4.31** and dilithium reagent **4.32** *in situ* (Scheme 4.9). Reaction of **4.32** with benzophenone would produce **4.30**.



Scheme 4.9 Lithiation of **4.7** with *n*-BuLi followed by reactions with benzophenone

The reaction clearly had potential as a synthetic method and therefore the same lithiation procedure was used for reactions with a range of other electrophiles, including cyclohexanone, 2-butanone, 4-anisaldehyde, 4-(dimethylamino)benzaldehyde, dimethylformamide and iodine (Scheme 4.10). Following work-up of the reaction mixtures the crude products were purified by column chromatography (silica gel; Et_2O–hexane, in 1:5 by volume) to give the corresponding substituted products **4.33**–**4.38** (Scheme 4.10) in 80–98% yields (Table 4.3).



Scheme 4.10 Lithiation of **4.7** with *n*-BuLi followed by reactions with electrophiles

Table 4.3 Synthesis of 2-substituted derivatives **4.30** and **4.33**–**4.38** from lithiation and substitution of **4.7** according to Scheme 4.10

Product	Electrophile	E	Yield (%)[a]
4.30	Ph_2CO	$Ph_2C(OH)$	92
4.33	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	88
4.34	EtCOMe	EtC(OH)Me	95
4.35	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	80
4.36	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	90
4.37	Me_2NCHO	CHO	98
4.38	I_2	I	89

[a] Yield of isolated product after purification by flash column chromatography.

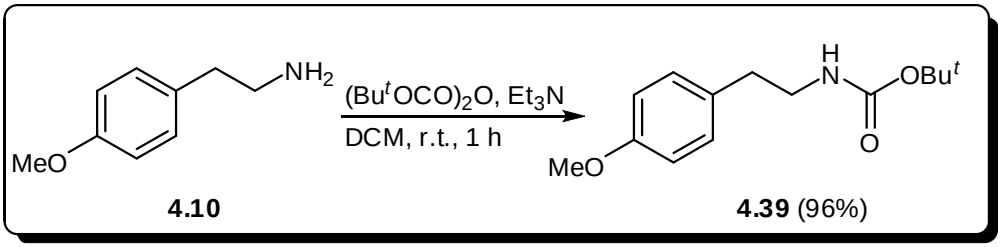
Clearly, the procedure outlined in Scheme 4.10 represents a simple, efficient and high yielding route for substitution of *N*-(4-methoxyphenethyl)pivalamide (**4.7**) *ortho*- to the pivaloylaminoethyl group. However, it was not clear why lithiation of **4.7** with *t*-BuLi at −75 to −50 °C gave side-chain substitution, while lithiation with *n*-BuLi at –20 to 0 °C gave ring substitution. One possibility was that at low temperature the lithiation step was under kinetic control, leading to the intermediate **4.29**, with only the *t*-BuLi sufficiently reactive to effect the lithiation under such conditions, but that at higher temperature the organolithium intermediate **4.29** was capable of isomerization to **4.32**, so that the reactions at higher temperature were under thermodynamic control. In order to test this possibility, the reaction of **4.7** was initially carried out at –75 to –50 °C with *t*-BuLi (3.0 molar equivalents) for 3 h (conditions previously shown to produce

4.29), and the mixture was then warmed to 0 °C and maintained for a further 2 h, after which benzophenone (1.4 molar equivalents) was added. The cooling bath was removed and the mixture was stirred for 2 h while warming to room temperature. Purification of the crude product by column chromatography gave **4.30** in 82% yield along with residual **4.7** (14%). This finding clearly indicated that the dilithium reagent **4.32** (Scheme 4.9) is thermodynamically more stable than the dilithium reagent **4.29** (Figure 4.7) at higher temperature.

Our attention was next turned to investigation of lithiation of the carbamate derivative under similar conditions to see what effect the substituent could have on the lithiation site. The first task was the synthesis of *tert*-butyl 2-(2-methylphenyl)ethylcarbamate.

4.7 Synthesis of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate (4.39)

tert-Butyl 2-(2-methylphenyl)ethylcarbamate (**4.39**) was synthesized from reaction of 2-(2-methylphenyl)ethanamine (**4.10**) with di-*tert*-butyl dicarbonate (Scheme 4.11) under conditions similar to those used for the synthesis of **4.11** (Scheme 4.6). Following work-up the crude product obtained was recrystallized from hexane to give pure **4.39** in 96% yield (Scheme 4.11) as a white solid.



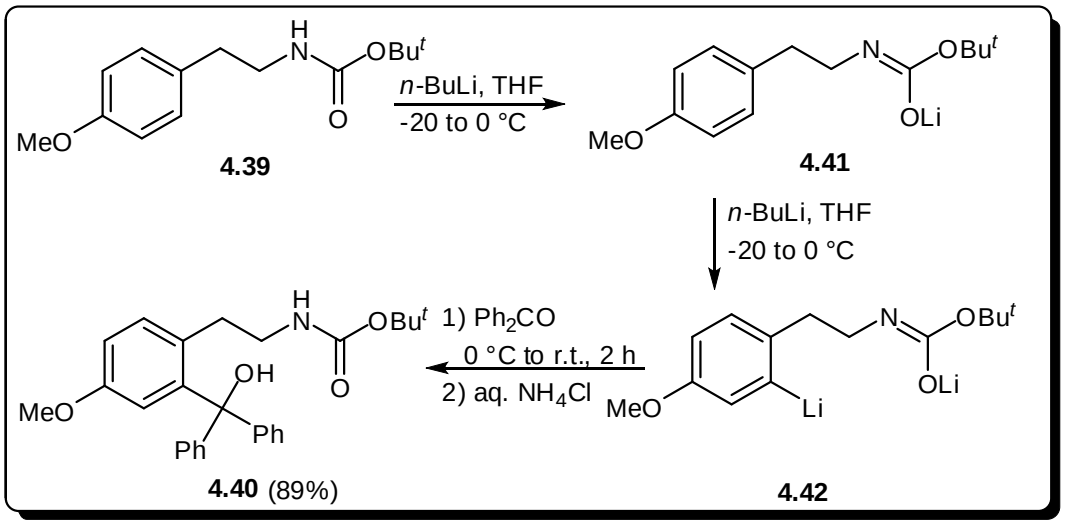
Scheme 4.11 Synthesis of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate (**4.39**)

The structure of compound **4.39** was confirmed by various spectroscopic techniques (see Section 4.10.7). Investigation of lithiation of compound **4.39** was next attempted under the conditions used by Schlosser[11] for side-chain lithiation of **4.7** (Scheme 4.4) and the conditions we optimized for directed lithiation for **4.11** and **4.7** to see what effect the substituents and conditions could have on the site of lithiation.

4.8 Lithiation and substitution of *tert*-butyl 2-(2-methylphenyl)ethyl carbamate (4.39)

First, lithiation of **4.39** was attempted under Schlosser's conditions,[11] followed by reaction with benzophenone. Following work-up and purification of the crude product by column chromatography a new product was obtained along with starting material **4.39** (75%). The new product was subjected to NMR and mass spectral analysis and was identified as the *ortho*-substituted product **4.40** (19% yield). No other product due to side-chain lithiation and substitution was isolated.

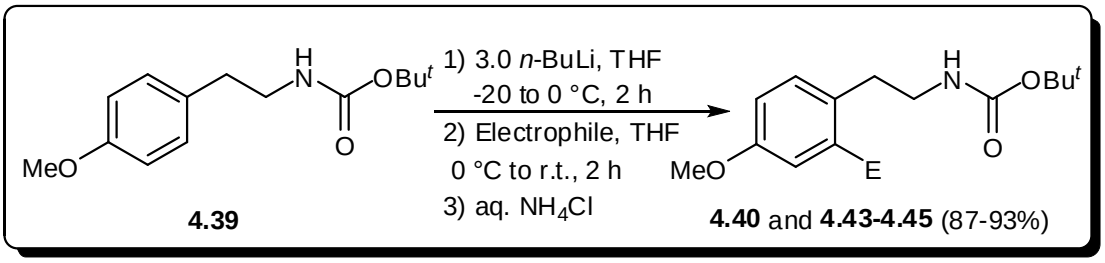
Next we attempted lithiation of **4.39** under the standard conditions that were used for **4.11** with *n*-BuLi, followed by reaction with benzophenone (1.2 equivalents). Product **4.40** (Scheme 4.12) was obtained in high yield as the only observable product (89%).



Scheme 4.12 Lithiation and substitution of **4.39** followed by reaction with benzophenone

It was of interest to see if reactions of the lithium intermediate **4.42** with other electrophiles would be useful and general. Consequently, reactions of **4.42**, prepared *in situ* from compound **4.41**, with other electrophiles (4-methoxyacetophenone, dimethylformamide and iodoethane) were carried out (Scheme 4.13). Each reaction was conducted under identical conditions and then quenched by the addition of aq. NH_4Cl. Afterwards, the crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:1) to give the corresponding substituted derivatives **4.43–4.45** (Scheme

4.13) in high yields (Table 4.4). The structures of the products were confirmed by various spectroscopic techniques (See Section 4.10.8).



Scheme 4.13 Lithiation and substitution of *tert*-butyl 2-(2-methylphenyl)ethyl carbamate (**4.39**)

Table 4.4 Synthesis of substituted derivatives **4.40** and **4.43**–**4.45** from lithiation and substitution of **4.39** according to Scheme 4.13

Product	Electrophile	E	Yield %[a]
4.40	Ph_2CO	$Ph_2C(OH)$	89
4.43	4-$Me_2NC_6H_4COH$	4-$Me_2NC_6H_4C(OH)H$	93
4.44	Me_2NCHO	CHO	87
4.45	EtI	Et	90

[a] Yield of isolated product after purification by flash column chromatography.

4.9 Conclusions

In conclusion, *N*-(2-(4-methoxyphenyl)ethyl)amine derivatives undergo lithiation with *n*-BuLi at 0 ºC, followed by treatment with various electrophiles, to give high yields of the corresponding substituted products having the substituent *ortho*- to the directing group. This contrasts sharply with earlier results for the pivaloyl derivative using *t*-BuLi at lower temperature, which gave α-substitution. The variation arises because the dilithium reagent **4.29**, formed at low temperature with *t*-BuLi, is less stable than dilithium reagent **4.32**, to which it isomerises at 0 °C.

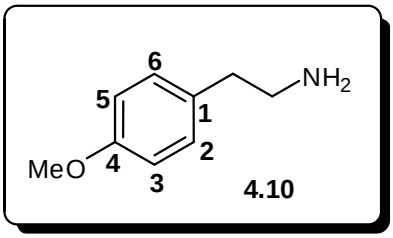
4.10 Experimental

4.10.1 General Experimental

A general experimental section outlining the instrumentation and reagents used is included in Chapter Two (Section 2.14.1). The term "Ar" is used to represent "4-methoxyphenyl" in the NMR spectra data in this experimental section. X-ray crystal structures were carried out at the X-Ray Crystallography Service, School of Chemistry, Cardiff University. The X-ray single-crystal diffraction data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K_{α}, (λ = 0.710 73 Å) radiation. Crystal and structure refinement data are shown in the supplementary information. The structures were solved by direct methods using SHELXS-96[13] and refined with all data on F^2 full-matrix least squares using SHELXL-97.[14] Non-hydrogen atoms were generally refined anisotropically. Hydrogen atom positions were located from difference Fourier maps and a riding model with atomic displacement parameters 1.2 times (1.5 times for methyl groups) those of the atom to which they are bonded was used for subsequent refinements.

4.10.2 Synthesis of 2-(4-methoxyphenyl)ethanamine (4.10)

A solution of $AlCl_3$ (6.70 g, 50 mmol) in anhydrous diethyl ether (50 mL) was added to lithium aluminium hydride (5.70 g, 150.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. A solution of 2-(4-methoxyphenyl)acetonitrile (**4.9**; 10.00 g, 68.0 mmol) in anhydrous diethyl ether (15 mL) was added to the mixture at 0 °C. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (25 mL) and quenched with water. After the solution was acidified with conc. sulfuric acid, it was basified with sodium hydroxide (6 M). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2-(4-methoxyphenyl)ethanamine (**4.10**; 9.86 g, 65.3 mmol, 96%) as a white crystalline solid.



4.10

mp 113–115 °C.

IR (FT): ν_{max} = 3319- 3201, 2959, 1512 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.75 (d, *J* = 8 Hz, 2 H, H-3/H-5), 3.69 (s, 3 H, OCH_3), 2.83 (t, *J* = 7 Hz, 2 H, C*H*$_2$$NH_2$), 2.59 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.22 (br., exch., 2 H, NH_2).

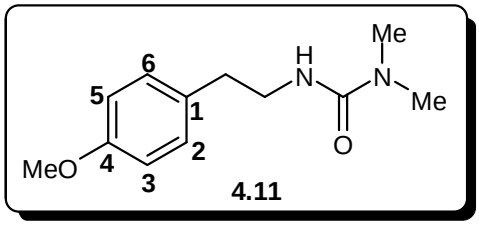
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C-4), 1391.9 (s, C-1), 129.7 (d, C-2/C-6), 113.9 (d, C-3/C-5), 55.2 (q, OCH_3), 43.7 (t, CH_2NH_2), 39.2 (t, CH_2Ar).

MS (ES^+): *m/z* (%) = 151 (50, $[M]^+$), 134 (20), 122 (100), 107 (62), 91 (90), 77 (91).

HRMS (ES^+): *m/z* [M^+] calcd for $C_9H_{13}NO$: 151.0997; found: 151.1000.

4.10.3 Synthesis of *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (4.11)

A stirred mixture of 2-(4-methoxyphenyl)ethanamine (**4.10**; 9.86 g, 65.2 mmol), dimethylcarbamoyl chloride (8.41 g, 78.3 mmol) and triethylamine (9.89 g, 97.8 mmol) in DCM (100 mL) was heated under reflux for 1 h. The mixture was allowed to cool and the solid formed was collected by filtration and then washed with H_2O (2 × 25 mL). The solid was purified by crystallization from hexane to give pure *N*′-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (**4.11**, 14.04 g, 63.3 mmol, 97%) as a white crystalline solid.



4.11

mp 80–82 °C.

IR (FT): ν_{max} = 3341, 2933, 1634, 1538, 1357 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.85 (d, *J* = 8 Hz, 2 H, H-3/H-5), 4.42 (br., exch., 1 H, NH), 3.80 (s, 3 H, OCH_3), 3.45 (app. t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.86 [s, 6 H, $N(CH_3)_2$], 2.76 (t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C-4), 158.2 (s, C=O), 131.5 (s, C-1), 129.7 (d, C-2/C-6), 114.0 (d, C-3/C-5), 55.2 (q, OCH_3), 42.3 (t, CH_2NH), 36.1 [q, $N(CH_3)_2$], 35.5 (t, CH_2Ar).

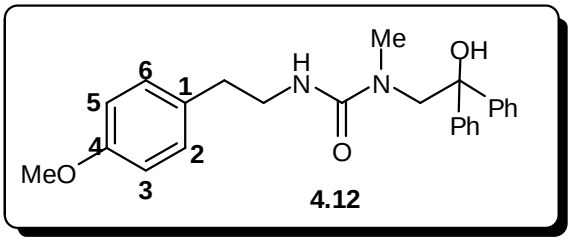
MS (EI): *m/z* (%) = 222 (80, $[M]^+$), 190 (25), 177 (40), 134 (100), 72 ($[Me_2NCO^+]$, 98).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{18}N_2O_2$: 222.1368; found: 222.1374.

4.10.4 Lithiation and substitution of *N′*-(2-(4-methoxyphenyl)ethyl)-*N*,*N*-dimethylurea (4.11): synthesis of substituted derivatives 4.12 and 4.15–4.27; general procedure

A solution of *n*-BuLi in hexane (1.85 mL, 1.6 M, 2.97 mmol) was added to a stirred solution of *N'*-(2-(4-methoxyphenyl)ethyl)*N*,*N*-dimethylurea (**4.11**; 0.20 g, 0.90 mmol) at –20 °C in anhydrous THF (15 mL) under a N_2 atmosphere. The mixture was stirred at 0 °C for 2 h. The mixture was re-cooled to –60 °C and the electrophile (1.26 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and diluted with diethyl ether (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane–Et_2O 1:1 by volume) to give a mixture of two products. The overall yields obtained were in the range of 88–96% (Table 4.2).

***N*-(2-Hydroxy-2,2-diphenylethyl)-*N′*-(4-methoxyphenethyl)-*N*-methylurea (4.12)**



4.12

From benzophenone (0.23 g, 1.26 mmol); yield: 0.025 g (0.060 mmol, 7%); colourless oil.

IR (FT): ν_{max} = 3336, 2952, 1611, 1511, 1301, 1246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7 Hz, 4 H, H-2/H-6 of 2 C_6H_5), 7.24 (app. t, *J* = 7 Hz, 4 H, H-3/H-5 of 2 C_6H_5), 7.18–7.13 (m, 2 H, H-4 of 2 C_6H_5), 7.00 (d, *J* = 8

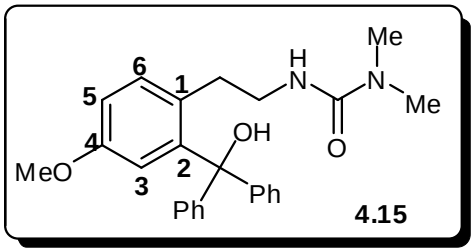
Hz, 2 H, H-2/H-6), 6.75 (d, *J* = 8 Hz, 2 H, H-3/H-5), 6.52 (br, exch., 1 H, OH), 4.38 (t, exch., *J* = 7 Hz, 1 H, NH), 4.05 (s, 2 H, C*H*$_2$C–OH), 3.70 (s, 3 H, OCH_3), 3.36 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.67 (t, *J* = 7 Hz, 2 H, CH_2Ar),), 2.16 (s, 3 H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (s, C-4), 158.2 (s, C=O), 145.8 (s, C-1 of 2 C_6H_5), 131.1 (s, C-1), 129.8 (d, C-2/C-6), 128.0 (d, C-2/C-6 of 2 C_6H_5), 126.9 (d, C-4 of 2 C_6H_5), 126.5 (d, C-3/C-5 of 2 C_6H_5), 114.0 (d, C-3/C-5), 78.6 (s, C-OH), 61.0 (t, *C*H_2C–OH), 55.2 (q, OCH_3), 42.4 (t, CH_2NH), 36.8 (q, NCH_3), 35.1 (t, CH_2Ar).

MS (EI): *m/z* (%) = 386 (40, $[M - H_2O]^+$), 298 (80), 182 (83), 121 (97), 83 (100).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O_2$: 386.1994; found: 386.1989.

N′-(2-(hydroxydiphenylmethyl)-4-methoxyphenethyl)-*N*,*N*-dimethylurea (4.15)



From benzophenone (0.23 g, 1.26 mmol); yield: 0.30 g (0.76 mmol, 85%); white solid; mp 157–159 °C.

IR (FT): ν_{max} = 3227, 2952, 1620, 1541, 1318, 1242 cm^{-1}.

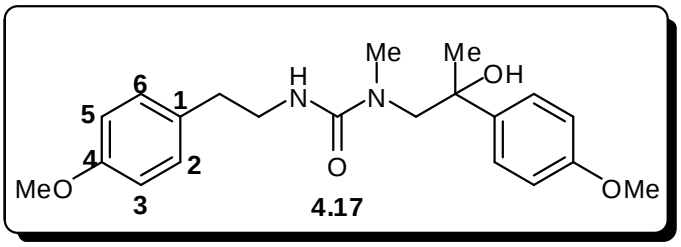
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.16 (m, 10 H, 2 C_6H_5), 7.08 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (dd, *J* = 3, 8 Hz , 1 H, H-5), 6.14 (d, *J* = 3 Hz, 1 H, H-3), 4.87 (s, exch., 1 H, OH), 4.72 (br., exch., 1 H, NH), 3.52 (s, 3 H, OCH_3), 3.23 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.73 [s, 6 H, $N(CH_3)_2$], 2.50 (t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C-4), 156.9 (s, C=O), 147.3 (s, C-1 of 2 C_6H_5), 146.8 (s, C-2), 132.6 (d, C-6), 130.9 (s, C-1), 127.8 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.0 (d, C-4 of 2 C_6H_5), 117.0 (d, C-3), 111.9 (d, C-5), 82.4 (s, C–OH), 54.9 (q, OCH_3), 42.6 (t, CH_2NH), 36.0 [q, $N(CH_3)_2$], 33.5 (t, CH_2Ar).

MS (EI): *m/z* (%) = 386 (25, $[M - H_2O]^+$), 316 (98), 285 (99), 209 (97), 165 (100), 83 (98).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O_2$: 386.1994; found: 386.1992.

_N′_-(2-Hydroxy-2-(4-methoxyphenyl)propyl)-_N_-(2-(4-methoxyphenyl)ethyl)-_N_-methylurea (4.17)



4.17

From 4'-methoxyacetophenone (0.19 g, 1.26 mmol); yield: 0.04 g (0.10 mmol, 12%); colourless oil.

IR (FT): ν_{max} = 3327, 2933, 1611, 1543, 1300, 1247 cm^{-1}.

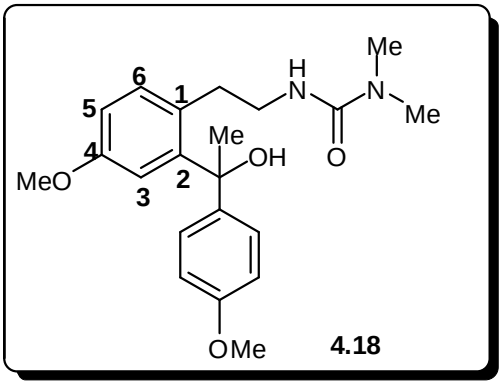
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$CH_3OC_6H_4$), 7.11 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$CH_3OC_6H_4$), 6.85 (d, *J* = 8 Hz, 2 H, H-3/H-5), 5.24 (br. s, exch., 1 H, OH), 4.78 (br., exch., 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.67 (d, *J* = 15 Hz, 1 H, C$H_a$$H_b$C–OH), 3.51-3.37 (m, 2 H, CH_2NH), 3.28 (d, *J* = 15 Hz, 1 H, CHaH_bC–OH), 2.78–2.75 (m, 2 H, CH_2Ar),), 2.48 (s, 3 H, NCH_3), 1.55 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (s, C-4), 158.4 (s, C-4 of 4-$CH_3OC_6H_4$), 158.2 (s, C=O), 138.5 (s, C-1 of 4-$CH_3OC_6H_4$), 131.2 (s, C-1), 129.8 (d, C-2/C-6), 126.5 (d, C-2/C-6 of 4-$CH_3OC_6H_4$), 114.0 (d, C-3/C-5 of 4-$CH_3OC_6H_4$), 113.4 (d, C-3/C-5), 75.4 (s, C–OH), 62.8 (t, *C*H_2C–OH), 55.26 (q, OCH_3), 55.24 (q, OCH_3), 42.3 (t, CH_2NH), 37.1 (q, NCH_3), 35.2 (t, CH_2Ar), 27.2 (q, CH_3).

MS (EI): *m/z* (%) = 354 (6, $[M - H_2O]^+$), 222 (77), 177 (94), 135 (97), 121 (100), 107 (55), 91 (70), 77 (87).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{21}H_{26}N_2O_3$: 354.1943; found: 354.1951.

_N′_-(2-(2-(1-Hydroxy-1-(4-methoxyphenyl)ethyl)-4-methoxyphenyl)ethyl)-_N,N_-dimethylurea (4.18)



From 4'-methoxyacetophenone (0.19 g, 1.26 mmol); yield: 0.27 g (0.73 mmol, 82%); white solid; mp 137–140 °C.

IR (FT): ν_{max} = 3342, 2933, 1633, 1537, 1299, 1246 cm^{-1}.

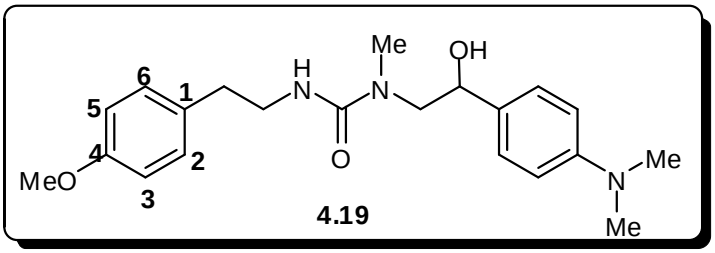
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (s, exch., 1 H, OH), 7.25 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$CH_3OC_6H_4$), 7.19 (d, *J* = 3 Hz, 1 H, H-3), 7.12 (d, *J* = 8 Hz, 1 H, H-6), 6.82–6.80 (m, 3 H, H-5 and H-3/H-5 of 4-$CH_3OC_6H_4$), 4.58 (br., exch., 1 H, NH), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.25 (m, 1 H, C$H_a$$H_b$NH), 3.04 (m, 1 H, CH_aH_bNH), 2.82 [s, 6 H, $N(CH_3)_2$], 2.64 (m, 1 H, C$H_a$$H_b$Ar), 2.45 (m, 1 H, CH_aH_bAr), 1.90 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C-4), 158.2 (s, C-4 of 4-$CH_3OC_6H_4$), 157.4 (s, C=O), 146.6 (s, C-2), 141.4 (s, C-1 of 4-$CH_3OC_6H_4$), 132.6 (d, C-6), 130.3 (s, C-1), 126.4 (d, C-2/C-6 of 4-$CH_3OC_6H_4$), 113.7 (d, C-3), 113.3 (d, C-3/C-5 of 4-$CH_3OC_6H_4$), 111.6 (d, C-5), 76.5 (s, C–OH), 55.28 (q, OCH_3), 55.22 (q, OCH_3), 42.5 (t, CH_2NH), 36.1 [q, $N(CH_3)_2$], 33.1 (q, CH_3), 33.0 (t, CH_2Ar).

MS (EI): *m/z* (%) = 354 (60, $[M - H_2O]^+$), 312 (45), 266 (100), 253 (93), 222 (50), 163 (90), 134 (98), 83 (99).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{21}H_{26}N_2O_3$:354.1943; found: 354.1936.

_N′_-(2-(4-(Dimethylamino)phenyl)-2-hydroxyethyl)-_N_-(4-methoxyphenethyl)-_N_-methylurea (4.19)



From 4-dimethylaminobenzaldehyde (0.19 g, 1.26 mmol); yield: 0.03 g (0.09 mmol, 10%); colourless oil.

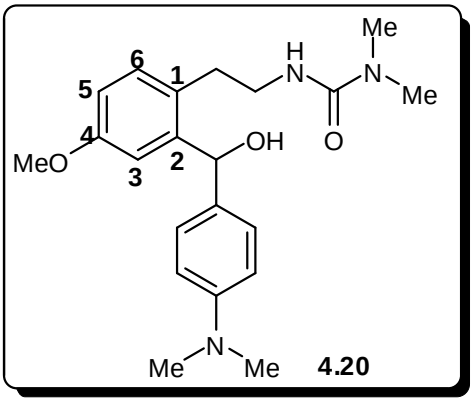
IR (FT): ν_{max} = 3371, 2926, 1611, 1520, 1349, 1245 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$(CH_3)_2NC_6H_4$), 7.05 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.79 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-$(CH_3)_2NC_6H_4$), 6.65 (d, *J* = 8 Hz, 2 H, H-3/H-5), 6.57 (br., exch., 1 H, OH), 4.73 (dd, *J* = 2, 8 Hz, 1 H, CH), 4.70 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.48 (m, 1 H, C$H_a$$H_b$CH–OH), 3.42–3.40 (m, 5 H, NCH_3 and CH_2NH), 3.38 (m, 1 H, CH_aH_bCH–OH), 2.87 [s, 6 H, $N(CH_3)_2$], 2.70 (app. t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C-4), 157.9 (s, C=O), 150.3 (s, C-4 of 4-$(CH_3)_2NC_6H_4$), 131.4 (s, C-1), 130.0 (s, C-1 of 4-$(CH_3)_2NC_6H_4$), 129.8 (d, C-2/C-6), 126.7 (d, C-2/C-6 of 4-$(CH_3)_2NC_6H_4$), 114.0 (d, C-3/C-5), 112.5 (d, C-3/C-5 of 4-$(CH_3)_2NC_6H_4$), 73.6 (s, C–OH), 58.2 (t, *C*H_2CHOH), 55.2 (q, OCH_3), 42.4 (t, CH_2NH), 40.6 [q, $N(CH_3)_2$], 36.0 (q, NCH_3), 35.4 (t, CH_2Ar). MS (EI): *m/z* (%) = 371 (14, $[M]^+$), 353 (92), 232 (95), 176 (51), 134 (100), 121 (82), 91 (26), 77 (32).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{21}H_{29}N_3O_3$: 371.2209; found: 371.2209.

_N′_-(2-(2-((4-(Dimethylamino)phenyl)(hydroxy)methyl)-4-methoxyphenyl)ethyl)-_N_,_N_-dimethylurea (4.20)



From 4-dimethylaminobenzaldehyde (0.19 g, 1.26 mmol); yield: 0.26 g (0.72 mmol, 80%); colourless oil.

IR (FT): ν_{max} = 3361, 2926, 1612, 1521, 1351, 1245 cm^{-1}.

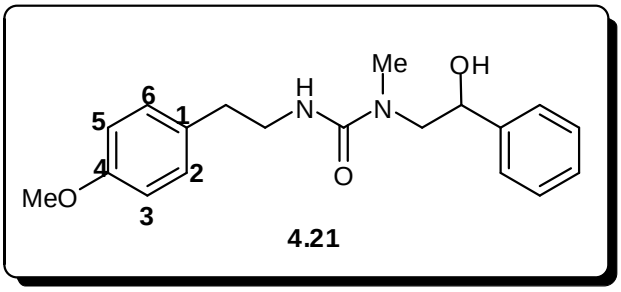
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 8 Hz, 1 H, H-6), 6.95 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$(CH_3)_2NC_6H_4$), 6.70 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.55 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-$(CH_3)_2NC_6H_4$), 6.50 (d, *J* = 2 Hz, 1 H, H-3), 6.02 (s, exch., 1 H, OH), 5.96 (s, 1 H, CH), 4.24 (t, exch., *J* = 7 Hz, 1 H, NH), 3.64 (s, 3 H, OCH_3), 3.53 (m, 1 H, C$H_a$$H_b$NH), 3.18 (m, 1 H, $CH_a$$H_b$NH), 2.90–2.82 [m, 7 H, C$H_a$$H_b$Ar and $(CH_3)_2$N of 4-$(CH_3)_2NC_6H_4$], 2.77 [s, 6 H, $N(CH_3)_2$], 2.63 (m, 1 H, C$H_a$$H_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6 (s, C-4), 157.5 (s, C=O), 149.6 (s, C-4 of 4-$(CH_3)_2NC_6H_4$), 137.4 (s, C-2), 132.0 (s, C-1 of 4-$(CH_3)_2NC_6H_4$), 130.7 (s, C-1), 129.5 (d, C-2/C-6 of 4-$(CH_3)_2NC_6H_4$), 126.8 (d, C-6), 113.3 (d, C-3), 112.7 (d, C-5), 112.0 (d, C-3/C-5 of 4-$(CH_3)_2NC_6H_4$), 77.4 (s, C-OH), 55.3 (q, OCH_3), 40.6 (t, CH_2NH), 40.3 [q, $N(CH_3)_2$ of 4-$(CH_3)_2NC_6H_4$], 38.8 [q, $N(CH_3)_2$], 27.8 (t, CH_2Ar).

MS (EI): *m/z* (%) = 353 (83, $[M - H_2O]^+$), 308 (67), 281 (100), 264 (64), 236 (42), 165 (31), 83 (45), 72 (65).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{21}H_{27}N_3O_2$: 353.2103; found: 353.2114.

_N_-(2-Hydroxy-2-phenylethyl)-_N′_-(2-(4-methoxyphenyl)ethyl)-_N_-methylurea (4.21)



4.21

From benzaldehyde (0.13 g, 1.26 mmol); yield: 0.016 g (0.05 mmol, 6%); colourless oil.

IR (FT): ν_{max} = 3338, 2932, 1639, 1541, 1246 cm^{-1}.

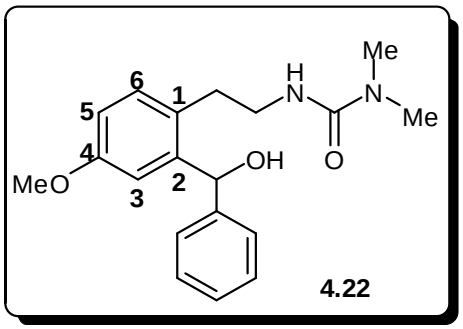
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7 Hz, 1 H, H-4 of C_6H_5), 7.29–7.25 (m, 4 H, H-2/H-3/H-5/H-6 of C_6H_5), 7.05 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 8 Hz, 2 H, H-3/H-5), 4.82 (dd, *J* = 3, 8 Hz, 1 H, CH), 4.65 (br., exch., 1 H, NH), 4.60 (br. s, exch., 1 H, OH), 3.72 (s, 3 H, OCH_3), 3.47 (m, 1 H, C$H_a$$H_b$CH–OH), 3.49–3.45 (m, 3 H, $CH_a$$H_b$CH–OH and C$H_2$NH), 2.70 (app. t, *J* = 7 Hz, 2 H, CH_2Ar), 2.58 (s, 3 H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0 (s, C-4), 158.2 (s, C=O), 142.4 (s, C-1 of C_6H_5), 131.2 (s, C-1), 129.8 (d, C-2/C-6), 128.4 (d, C-3/C-5 of C_6H_5), 127.5 (d, C-4 of C_6H_5), 125.8(d, C-2/C-6 of C_6H_5), 114.0 (d, C-3/C-5), 73.9 (d, CHOH), 58.3 (t, CH_2CH–OH), 55.2 (q, OCH_3), 42.3 (t, CH_2NH), 36.0 (q, NCH_3), 35.3 (t, CH_2Ar).

MS (EI): *m/z* (%) = 329 (17, $[MH]^+$), 222 (100), 207 (17), 190 (32), 178 (90), 150 (9), 134 (99), 121 (97), 105 (93), 91 (96).

HRMS (EI): *m/z* $[MH]^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1865; found: 329.1875.

_N′_-(2-(2-(Hydroxy(phenyl)methyl)-4-methoxyphenyl)ethyl)-_N_,_N_-dimethylurea (4.22)



4.22

From benzaldehyde (0.13 g, 1.26 mmol); yield: 0.24 g (0.73 mmol, 82%); colourless oil.

IR (FT): ν_{max} = 3337, 2927, 1630, 1537, 1249 cm^{-1}.

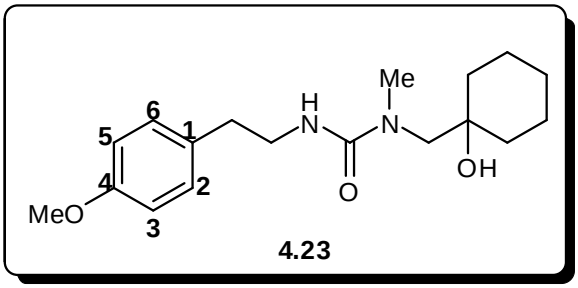
^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 7 Hz, 2 H, H-3/H-5 of C_6H_5), 7.26 (t, *J* = 8 Hz, 1 H, H-4 of C_6H_5), 7.20–7.17 (m, 3 H, OH, H-2/H-6 of C_6H_5), 7.00 (d, *J* = 8 Hz, 1 H, H-6), 6.79 (d, *J* = 3 Hz, 1 H, H-3), 6.70 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.04 (s, 1 H, CH), 4.48 (br., exch., 1 H, NH), 3.66 (s, 3 H, OCH_3), 3.43–3.25 (m, 2 H, C*H*$_2$NH), 2.87 (m, 1 H, C*H*$_a$H$_b$Ar), 2.76 [s, 6 H, N$(CH_3)_2$], 2.66 (m, 1 H, CH$_a$*H*$_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C-4), 158.3 (s, C=O), 143.5 (s, C-1 of C_6H_5), 135.1 (s, C-2), 131.3 (d, C-6), 129.0 (s, C-1), 128.3 (d, C-3/C-5 of C_6H_5), 127.3 (d, C-4 of C_6H_5), 126.8 (d, C-2/C-6 of C_6H_5), 113.7 (d, C-3), 113.0 (d, C-5), 72.7 (d, CH), 55.2 (q, OCH_3), 42.5 (t, CH_2NH), 36.2 [q, N$(CH_3)_2$], 32.8 (t, CH_2Ar).

MS (EI): *m/z* (%) = 328 (40, $[M]^+$), 310 (93), 282 (50), 265 (24), 238 (100), 209 (96), 194 (88), 149 (89), 134 (58), 121 (87), 105 (83), 77 (95).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{19}H_{24}N_2O_3$: 328.1787; found: 328.1787.

_N_-((1-Hydroxycyclohexyl)methyl)-_N′_-(4-methoxyphenethyl)-_N_-methylurea (4.23)



4.23

From cyclohexanone (0.12 g, 1.26 mmol); yield: 0.048 g (0.15 mmol, 17%); colourless oil.

IR (FT): ν_{max} = 3348, 2931, 1633, 1539, 1245 cm^{-1}.

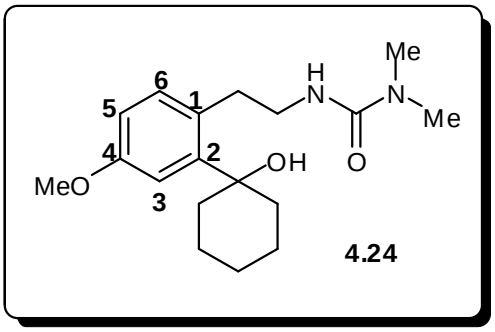
^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 9 Hz, 2 H, H-3/H-5), 4.97 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.36 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 3.15 (s, 2 H, C*H*$_2$C–OH), 2.82 (s, 3 H, NCH_3), 2.69 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.54–1.18 (m, 10 H, *c*-Hex).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (s, C-4), 158.2 (s, C=O), 131.5 (s, C-1), 129.8 (d, C-2/C-6), 114.0 (d, C-3/C-5), 73.0 (s, C-1 of *c*-Hex), 60.6 (t, *C*H_2C–OH), 55.3 (q, OCH_3), 42.3 (t, CH_2NH), 37.8 (q, NCH_3), 35.7 (t, CH_2Ar), 35.3 (t, C-2/C-6 of *c*-Hex), 25.8 (t, C-4 of *c*-Hex), 22.0 (t, C-3/C-5 of *c*-Hex).

MS (EI): *m/z* (%) = 320 (12, $[M]^+$), 222 (98), 177 (89), 150 (11), 134 (100), 121 (97), 99 (83), 77 (81).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{28}N_2O_3$: 320.2100; found: 320.2100.

_N′_-(2-(2-(1-Hydroxycyclohexyl)-4-methoxyphenyl)ethyl)-_N,N_-dimethylurea (4.24)



From cyclohexanone (0.12 g, 1.26 mmol); yield: 0.22 g (0.69 mmol, 77%); colourless oil.

IR (FT): ν_{max} = 3349, 2932, 1634, 1538, 1245 cm^{-1}.

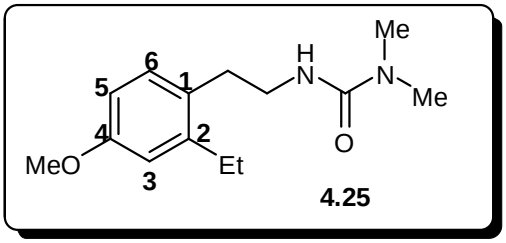
^1H NMR (500 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8 Hz, 1 H, H-6), 6.87 (d, *J* = 3 Hz, 1 H, H-3), 6.78 (dd, *J* = 3, 8 Hz, 1 H, H-5), 4.97 (br. s, exch., 1 H, OH), 4.28 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.37 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 3.07 (app. t, *J* = 7 Hz, 2 H, CH_2Ar), 2.77 [s, 3 H, $N(CH_3)_2$], 1.78–1.18 (m, 10 H, *c*-Hex).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9 (s, C-4), 157.7 (s, C=O), 142.3 (s, C-2), 133.2 (d, C-6), 129.8 (s, C-1), 114.0 (d, C-5), 111.1 (d, C-3), 74.5 (s, C-1 of *c*-Hex), 55.2 (q, OCH_3), 43.9 (t, CH_2NH), 38.5 (t, CH_2Ar), 36.3 [q, $N(CH_3)_2$], 35.3 (t, C-2/C-6 of *c*-Hex), 25.4 (t, C-4 of *c*-Hex), 22.1 (t, C-3/C-5 of *c*-Hex).

MS (ES): *m/z* (%) = 384 (20, $[M + MeCNNa]^+$), 359 (22, $[M + K]^+$), 343 (100, $[M + Na]^+$).

HRMS (ES): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{28}N_2O_3{}^{23}Na$: 343.1998; found: 343.1995.

_N′_-(2-(2-Ethyl-4-methoxyphenyl)ethyl)-_N,N_-dimethylurea (4.25)



From ethyliodide (0.20 g, 1.26 mmol); yield: 0.19 g (0.77 mmol, 86%); colourless oil.

IR (FT): ν_{max} = 3381, 2932, 1634, 1531, 1246 cm^{-1}.

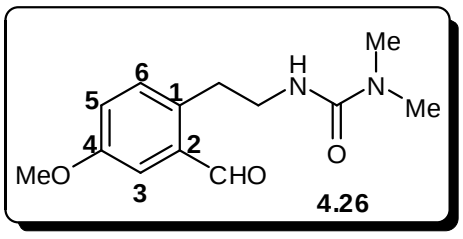
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (d, *J* = 3 Hz, 1 H, H-3), 6.62 (dd, *J* = 3, 8 Hz, 1 H, H-5), 4.37 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.34 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.80 [s, 3 H, $N(CH_3)_2$], 2.72 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.60 (q, *J* = 8 Hz, 2 H, C*H*$_2$$CH_3$), 1.15 (t, *J* = 8 Hz, 2 H, CH_2C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.34 (s, C-4), 158.27 (s, C=O), 132.7 (s, C-2), 131.1 (s, C-1), 130.6 (d, C-6), 114.4 (d, C-5), 111.0 (d, C-3), 55.2 (q, OCH_3), 41.9 (t, CH_2NH), 36.2 [q, $N(CH_3)_2$], 32.5 (t, CH_2Ar), 25.7 (t, *C*H_2CH_3), 15.8 (q, CH_2*C*H_3).

MS (AP): *m/z* (%) = 251 (100, $[M + H]^+$), 206 (8), 163 (5), 135 (10), 90 (4).

HRMS (AP): *m/z* $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2$: 251.1760; found: 251.1771.

_N′_-(2-(2-Formyl-4-methoxyphenyl)ethyl)-_N,N_-dimethylurea (4.26)



From dimethylformamide (0.09 g, 1.26 mmol); yield: 0.20 g (0.81 mmol, 90%); colourless oil.

IR (FT): ν_{max} = 3346, 2932, 1700, 1685, 1540, 1362 cm^{-1}.

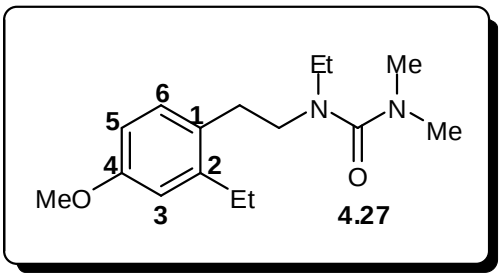
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, CHO), 7.58 (d, *J* = 2 Hz, 1 H, H-3), 7.35 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.88 (d, *J* = 8 Hz, 1 H, H-6), 4.48 (br., exch., 1 H, NH), 3.85 (s, 3 H, OCH_3), 3.39 (app. q, *J* = 7 Hz, 2H, C*H*$_2$NH), 2.80 [s, 6 H, $N(CH_3)_2$], 2.73 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.9 (s, CHO), 160.63 (s, C=O), 160.61 (s, C-4), 140.7 (s, C-2), 140.5 (s, C-1), 136.5 (d, C-6), 128.4 (d, C-5), 112.0 (d, C-3), 55.8 (q, OCH_3), 42.1 (t, CH_2NH), 36.3 [q, $N(CH_3)_2$], 35.4 (t, CH_2Ar).

MS (AP): *m/z* (%) = 251 (100, $[M + H]^+$), 224 (9), 206 (10), 135 (22), 124 (13), 84 (6).

HRMS (AP): *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_3$: 251.1760; found: 251.1764.

_N′_-Ethyl-_N′_-(2-(2-ethyl-4-methoxyphenyl)ethyl)-_N,N_-dimethylurea (4.27)



From ethyl iodide (0.20 g, 1.26 mmol); yield: 0.025 g (0.090 mmol, 10%); colourless oil.

IR (FT): νmax = 2935, 1652, 1505, 1251 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8 Hz, 1 H, H-6), 6.67 (d, *J* = 3 Hz, 1 H, H-3), 6.62 (dd, *J* = 3, 8 Hz, 1 H, H-5), 3.71 (s, 3 H, OCH_3), 3.19–3.10 (m, 4 H, $ArCH_2CH_2N$ and NCH_2CH_3), 2.73 [s, 6 H, $N(CH_3)_2$], 2.71 (q, *J* = 7 Hz, 2 H, $ArCH_2CH_3$), 2.60 (t, *J* = 7 Hz, 2 H, $ArCH_2CH_2N$), 1.16 (t, *J* = 7 Hz, 3 H, NCH_2CH_3), 1.05 (t, *J* = 7 Hz, 3 H, $ArCH_2CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3 (s, C=O), 158.3 (s, C-4), 143.7 (s, C-2), 131.5 (s, C-1), 130.7 (d, C-6), 114.3 (d, C-5), 111.0 (d, C-3), 55.2 (q, OCH_3), 49.2 (t, $ArCH_2CH_2N$), 43.5 (t, NCH_2CH_3), 38.7 [q, $N(CH_3)_2$], 30.6 (t, $ArCH_2CH_2N$), 25.7 (t, $ArCH_2CH_3$), 15.4 (q, $ArCH_2CH_3$), 13.5 (q, NCH_2CH_3).

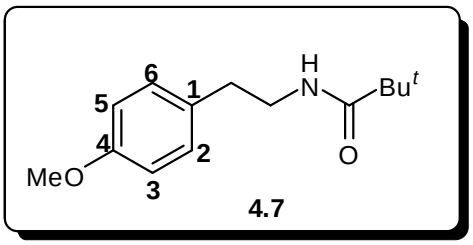
MS (EI): *m/z* (%) = 278 (17, $[M]^+$), 220 (22), 205 (64), 162 (25), 129 (60), 85 (100), 72 (80).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{26}N_2O_2$: 278.1994; found: 278.1991.

4.10.5 Synthesis of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (4.7)

To a cooled solution (0 °C) of 2-(4-methoxyphenyl)ethanamine (**4.10**, 5.00 g, 33.1 mmol) and Et_3N (5.02 g, 49.6 mmol) in DCM (50 mL) pivaloyl chloride (4.40 g, 39.7 mmol) was slowly added in a dropwise manner over 30 min. The mixture was

stirred for 1 h at room temperature. The mixture was washed with H_2O (2 x 25 mL). The organic layer was concentrated and the solid obtained was purified by crystallization from hexane to give pure *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**4.7**, 7.09 g, 30.1 mmol, 91%) as a white crystalline solid.



4.7

mp 71–73 °C.

IR (FT): ν_{max} = 3350, 2959, 1655, 1534, 1365 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 9 Hz, 2 H, H-3/H-5), 5.60 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.39 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.68 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.07 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3 (s, C=O), 158.3 (s, C-4), 131.0 (s, C-1), 129.7 (d, C-2/C-6), 114.0 (d, C-3/C-5), 55.3 (q, OCH_3), 40.8 (t, CH_2NH), 38.6 [s, *C*$(CH_3)_3$], 34.7 (t, CH_2Ar), 27.5 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 235 (8, $[M]^+$), 220 (4), 192 (7), 134 (100), 121 (30), 105 (8), 91 (14), 77 (10), 65 (4), 57 (10).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{21}NO_2$: 235.1572; found: 235.1571.

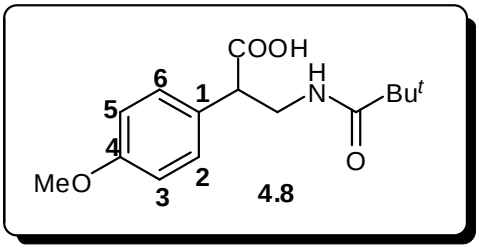
4.10.6 Lithiation and substitution of *N*-(4-methoxyphenethyl)pivalamide (4.7)

4.10.6.1 Synthesis of substituted derivatives 4.8 and 4.28; general procedure (under Schlosser's conditions)

A solution of *t*-BuLi in pentane (1.60 mL, 1.60 M, 2.56 mmol) was added to a stirred solution of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**4.9**; 0.20 g, 0.85 mmol) in anhydrous THF (15 mL) at °C under a N_2 atmosphere. The mixture was stirred at °C for 3 h. An excess of the electrophile [several pellets in the case of solid carbon dioxide or a solution of benzophenone (0.22 g, 1.2 mmol) in anhydrous THF (5 mL)] was added. The reaction mixture was stirred for 2 h and allowed to warm up to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL) in the

case of benzophenone or an aqueous HCl solution (10 mL; 10%) in the case of carbon dioxide, and the mixture was diluted with diethyl ether (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane–Et_2O 1:1 by volume) to give the pure product.

2-(4-Methoxyphenyl)-3-(pivaloylamino)propanoic acid (4.8)



4.8

From solid CO_2 (excess); yield: 0.17 g (0.61 mmol, 72%); white solid, mp 130–134 °C (lit.[10] 130–133 °C).

IR (FT): ν_{max} = 3386, 2962, 1730, 1643, 1511, 1367, 1251 cm^{-1}.

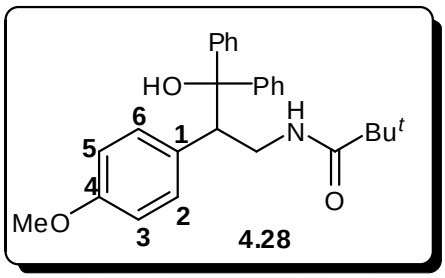
^1H NMR (500 MHz, $CDCl_3$): δ = 8.47 (br. s, 1 H, OH), 7.13 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 9 Hz, 2 H, H-3/H-5), 6.06 (br., exch., 1 H, NH), 3.83 (app. t, *J* = 7 Hz, 1 H, CH), 3.71 (s, 3 H, OCH_3), 3.56 (app. dd, *J* = 7, 13 Hz, 2 H, C*H*$_2$NH), 1.04 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 176.9 (s, COOH), 159.5 (s, C-4), 129.2 (d, C-2/C-6), 128.0 (s, C-1), 114.3 (d, C-3/C-5), 55.3 (q, OCH_3), 49.1 (d, CH), 42.2 (t, CH_2NH), 38.7 [s, *C*$(CH_3)_3$], 27.4 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 279 (8, $[M]^+$), 261 (98), 233 (99), 218 (5), 166 (99), 134 (100), 85 (98), 77 (97), 65 (20).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{21}NO_4$: 279.1471; found: 279.1469.

***N*-(3-Hydroxy-2-(4-methoxyphenyl)-3,3-diphenylpropyl)pivalamide (4.28)**



From benzophenone (0.22 g, 1.2 mmol); yield: 0.20 g, (0.49 mmol, 58%); white solid; mp 157–160 °C.

IR (FT): ν_{max} = 3399, 2960, 1641, 1511, 1301, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 9 Hz, 2 H, H-2/H-6), 7.28 (app. t, *J* = 7 Hz, 2 H, H-3/H-5 of one C_6H_5), 7.22 (d, *J* = 7 Hz, 2 H, H-2/H-6 of one C_6H_5), 7.13 (t, *J* = 7 Hz, 1 H, H-4 of one C_6H_5), 7.06 (d, *J* = 7 Hz, 2 H, H-2/H-6 of other C_6H_5), 7.00 (app. t, *J* = 7 Hz, 2 H, H-3/H-5 of other C_6H_5), 6.90 (t, *J* = 7 Hz, 1 H, H-4 of other C_6H_5), 6.61 (d, *J* = 9 Hz, 2 H, H-3/H-5), 5.39 (br., exch., 1 H, NH), 4.08 (app. t, *J* = 7 Hz, 1 H, CH), 3.81 (app. dt, *J* = 7, 14 Hz, 1 H, CH_aH$_b$), 3.64 (s, 3 H, OCH_3), 3.34 (m, 1 H, CH$_a$$H_b$), 0.85 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 158.3 (s, C-4), 146.5, 146.1 (2 s, C-1 of 2 C_6H_5), 131.0 (d, C-3/C-5 of one C_6H_5), 130.8 (s, C-1), 128.4 (d, C-3/C-5 of other C_6H_5), 127.6 (d, C-2/C-6), 126.8, 126.0 (2 d, C-4 of 2 C_6H_5), 125.9, 125.7 (2 d, C-2/C-6 of 2 C_6H_5), 113.5 (d, C-3/C-5), 79.7 (s, C–OH), 55.1 (q, OCH_3), 51.6 (d, CH), 41.2 (t, CH_2), 38.5 [s, *C*$(CH_3)_3$], 27.3 [q, C(*C*$H_3)_3$].

MS (ES^-): *m/z* (%) = 454 (32, $[M + {}^{37}Cl]^-$), 452 (100, $[M + {}^{35}Cl]^-$), 339 (5).

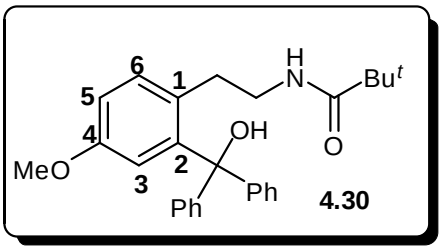
HRMS (ES^-): *m/z* $[M + {}^{35}Cl]^-$ calcd for $C_{27}H_{31}NO_3Cl$: 452.1992; found: 452.2008.

4.10.6.2 Synthesis of substituted derivatives 4.30 and 4.33–4.38; general procedure

A solution of *n*-BuLi in hexane (1.75 mL, 1.60 M, 2.80 mmol) was added to a stirred solution of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**4.7**; 0.20 g, 0.85 mmol) at -20 °C in anhydrous THF (15 mL) under a N_2 atmosphere. The mixture was stirred at 0 °C for 2 h. The electrophile (*ca.* 1.2 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at 0 °C to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20

mL) and the mixture was diluted with diethyl ether (20 mL). The organic layer was separated, washed with H_2O (2 x 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane–Et_2O 1:1 by volume) to give the pure products. The yields obtained were in the range of 81-98% over all (Table 4.3).

_N_-(2-(2-(Hydroxydiphenylmethyl)-4-methoxyphenyl)ethyl)pivalamide (4.30)



From benzophenone (0.22 g, 1.2 mmol); yield: 0.32 g (0.78 mmol, 92%); white solid; mp 179–181 °C.

IR (FT): ν_{max} = 3321, 2958, 1627, 1575, 1292, 1243 cm^{-1}.

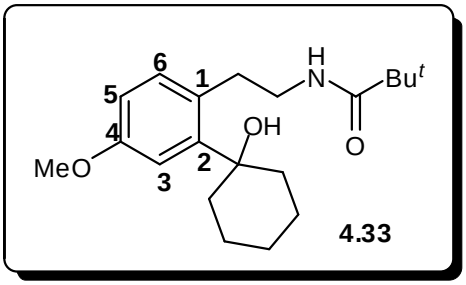
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 11 H, OH and 2 C_6H_5), 7.16 (d, *J* = 8 Hz, 1 H, H-6), 6.79 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.24 (d, *J* = 3 Hz, 1 H, H-3), 6.15 (br, exch., 1 H, NH), 3.63 (s, 3 H, OCH_3), 3.37 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.60 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.11 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8 (s, C=O), 156.9 (s, C-4), 147.1 (s, C-1 of 2 C_6H_5), 146.6 (s, C-2), 132.8 (d, C-6), 130.7 (s, C-1), 127.9 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.2 (d, C-4 of 2 C_6H_5), 117.1 (d, C-3), 111.9 (d, C-5), 83.0 (s, C–OH), 55.0 (q, OCH_3), 41.1 (t, CH_2NH), 38.4 [s, *C*$(CH_3)_3$], 32.5 (t, CH_2Ar), 27.5 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 399 (77, $[M - H_2O]^+$), 298 (99), 285 (90), 261 (33), 239 (10), 222 (26), 209 (31), 193 (73), 165 (53), 152 (13), 105 (48), 83 (100).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{27}H_{29}NO_2$: 399.2198; found: 399.2187.

_N_-(2-(2-(1-Hydroxycyclohexyl)-4-methoxyphenyl)ethyl)pivalamide (4.33)



From cyclohexanone (0.12 g, 1.2 mmol); yield: 0.24 g (0.74 mmol, 88%); colourless oil

IR (FT): ν_{max} = 3369, 2931, 1645, 1529, 1365, 1238 cm^{-1}.

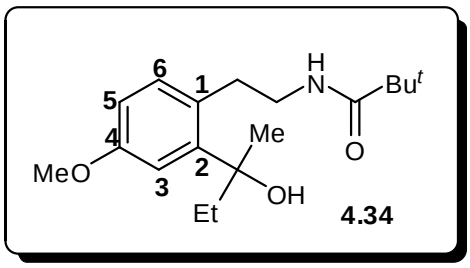
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 2 Hz, 1 H, H-3), 6.97 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.80 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (s, exch., 1 H, OH), 5.54 (br., exch., 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.38 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.68 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.95–1.50 (m, 10 H, *c*-Hex), 1.08 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 156.0 (s, C-4), 140.0 (s, C-2), 126.3 (d, C-6), 126.0 (s, C-1), 111.5 (d, C-3), 111.0 (d, C-5), 73.0 (s, C–OH), 55.4 (q, OCH_3), 40.9 (t, CH_2NH), 38.6 [s, *C*(CH_3)$_3$], 36.7 (d, C-2/C-6 of *c*-Hex), 35.1 (t, ArCH_2), 27.5 [q, C(*C*H_3)$_3$], 25.9 (d, C-4 of *c*-Hex), 21.9 (d, C-3/C-5 of *c*-Hex).

MS (ES$^+$): *m/z* (%) = 356 (100, [M + Na]$^+$), 316 (5), 299 (10), 158 (3).

HRMS (ES$^+$): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{31}NO_3{}^{23}$Na: 356.2202; found: 356.2215.

_N_-(2-(2-(2-Hydroxybutan-2-yl)-4-methoxyphenyl)ethyl)pivalamide (4.34)



From 2-butanone (0.086 g, 1.2 mmol); yield: 0.24 g (0.80 mmol, 95%); colourless oil.

IR (FT): ν_{max} = 3348, 2964, 1639, 1531, 1355, 1240 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 2 Hz, 1 H, H-3), 6.98 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.79 (d, *J* = 8 Hz, 1 H, H-6), 5.56 (br., exch., 1 H, NH), 3.88 (br. s, exch., 1 H, OH), 3.80 (s, 3 H, OCH_3), 3.40 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.68 (app. t, *J* = 7 Hz, 2

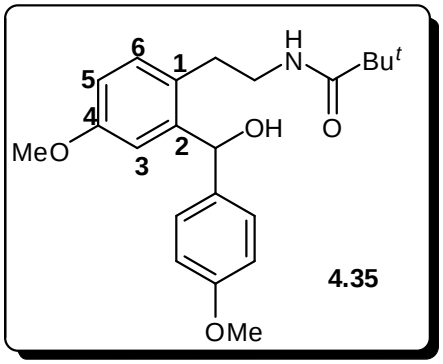
H, CH_2Ar), 1.92–1.75 (m, 2 H, C*H*$_2$CH$_3$), 1.47 (s, 3 H, C*H*$_3$C–OH), 1.07 [s, 9 H, C(CH$_3$)$_3$], 0.73 (app. t, *J* = 7 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3 (s, C=O), 155.6 (s, C-4), 135.0 (s, C-2), 131.1 (s, C-1), 127.4 (d, C-6), 113.8 (d, C-3), 111.6 (d, C-5), 75.3 (s, C–OH), 55.4 (q, OCH_3), 40.8 (t, CH_2NH), 38.6 [s, *C*(CH$_3$)$_3$], 35.0 (t, *C*H$_2$CH$_3$), 34.7 (t, CH_2Ar), 27.5 [q, C(*C*H$_3$)$_3$], 26.7 (q, *C*H$_3$C–OH), 8.8 (q, CH$_2$*C*H$_3$).

MS (AP$^+$): *m/z* (%) = 290 (100, [M – H_2O]$^+$), 222 (3), 189 (2), 153 (3), 124 (3).

HRMS (AP$^+$): *m/z* [M – H_2O]$^+$ calcd for $C_{18}H_{28}NO_2$: 290.2120; found: 290.2119.

N-(2-(2-(Hydroxy(4-methoxyphenyl)methyl)-4-methoxyphenyl)ethyl)pivalamide (4.35)



From 4-methoxybenzaldehyde (0.16 g, 1.2 mmol); yield: 0.25 g (0.68 mmol, 81%); colourless oil.

IR (FT): ν_{max} = 3349, 2927, 1610, 1511, 1368, 1246 cm^{-1}.

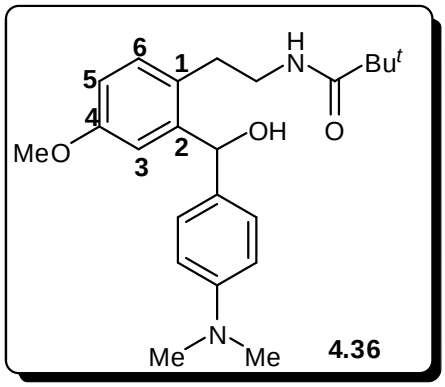
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-CH$_3$OC$_6$H$_4$), 7.05 (d, *J* = 8 Hz, 1 H, H-6), 6.78 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.76 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-CH$_3$OC$_6$H$_4$), 6.73 (d, *J* = 3 Hz, 1 H, H-3), 5.63 (d, *J* = 1 Hz, 1 H, CH), 5.36 (br., exch., 1 H, NH), 5.05 (d, exch., *J* = 1 Hz, 1 H, OH), 3.74 (s, 3 H, OCH_3),, 3.73 (s, 3 H, OCH_3), 3.40 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.44 (app. t, *J* = 7 Hz, 2 H, CH_2Ar), 1.03 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 159.4 (s, C-4), 158.0 (s, C-4 of 4-CH$_3$OC$_6$H$_4$), 142.9 (s, C-1 of 4-CH$_3$OC$_6$H$_4$), 132.9 (s, C-2), 130.7 (d, C-6), 128.8 (s, C-1), 127.6 (d, C-2/C-6 of 4-CH$_3$OC$_6$H$_4$), 115.9 (d, C-3), 113.8 (d, C-3/C-5 of 4-CH$_3$OC$_6$H$_4$), 113.0 (d, C-5), 72.2 (d, CH), 55.33 (q, OCH_3), 55.31 (q, OCH_3), 40.1 (t, CH_2NH), 38.6 [s, *C*(CH$_3$)$_3$], 32.3 (t, $ArCH_2$), 27.6 [q, C(*C*H$_3$)$_3$].

MS (EI): *m/z* (%) = 353 (30, $[M - H_2O]^+$), 308 (32), 281 (40), 264 (25), 165 (100), 134 (92), 120 (54), 105 (81), 84 (99).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{22}H_{27}NO_3$: 353.1991; found: 353.1999.

_N_-(2-(2-((4-(Dimethylamino)phenyl)(hydroxy)methyl)-4-methoxyphenyl)ethyl)pivalamide (4.36)



From 4-dimethylaminobenzaldehyde (0.18 g, 1.2 mmol); yield: 0.29 g (0.76 mmol, 90%); colourless oil.

IR (FT): ν_{max} = 3343, 2956, 1612, 1520, 1350, 1249 cm^{-1}.

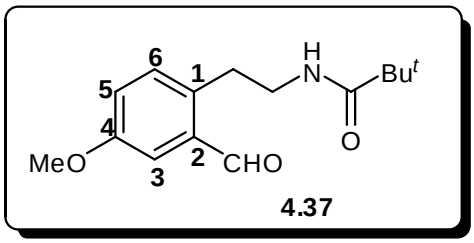
^1H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$(CH_3)_2NC_6H_4$), 7.02 (d, *J* = 3 Hz, 1 H, H-3), 6.96 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.61 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$(CH_3)_2NC_6H_4$), 5.91 (br. s, exch., 1 H, OH), 5.65 (br., exch., 1 H, NH), 3.71 (s, 3 H, OCH_3), 3.30 (m, 1 H, C$H_a$$H_b$NH), 3.22 (m, 1 H, $CH_a$$H_b$NH), 2.86 [s, 6 H, $N(CH_3)_2$], 2.78 (m, 1 H, C$H_a$$H_b$Ar), 2.57 (m, 1 H, $CH_a$$H_b$Ar), 1.03 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 159.1 (s, C-4), 150.1 (s, C-4 of 4-$(CH_3)_2NC_6H_4$), 143.5 (s, C-2), 141.2 (s, C-1 of 4-$(CH_3)_2NC_6H_4$), 128.3 (s, C-1), 127.9 (d, C-2/C-6 of 4-$(CH_3)_2NC_6H_4$), 126.7 (d, C-6), 113.0 (d, C-3), 112.6 (d, C-5), 112.4 (d, C-3/C-5 of 4-$(CH_3)_2NC_6H_4$), 72.8 (s, C–OH), 55.3 (q, OCH_3), 40.6 [q, $N(CH_3)_2$], 40.1 (t, CH_2NH), 38.5 [s, *C*$(CH_3)_3$], 31.5 (t, CH_2Ar), 27.5 [q, C(*C*$H_3)_3$].

MS (ES^-): *m/z* (%) = 421 (35, $[M + {}^{37}Cl]^-$), 419 (100, $[M + {}^{35}Cl]^-$), 383 (15), 374 (20), 327 (34), 292 (35), 291 (98), 283 (14), 220 (5).

HRMS (ES^-): *m/z* $[M + Cl]^-$ calcd for $C_{23}H_{32}N_2O_3{}^{35}Cl$: 419.2101; found: 419.2093.

_N_-(2-(2-Formyl-4-methoxyphenyl)ethyl)pivalamide (4.37)



4.37

From dimethylformamide (0.087 g, 1.2 mmol); yield: 0.22 g (0.83 mmol, 98%); colourless oil.

IR (FT): ν_{max} = 3380, 2928,1662, 1639, 1528, 1360, 1246 cm^{-1}.

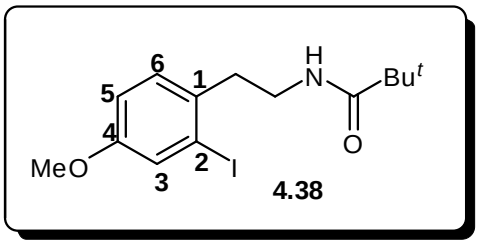
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, CHO), 7.57 (d, *J* = 2 Hz , 1 H, H-3), 7.33 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.89 (d, *J* = 8 Hz, 1 H, H-6), 5.59 (br., exch., 1 H, NH), 3.85 (s, 3 H, OCH_3), 3.40 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.72 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.07 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.6 (d, CHO), 178.4 (s, C=O), 160.6 (s, C-4), 141.0 (s, C-2), 138.5 (s, C-1), 136.3 (d, C-6), 128.4 (d, C-5), 112.0 (d, C-3), 55.8 (q, OCH_3), 40.9 (t, CH_2NH), 38.6 [s, *C*$(CH_3)_3$], 34.6 (t, CH_2Ar), 27.4 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 263 (54, $[M]^+$), 231 (15), 162 (100), 144 (90), 135 (83), 116 (28), 105 (31), 83 (99).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{21}NO_3$: 263.1521; found: 263.1524.

_N_-(2-(2-Iodo-4-methoxyphenyl)ethyl)pivalamide (4.38)



4.38

From iodine (0.31 g, 1.2 mmol); yield: 0.27 g (0.75 mmol, 89%); colourless oil.

IR (FT): ν_{max} = 3351, 2957, 1641, 1511, 1365, 1246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 3 Hz, 1 H, H-3), 7.02 (d, *J* = 8 Hz, 1 H, H-6), 6.78 (dd, *J* = 3, 8 Hz, 1 H, H-5), 5.62 (br., exch., 1 H, NH), 3.69 (s, 3 H, OCH_3), 3.40 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.83 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.09 [s, 9 H, $C(CH_3)_3$].

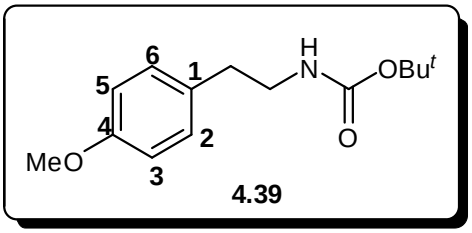
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 158.5 (s, C-4), 133.7 (s, C-1), 130.2 (d, C-6), 124.6 (d, C-3), 114.5 (d, C-5), 100.3 (s, C-2), 55.5 (q, OCH_3), 39.7 (t, CH_2NH), 39.0 (t, CH_2Ar), 38.7 [s, *C*$(CH_3)_3$], 27.6 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 361 (15, $[M]^+$), 259 (100), 246 (98), 234 (69), 148 (48), 134 (99), 121 (74), 83 (92).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{20}NO_2I$: 361.0539; found: 361.0533.

4.10.7 Synthesis of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate (4.39)

To a cooled solution (0 °C) of 2-(4-methoxyphenyl)ethanamine **(4.10**; 5.00 g, 33.1 mmol) and Et_3N (5.02 g, 49.7 mmol) in DCM (50 mL) di-*tert*-butyl dicarbonate (8.67 g, 39.7 mmol) was slowly added in a dropwise manner. The cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. The mixture was poured onto H_2O (50 mL). The organic layer was separated, washed with H_2O (2 × 50 mL) and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from hexane to give pure **4.39** (7.98 g, 31.8 mmol, 96%) as a white solid.



4.39

mp 68–70 °C.

IR (FT): ν_{max} = 3360, 2932, 1682, 1540, 1365 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.87 (d, *J* = 9 Hz, 2 H, H-3/H-5), 4.54 (br., exch., 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.36 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH$_2$), 2.76 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.46 [s, 9 H, C$(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C-4), 155.9 (s, C=O), 131.0 (s, C-1), 129.7 (d, C-2/C-6), 114.0 (d, C-3/C-5), 79.2 [s, *C*$(CH_3)_3$], 55.3 (q, OCH_3), 42.0 (t, CH_2NH), 35.3 (t, CH_2Ar), 28.4 [q, C(*C*$H_3)_3$].

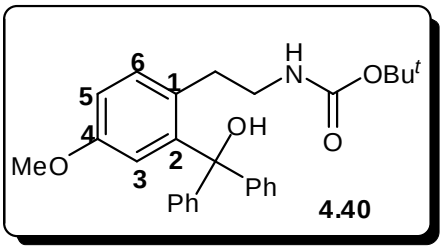
MS (EI): *m/z* (%) = 251 (3, $[M]^+$), 218 (22), 195 (58), 177 (90), 151 (78), 122 (100), 85 (98), 65 (88).

HRMS (EI): *m/z* $[M^+]$ calcd for $C_{14}H_{21}NO_3$: 251.1521; found: 251.1519.

4.10.8 Lithiation and substitution of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate: synthesis of substituted derivatives 4.40 and 4.43–4.45; general procedure

A solution of *n*-BuLi in hexane (1.64 mL, 1.6 M, 2.62 mmol) was added to a stirred solution of *tert*-butyl 2-(4-methoxyphenyl)ethylcarbamate (**4.39**; 0.20 g, 0.79 mmol) at –20 °C in anhydrous THF (15 mL) under a N_2 atmosphere. The mixture was stirred at 0 °C for 2 h. The electrophile (1.1 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and diluted with diethyl ether (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane–Et_2O 1:1 by volume) to give the pure products. The overall yields obtained were in the range of 87–93% (Table 4.4).

***tert*-Butyl 2-(2-(hydroxydiphenylmethyl)-4-methoxyphenyl)ethylcarbamate (4.40)**



4.40

From benzophenone (0.20 g, 1.1 mmol); yield: 0.30 g (0.70 mmol, 89%); colourless oil. IR (FT): ν_{max} = 3351, 2977, 1620, 1541, 1318, 1242 cm^{-1}.

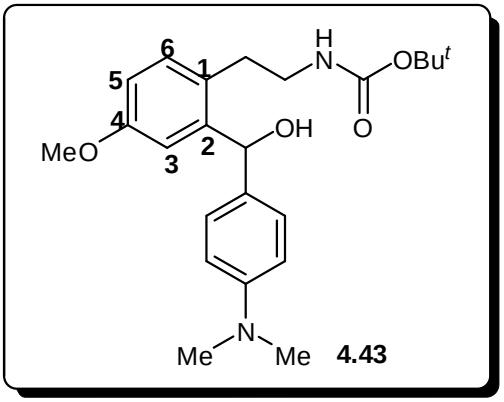
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.14 (m, 10 H, 2 C_6H_5), 7.02 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.80 (d, *J* = 8 Hz, 1 H, H-6), 6.24 (d, *J* = 2 Hz, 1 H, H-3), 5.18 (s, exch., 1 H, OH), 4.37 (br., exch., 1 H, NH), 3.50 (s, 3 H, OCH_3), 3.10 (br. app. q, 2 H, C*H*$_2$NH), 2.60 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.33 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C-4), 155.8 (s, C=O), 146.6 (s, C-1 of 2 C_6H_5), 135.7 (s, C-2), 131.0 (s, C-1), 130.6 (d, C-6), 127.8 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.0 (d, C-4 of 2 C_6H_5), 114.0 (d, C-3), 112.5 (d, C-5), 82.0 (s, C–OH), 79.1 [s, *C*$(CH_3)_3$], 55.9 (q, OCH_3), 41.8 (t, CH_2NH), 35.4 (t, CH_2Ar), 28.5 [q, C(*C*$H_3)_3$].

MS (ES^+): *m/z* (%) = 456 (100, $[M + Na]^+$), 416 (5), 205 (2).

HRMS (ES^+): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{31}NO_4{}^{23}Na$: 456.2151; found: 456.2141.

tert-Butyl 2-(2-((4-(dimethylamino)phenyl)(hydroxy)methyl)-4-methoxyphenyl)ethylcarbamate (4.43)



4.43

From 4-dimethylaminobenzaldehyde (0.16 g, 1.1 mmol); yield: 0.29 g (0.73 mmol, 93%); white solid; mp 179–181 °C.

IR (FT): ν_{max} = 3361, 2974, 1612, 1520, 1364, 1248 cm^{-1}.

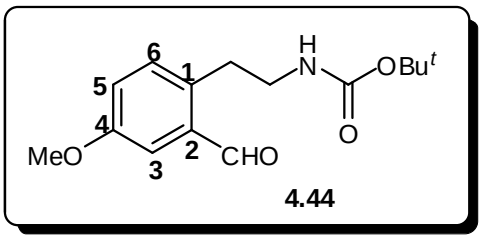
^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$(CH_3)_2NC_6H_4$), 7.07 (br. s, 1 H, H-3), 6.98 (dd, *J* = 1, 8 Hz, 1 H, H-5), 6.73 (d, *J* = 8 Hz, 1 H, H-6), 6.62 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$(CH_3)_2NC_6H_4$), 5.88 (br., exch., 1 H, NH), 4.45 (br. s, exch., 1H, OH), 3.70 (s, 3 H, OCH_3), 3.25 (app. q, *J* = 7, 2 H, C*H*$_2$NH), 2.85 (s, 6 H, $N(CH_3)_2$), 2.64 (app. t, *J* = 7 Hz, 2 H, CH_2Ar), 1.36 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9 (s, C-4), 155.4 (s, C=O), 149.9 (s, C-4 of 4-$(CH_3)_2NC_6H_4$), 132.6 (s, C-2), 131.4 (s, C-1 of 4-$(CH_3)_2NC_6H_4$), 131.0 (s, C-1), 128.4 (d, C-6), 127.9 (d, C-3), 127.6 (d, C-2/C-6 of 4-$(CH_3)_2NC_6H_4$), 112.4 (d, C-3/C-5 of 4-$(CH_3)_2NC_6H_4$), 110.9 (d, C-5), 79.2 [s, *C*$(CH_3)_3$], 72.0 (d, CH), 55.6 (q, OCH_3), 41.9 (t, CH_2NH), 40.6 (q, $N(CH_3)_2$), 35.5 (t, CH_2Ar), 28.5 [q, C(*C*$H_3)_3$].

MS (ES+): *m/z* (%) = 400 (69, $[M]^+$), 384 (88), 310 (99), 296 (37), 284 (70), 267 (28), 255 (96), 240 (100), 224 (31), 148 (48), 134 (98), 120 (44), 104 (16), 83 (93).

HRMS (ES+): *m/z* $[M]^+$ calcd for $C_{23}H_{32}N_2O_4$: 400.2366; found: 400.2362.

tert-Butyl 2-(2-formyl-4-methoxyphenyl)ethylcarbamate (4.44)



4.44

From dimethylformamide (0.080 g, 1.1 mmol); yield: 0.19 g (0.68 mmol, 87%); colourless oil.

IR (FT): ν_{max} = 3359, 2927, 1680, 1606, 1499, 1358, 1244 cm^{-1}.

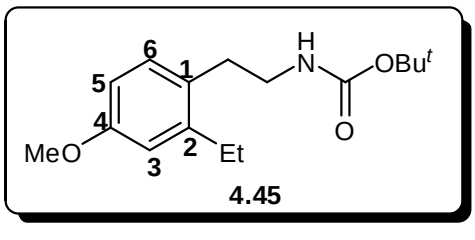
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.37 (s, 1 H, CHO), 7.57 (d, *J* = 2 Hz, 1 H, H-3), 7.32 (br. d, *J* = 8 Hz, 1 H, H-5), 6.87 (d, *J* = 8 Hz, 1 H, H-6), 4.50 (br., exch., 1 H, NH), 3.84 (s, 3 H, OCH_3), 3.25 (app. q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.70 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.35 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.7 (d, CHO), 160.6 (s, C-4), 155.8 (s, C=O), 136.3 (s, C-2), 131.3 (s, C-1), 128.4 (d, C-6), 124.8 (d, C-5), 112.0 (d, C-3), 79.3 [s, *C*$(CH_3)_3$], 55.7 (q, OCH_3), 41.7 (t, CH_2NH), 35.1 (t, CH_2Ar), 28.4 [q, C(*C*$H_3)_3$].

MS (ES+): *m/z* (%) = 597 (57, $[2M + K]^+$), 581 (100, $[2M + Na]^+$), 343 (63, $[M + MeCNNa]^+$), 318 (60, $[M + K]^+$), 302 (23, $[M + Na]^+$), 287 (18).

HRMS (ES+): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{21}NO_4{}^{23}Na$: 302.1368; found: 302.1375.

tert-Butyl 2-(2-ethyl-4-methoxyphenyl)ethylcarbamate (4.45)



4.45

From ethyl iodide (0.17 g, 1.1 mmol); yield: 0.19 g (0.71 mmol, 90%); colourless oil

IR (FT): ν_{max} = 3355, 2932, 1610, 1501, 1365, 1250 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91–6.89 (m, 2 H, H-3 and H-5), 6.70 (d, *J* = 8 Hz, 1 H, H-6), 4.46 (br., exch., 1 H, NH), 3.73 (s, 3 H, OCH_3), 3.26 (br. app. q, 2 H, C*H*$_2$NH), 2.64 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.54 (q, *J* = 7 Hz, 2 H, C*H*$_2$$CH_3$), 1.37 [s, 9 H, $C(CH_3)_3$], 1.11 (t, *J* = 7 Hz, 3 H, CH_2C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (s, C-4), 155.9 (s, C=O), 132.8 (s, C-2), 130.7 (s, C-1), 129.5 (d, C-6), 126.8 (d, C-3), 110.3 (d, C-5), 79.1 [s, *C*(*C*H_3)$_3$], 55.4 (q, OCH_3), 42.0 (t, CH_2NH), 35.4 (t, CH_2Ar), 28.4 [q, C(*C*H_3)$_3$], 23.2 (t, *C*H_2CH_3), 14.2 (q, CH_2*C*H_3).

MS (ES^+): *m/z* (%) = 279 (45, $[M]^+$), 223 (91), 206 (48), 162 (100), 135 (87), 121 (47), 105 (36), 85 (99).

HRMS (ES^+): *m/z* $[M]^+$ calcd for $C_{16}H_{25}NO_3$: 279.1834; found: 279.1835.

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Chapter Five

Lithiation and Substitution of 3-(Aminomethyl)pyridine Derivatives

Chapter Five

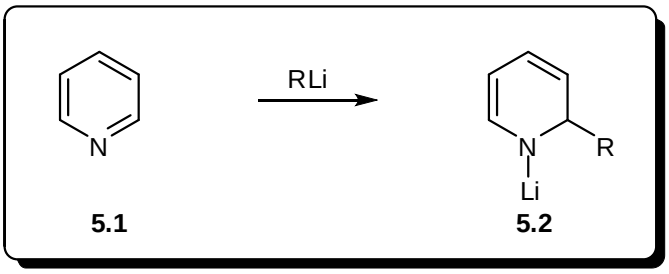
Lithiation and Substitution of 3-(Aminomethyl)pyridine Derivatives

5.1 Introduction

In previous chapters, we have investigated the effect of various substituents and directing metalating groups (urea, pivalamide and carbmate-containing groups) on the site of lithiation of simple aromatics.[1] It was of interest to see if lithiation of analogous pyridines could take place in similar manner.

The chemistry of heterocyclic compounds is extremely important for the synthesis of valuable bioorganic and pharmaceutical compounds.[2] Lithiation and substitution of heterocycles followed by treatment with electrophiles provides a convenient route for the synthesis of various substituted derivatives.[3,4]

For example, ring lithiation of pyridine could be achieved by the use of less nucleophilic lithium reagents such as lithium diisopropylamide (LDA)[5-7] and lithium tetramethylpiperidide (LTMP),[8] at low temperature, to avoid the nucleophilic addition of alkyllithiums to the azomethine bond of **5.1** (Scheme 5.1) to produce the lithium intermediate **5.2**.[7]



Scheme 5.1 Nucleophilic addition of alkyllithiums to pyridine **5.1**

Substitution of a pyridine ring can affect the pKa of neighbouring protons, coordination and disaggregation of the lithium reagent, and the stability of a neighbouring carbanion. The regioselective lithiation of pyridines containing a DMG could be controlled by such effects under thermodynamic or kinetic control. Lithiation of pyridines by lithium amides is thermodynamically controlled (because the reaction takes place only at relatively higher temperatures) and is favoured at the 3- and 4-positions more than at the 2-position as a result of stabilization by chelation of the

metal with the DMG (**A**, Figure 5.1), stabilization by an electron-withdrawing effect of the DMG (**B**) and particularly as a result of destabilization by electronic repulsion between the carbanion and the lone pair of the nitrogen (**C**). At low temperature, lithiation using alkyllithium reagents takes place mainly under kinetic control and the 2-position in pyridines is then the favoured site. Specifically for pyridines containing a DMG at the 3-position, lithiation at C-2 could be as a result of the acid-base (inductive) mechanism (**D**) and chelation in the transition state (**E**, Figure 5.1).[9]

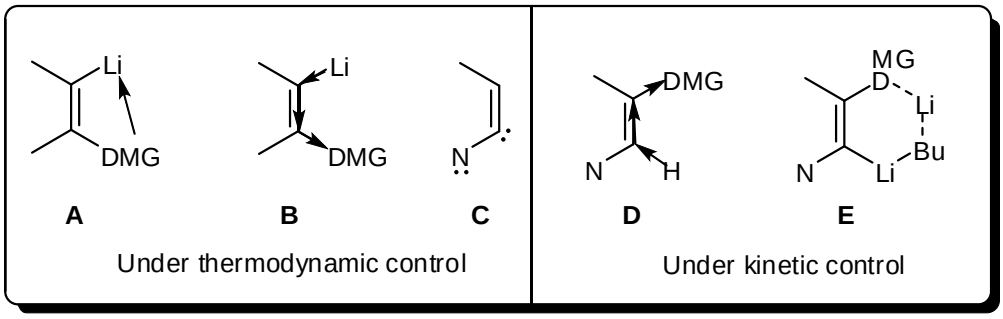


Figure 5.1 Factors affecting the lithiation rate of a pyridine ring with a DMG

Transition state (**E**) involves coordination of the DMG heteroatom to the Lewis acidic metal, which increases the proximity effect of the complexed base and causes disaggregation of the lithium reagent. For pyridines substituted at the 2- and/or 4-position, the azine nitrogen, under kinetic control, can promote deprotonation at C-2 through the complexed bases F and G (Figure 5.2). For example, if *n*-BuLi in the presence lithium 2-(dimethylamino)ethanolate (BuLi-LiDMAE) is used as the lithium reagent for pyridines containing a DMG such as OMe or Cl at C-2, product substituted at C-6 will be obtained.[9]

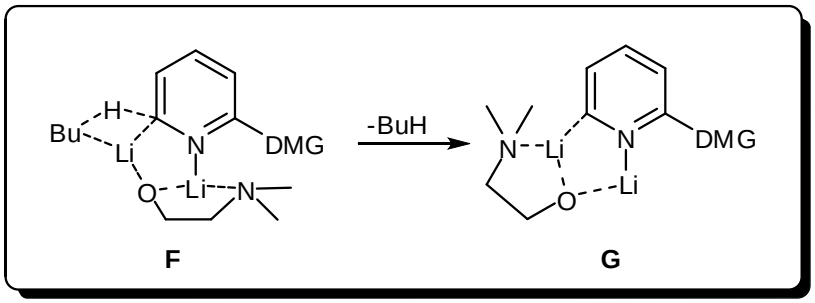
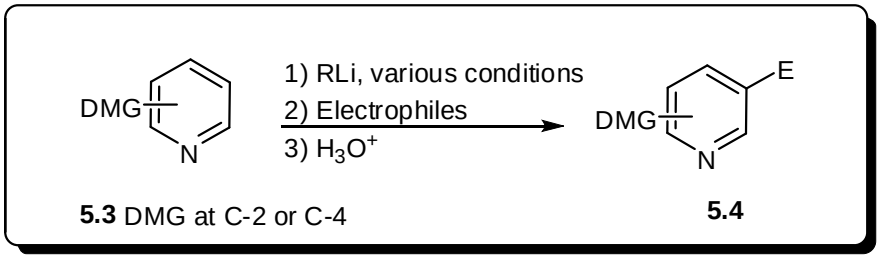


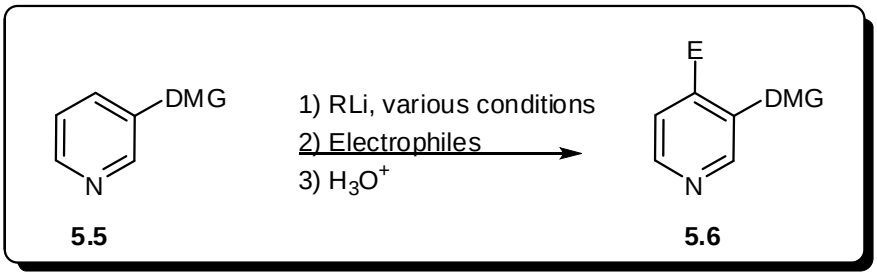
Figure 5.2 α-Lithiation of pyridines

Regioselective lithiation of pyridine containing directing metalting groups (DMGs) mostly relies on the position of the DMG. Pyridines **5.3**, containing various DMGs directly attached to the ring (*e.g.* $NHCOBu^t$, $NHCO_2Bu^t$, $CONHPh$, $CONR_2$, $SOBu^t$, SOAr, CO_2H, OCH_2OEt, OMe, CF_3, F, Cl) at the C-2[9] or C-4[10] position, with various lithium reagents invariably takes place at C-3 to give the corresponding 3-substituted derivatives **5.4** after reactions of the lithium reagents produced with electrophiles (Scheme 5.2).[10,11]



Scheme 5.2 Regioselective lithiation of pyridines **5.3**

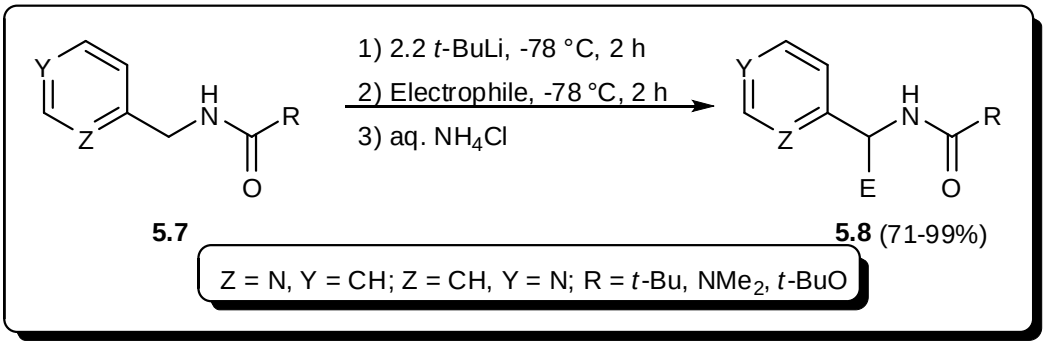
Lithiation of pyridines **5.5**, containing a DMG (*e.g.* SO_2NHBu^t, $NHCOBu^t$, $NHCO_2Bu^t$, $CONR_2$, $OCSNEt_2$, SOAr, CO_2H, OEt, OMe, F, Cl) at the C-3 position, with various lithium reagents takes place predominately at C-4 to give the corresponding 4-substituted derivatives **5.6** on reactions with electrophiles (Scheme 5.3).[11]



Scheme 5.3 Regioselective lithiation of pyridine **5.5**

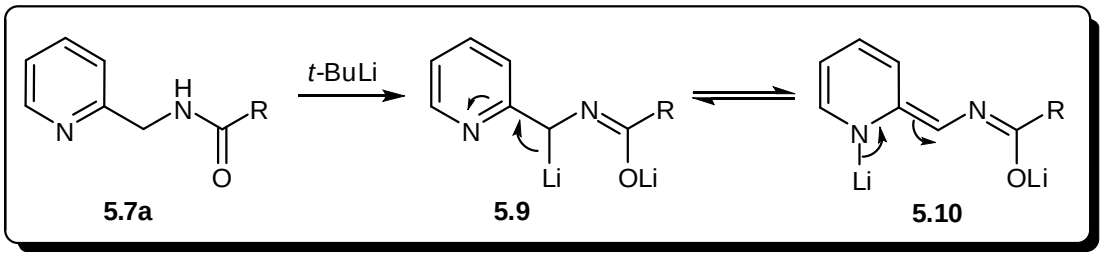
The literature indicates that several protocols for α-lithiation and directed *ortho*-metallation (DoM) of pyridines and related heterocycles are available, depending on the solvent, temperature or lithium reagent.[9-11] Very recently, the Smith group has investigated the effect of an extra CH_2 between the DMG and the pyridine ring.[12] It was found that the lithiation and substitution of 2- and 4-substituted

N-(pyridinylmethyl)amines **5.7** (urea, pivalamide and carbamate-containing groups) provided easy access to various side-chain (methylene) substituted derivatives **5.8** in high yields (Scheme 5.4).[12] Although I contributed to that work, the principles were already established by another member of the group, so no further description of the work is given here.



Scheme 5.4 Lithiation of various *N*-(pyridinylmethyl)amines **5.7**

Presumably, the highly selective side-chain lithiation of compounds **5.7** arises because of significant acidity of the CH_2 protons as a result of the ring nitrogen. Two dilithium intermediates (**5.9** and **5.10)** could result from lithiation at the CH_2 group (Scheme 5.5), and presumably could be in equilibrium. As a result, lithiation on the CH_2 group in the 2- and 4-substiuted pyridines **5.7** would be favoured over ring lithiation to a greater extent than for the simple benzyl analogues.[12]

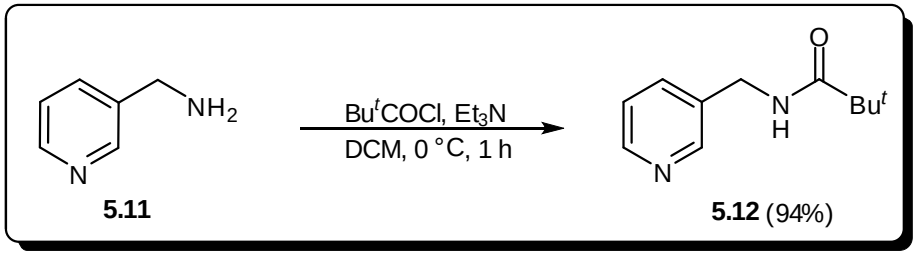


Scheme 5.5 Lithium reagents obtained from **5.7a** on reaction with *t*-BuLi

It was hoped that ring substitution of 3-substituted pyridines would take place under conditions similar to those reported in Scheme 5.4. Therefore, we decided to attempt lithiation and substitution of *N*-(pyridine-3-ylmethyl)pivalamide, *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea and *tert*-butyl pyridine-3-ylmethylcarbamate to enable convenient syntheses of the corresponding substituted derivatives.

5.2 Synthesis of *N*-(pyridine-3-ylmethyl)pivalamide (5.12)

The first task was the synthesis of *N*-(pyridine-3-ylmethyl)pivalamide (**5.12**). Synthesis of **5.12** was achieved based on a literature procedure for analogous compounds.[12] Reaction of 3-(aminomethyl)pyridine (**5.11**) with pivaloyl chloride (Bu^tCOCl; 1.2 mmol equivalents) in dichloromethane (DCM) in the presence of triethylamine (TEA) at 0 °C for 1 h. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give **5.12** in 94% yield (Scheme 5.6).



Scheme 5.6 Synthesis of *N*-(pyridine-3-ylmethyl)pivalamide (**5.12**)

The structure of compound **5.12** was confirmed by various spectroscopic techniques (see Section 5.7.2). Having successfully produced **5.12** our attention was next turned to its lithiation and substitution under various reaction conditions.

5.3 Lithiation of and substitution of *N*-(pyridine-3-ylmethyl)pivalamide (5.12)

Initially, *N*-(pyridine-3-ylmethyl)pivalamide (**5.12**) was treated with *n*-BuLi (2.2 equivalents) in anhydrous THF at -78 °C for 2 h. The mixture was then treated with benzophenone (2.2 equivalents) at -78 °C for 2 h. The reaction was quenched by the addition of aqueous ammonium chloride solution and worked-up. The TLC of the crude products showed the formation of three new products along with starting material. The crude products were separated and purified by column chromatography (silica gel; EtOAc–hexane; 1:3). The starting material **5.12** was recovered (10%) and its NMR spectra matched those recorded for **5.12** produced as in Scheme 5.6. The other products were subjected to NMR and mass spectral analysis to establish their structures.

The ^1H NMR spectrum of the first product showed signals for three aromatic protons, CH_2 protons and *tert*-butyl protons. It also showed protons for a *n*-butyl group,

indicating that this product might be produced as a result of nucleophilic addition of *n*-BuLi at one of the double bonds in the pyridine ring. The aromatic protons resonated as a doublet (J = 5 Hz) at 8.36 ppm, a singlet at 8.35 ppm and a doublet (J = 5 Hz) at 7.05 ppm. Such patterns (two low field protons) suggested that the nucleophilic addition had taken place at C-4. Therefore, the structure of the first product was identified as *N*-((4-butylpyridin-3-yl)methyl)pivalamide (**5.13**; Figure 5.3) and was produced in 6% yield. Clearly lithium intermediate **5.14** (Figure 5.3) was produced *in situ* due to addition of *n*-butyllithium at C-4, followed by oxidation.

The ^{13}C NMR spectrum of compound **5.13** showed five aromatic carbons that resonated at 149.6, 131.7, 140.5, 124.1 and 148.9 ppm, respectively which matched the values predicated by ChemDraw (149.9, 132.8, 140.1, 124.3 and 147.1 ppm, for C-1, C-2, C-3, C-4, C-5 and C-6, respectively). Moreover, the electron–impact mass spectrum of **5.13** showed an intense peak at *m/z* = 248 and the high resolution mass of this peak confirmed its formula as $C_{15}H_{24}N_2O$ (M).

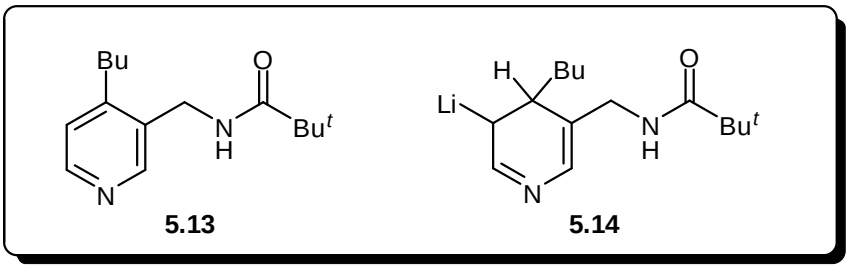


Figure 5.3 Structures of **5.13** and **5.14**

The ^{1}H NMR spectrum of the second product showed signals for fourteen aromatic protons, nine protons for a *tert*-butyl group and one proton that resonated as a doublet (J = 6 Hz) at 5.96 ppm. It also showed the absence of the doublet normally resonating at *ca.* 4 ppm corresponding to the CH_2 protons, which suggested that lithiation and substitution had taken place on the CH_2 itself. Indeed, the ^{13}C NMR spectrum showed the presence of a carbon (doublet according to DEPT spectra) that resonated at 57.7 ppm, corresponding to the CH carbon. Also, in the ^{13}C NMR spectrum the carbons of the two phenyl groups appeared as separated signals, verifying that the phenyl groups are diastereotopic. Therefore, the second product was identified as *N*-(2-hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethyl)pivalamide (**5.15**; Figure 5.4) and was isolated in 30% yield. The product **5.15** would have been produced from reaction of

dilithium intermediate **5.16** with benzophenone. Clearly, monolithium intermediate **5.17** was produced *in situ* and was converted to **5.16** (Figure 5.4). The structure of **5.15** was confirmed further by low and high resolution mass spectroscopy. The chemical ionization mass spectrum of **5.15** showed an intense pseudo molecular ion peak at *m/z* = 375 and the high resolution mass of this peak confirmed its formula as $C_{24}H_{27}N_2O_2$ (MH).

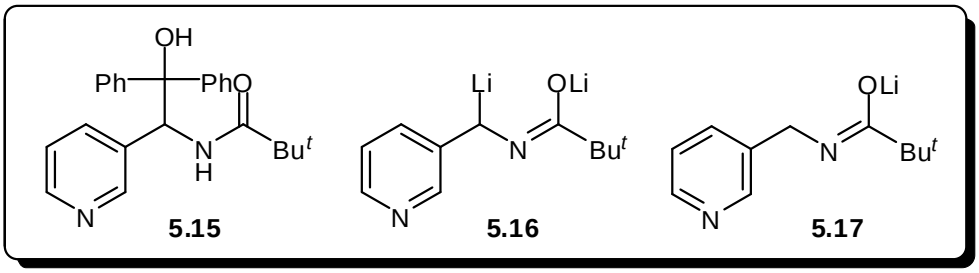


Figure 5.4 Structures of **5.15–5.17**

The ^{1}H NMR spectrum of the third product showed signals for thirteen aromatic protons, two protons corresponding to the CH_2 group, and nine protons of a *tert*-butyl group, indicating that lithiation followed by substitution had taken place. The three protons belonging to the pyridine ring showed two protons that resonated at relatively low field and one at relatively high field, similar to that of **5.13**, indicating that the lithiation and substitution had taken place at C-4. Also, the ^{13}C NMR spectrum confirmed that substitution had taken place at C-4 and showed the presence of the CH_2 carbon. Therefore, the third product was identified as *N*-((4-(hydroxydiphenylmethyl)pyridin-3-yl)methyl)pivalamide (**5.18**; Figure 5.4) and was isolated in 49% yield. Clearly, monolithium reagent **5.17** (Figure 5.4) and dilithium reagent **5.19** (Figure 5.5) were produced *in situ*. Reaction of benzophenone with **5.19** would have produced **5.18** (Figure 5.4). The electron–impact mass spectrum of **5.18** showed an intense molecular ion peak at *m/z* = 374 and the high resolution mass of this peak confirmed its formula as $C_{24}H_{26}N_2O_2$ (M).

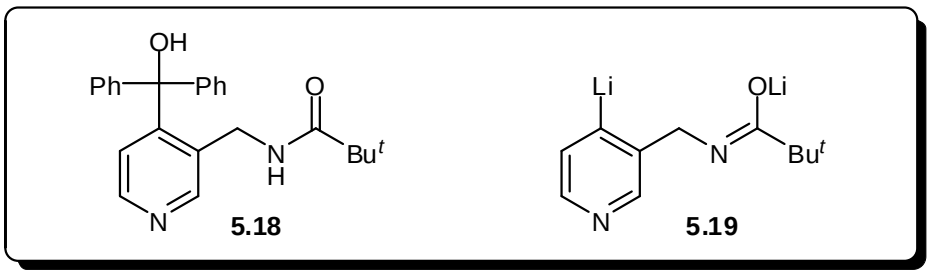


Figure 5.5 Structures of **5.18** and **5.19**

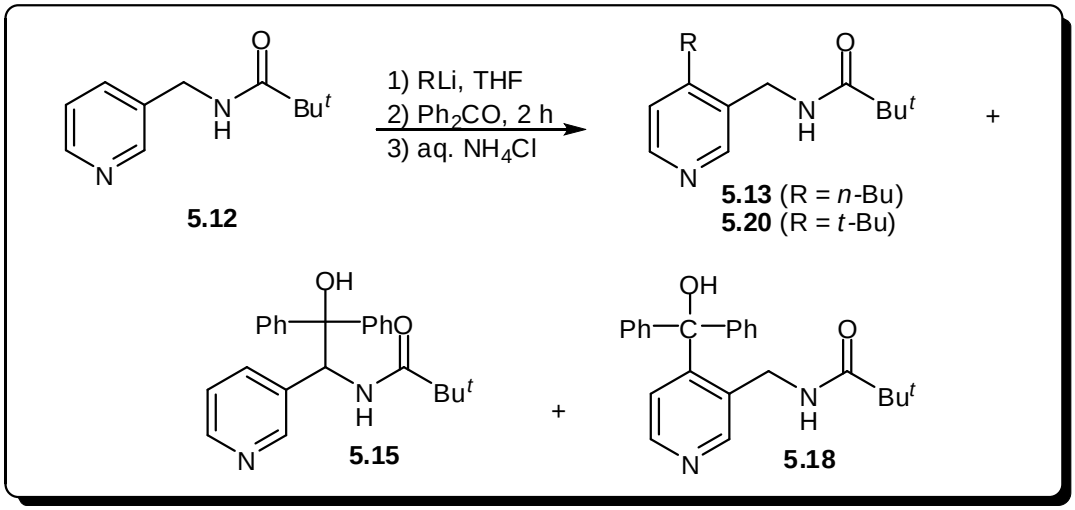
Several experiments were conducted in which lithium reagent, temperature and reaction time were varied in an attempt to study the lithiation of **5.12** and to optimise the conditions to be more selective (Table 5.1). The reaction of **5.12** with *n*-BuLi (3.3 equivalents) at −78 °C followed by reaction with benzophenone (3.3 equivalents) resulted in higher yields for **5.15** and **5.18** (59 and 41% yields, respectively) with no evidence for the formation of **5.13** (Table 5.1; Entry 2). The regioselectivity of the lithiation reaction had also been reversed, with the side-chain substitution product **5.15** being produced in higher yield than the ring substitution product **5.18**. It is not clear why lithiation of **5.12** with *n*-BuLi (2.2 or 3.3 mole equivalents) in THF at −78 °C followed by reaction with benzophenone gave products **5.15** and **5.18** but in reversed proportions. It could have something to do with the way the excess *n*-BuLi reacts that could lead to a rise in temperature, but without further information it is not easy to give a definitive explanation.

The reaction was next attempted at higher temperature in order to see what effect the temperature could have on the regioselectivity. The reaction was repeated with *n*-BuLi (3.3 equivalents) at −50 and at −20 to 0 °C (Table 5.1; Entries 3 and 4). Higher yields (24–36%) of **5.13** were obtained. Clearly, at higher temperature nucleophilic addition of *n*-BuLi became faster and competes with lithiation, which remained more selective towards side-chain substitution product **5.15** (37–48%) over ring substitution product **5.18** (22–25%).

In an attempt to eliminate the nucleophilic addition product, attention was next turned to lithiation of **5.12** with the less nucleophilic reagent lithium diisopropylamide (LDA) (Table 5.1; Entries 5–10). On reaction of **5.12** with LDA (3.3 equivalents) at −78 °C for 2 h followed by the reaction with benzophenone (3.3 equivalents) only starting material was recovered quantitatively (Table 5.1; Entry 5). Increasing the reaction time to 4 h under similar conditions led to the production of a small amount of side-chain

substitution product **5.15** (11%; Table 5.1; Entry 6) as the only product along with starting material **5.12** (82%).

Table 5.1 Products of lithiation of **5.12** under different reaction conditions

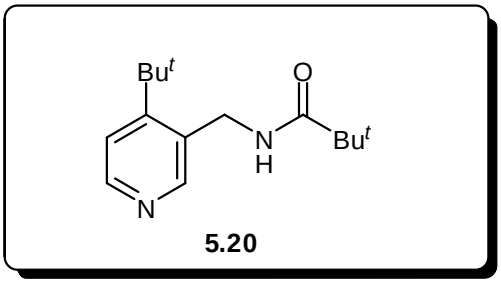


Entry	RLi (mole equiv.)	T (°C)	Time (h)	Yield (%)[a]		
				5.13 or **5.20**	**5.15**	**5.18**
1	*n*-BuLi (2.2)	–78	2	8 (6)[c]	30 (27)[b]	49 (44)[b]
2	*n*-BuLi (3.3)	–78	2	—	59	41
3	*n*-BuLi (3.3)	–50	2	24	48	25
4	*n*-BuLi (3.3)	–20 to 0	2	36	37	22
5	LDA(3.3)	–78	2	—	—	—
6	LDA (3.3)	–78	4	—	11[b,c]	—
7	LDA (3.3)	–78 to 0	4	—	34[c]	—
8	LDA (3.3)	–20 to 0	4	—	68[c]	—
9	LDA (3.3)	–20 to 0	6	—	72[c]	—
10	LDA (3.3)	0	4	—	63[c]	—
11	*t*-BuLi (3.3)	–78	2	—	—	96 (88)[b]
12	*t*-BuLi (3.3)	–50	2	22 (20)[b]	—	64 (63)[b]
13	*t*-BuLi (3.3)	–20 to 0	2	53	—	32

[a] Yield by ^{1}H NMR unless otherwise indicated.
[b.] Yield of isolated product after purification by column chromatography.
[c] Starting material **5.12** was also recovered.

The yield of **5.15** was improved to 34% (Table 5.1; Entry 7) when the reaction was carried out for 4 h at −78 to 0 °C and improved further to 68% when the reaction carried out at −20 to 0 °C (Table 5.1; Entry 8). In an attempt to increase the yield of **5.15** further two experiments were attempted in which the reaction time or the temperature were increased (Table 5.1; Entries 9 and 10). It was found that the yield of **5.15** was increased to 72% after purification when the reaction time was 6 h at −20 to 0 °C (Table 5.1; Entry 9). However, the yield was slightly decreased to 63% when the reaction was carried out at a higher temperature (0 °C) for 4 h (Table 5.1; Entry 10) possibly because the dilithium intermediate **5.16** was not highly stable at 0 °C and partially decomposed to the starting material **5.12**. Clearly, the reaction with LDA was highly regioselective towards formation of side-chain substitution product **5.15**, with no evidence for the formation of any other products, and a reasonable yield could be obtained following lithiation at −20 to 0 °C for a relatively long time.

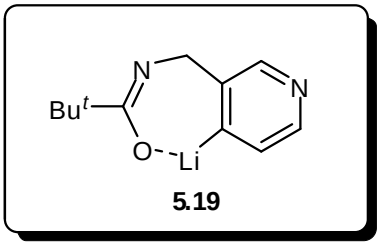
It was of interest to see what effect lithiation of **5.12** with *t*-BuLi would have, so reaction with 3.3 equivalents were attempted at various temperatures (−78 to 0 °C), followed by reaction with benzophenone (Table 5.1; Entries 9–11). It was found that at low temperature the reaction was highly regioselective towards the production of ring substitution product **5.18**. Product **5.18** was exclusively produced in 96% yield based on analysis of the ^{1}H NMR spectrum (88% isolated yield after purification: Table 5.1; Entry 11). At higher temperature (–50 °C) the yield of **5.18** was reduced to 64% along with product **5.20** (Figure 5.6), which was produced in 20% yield (Table 5.1; Entry 12). Product **5.20** resulted from addition of *t*-BuLi at C-4 followed by oxidation. The yield of **5.20** was increased further to 53% when the reaction was attempted at −20 to 0 °C, while the yield of **5.18** dropped to 32% (Table 5.1; Entry 13).



5.20

Figure 5.6 Structure of compound **5.20**

Clearly, the selectivity of lithiation and substitution of **5.12** relies on the nature of the lithium reagent, the temperature and the reaction time. The yield of ring substitution product **5.18** was high (88%) with *t*-BuLi at lower temperature (–78 °C), presumably because dilithium reagent **5.19** (Figure 5.7) is the kinetic product at low temperature. It appears that lithiation of **5.12** under such conditions selectively removes the aromatic proton, which is more appropriately positioned for directed metallation than the ones of the CH_2 group. Lithiation of **5.12** with *n*-BuLi was less regioselective, producing both side-chain and ring substitution products, although the ring substitution product was still a major one. The reason for the lower regioselectivity is not clear. In addition, because it is less hindered and more nucleophilic than *t*-BuLi, *n*-BuLi also gives rise to some addition product (**5.13**), even at low temperature. Both reagents become less selective for the ring substituted product at higher temperature, suggesting that **5.19** is not the most stable organolithium intermediate. Nevertheless, by use of *t*-BuLi at low temperature it had been possible to obtain an excellent yield of **5.18**.

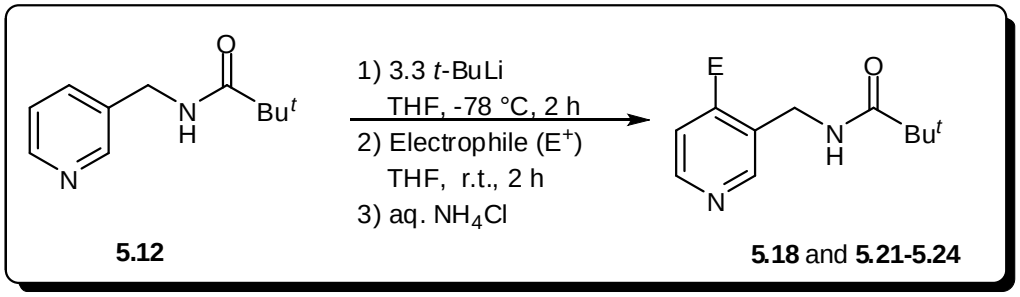


5.19

Figure 5.7 Stabilisation of lithium reagent **5.19** by coordination

It was therefore of interest to see if the reaction of the dilithium intermediate **5.19** with other electrophiles would be useful and general. Consequently, reactions of **5.19**, prepared *in situ* from **5.12** under the conditions described above (Table 5.1; Entry 11), with various other electrophiles (acetone, 4-methoxybenzaldehyde, 4-dimethylaminobenzaldehyde and iodoethane) were carried out. Each reaction was conducted under identical conditions. The crude products were purified by column chromatography (silica gel; EtOAc–hexane; in 1:3 by volume), to give the corresponding substituted derivatives **5.21**–**2.24** in excellent yields (Table 5.2).

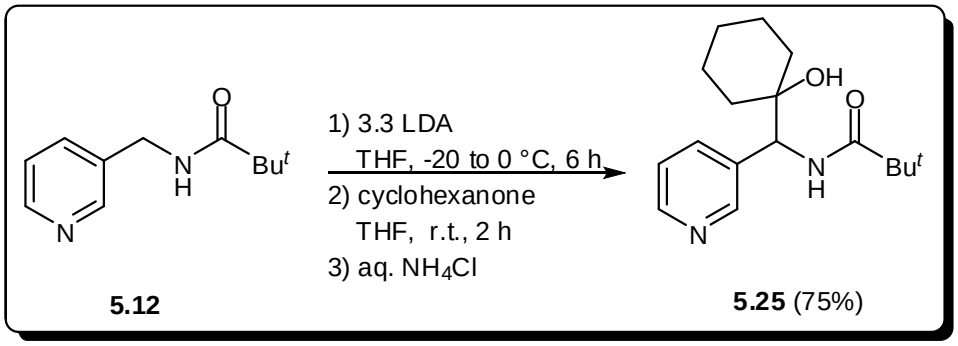
Table 5.2 Synthesis of substituted *N'*-(2-methylphenyl)ethyl)-*N*,*N*-dimethylureas **5.18** and **5.21–5.24**



Products	Electrophile	E	Yield (%)[a]
5.18	Ph_2CO	$Ph_2C(OH)$	88
5.21	Me_2CO	$Me_2C(OH)$	91
5.22	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	89
5.23	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	85
5.24	EtI	Et	90

[a] Yield of the pure isolated product.

The structures of the products were confirmed by various spectroscopic techniques (see Section 5.7.3 for details). For example, the ^{1}H NMR spectrum of product **5.22** showed that the two hydrogens of the CH_2 group appeared as separated signals (two double doublets, each with J = 6 and 15 Hz), indicating that they are diastereotopic. LDA is both less nucleophilic and less basic than the organolithium reagents, so that little reaction had taken place at –78 °C. However, at –20 to 0 °C it had given a good yield of side-chain substituted product **5.15** in a highly selective way. To test the generality for this side-chain substitution of **5.12**, cyclohexanone was used as an electrophile. It was found that lithiation of **5.12** with LDA under the conditions used with benzophenone (Table 5.1; Entry 9) followed by reaction with cyclohexanone gave **5.25** (Scheme 5.7) in 75% yield. The structure of **5.25** was confirmed by various spectroscopic techniques (see Section 5.7.3 for details). The two sides of the cyclohexane ring appeared as separated signals in their ^{13}C NMR spectrum confirming that they are diastereotopic.

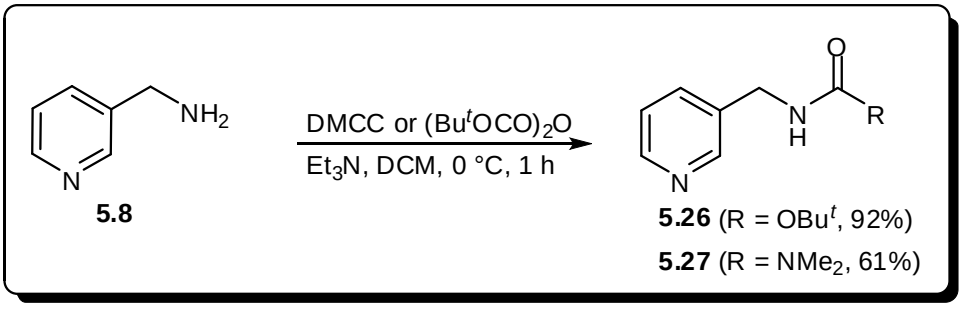


Scheme 5.7 Lithiation of **5.12** using LDA followed by reaction with cyclohexanone

Our attention was next turned to investigation of lithiation and substitution of the urea and carbamate derivatives under similar conditions to those used in the pivalamide case to see what effect the different acyl substituents could have on the lithiation site. Therefore we needed to synthesise such derivatives first.

5.4 Synthesis of 3-substituted pyridines 5.26 and 5.27

Syntheses of 3-substituted pyridines **5.26** and **5.27** (Scheme 5.7) were attempted using literature procedures that have been used for the production of analogous compounds.[12] Reaction of 3-(aminomethyl)pyridine (**5.11**) with di-*tert*-butyl dicarbonate ($(Bu^tOCO)_2O$, 1.2 equivalent) in the presence of triethylamine (TEA) at 0 °C gave a crude product that was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give *tert*-butyl pyridine-3-ylmethylcarbamate (**5.26**) in 92% yield (Scheme 5.8). Similarly, reaction of **5.11** with dimethylcarbamoyl chloride (DMCC, 1.2 equivalents) in dichloromethane (DCM) in the presence of triethylamine (TEA) at 0 °C for 1 h gave *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (**5.27**) in 61% yield (Scheme 5.8) after purification.



Scheme 5.8 Synthesis of 3-substituted pyridines **5.26** and **5.27**

The structures of **5.26** and **5.27** were confirmed by IR, NMR, MS and HRMS spectral data. For example, the electron-impact mass spectrum of **5.26** showed a molecular ion peak at *m/z* = 208, the high resolution mass of which confirmed its formula as $C_{11}H_{16}N_2O_2$ (M). The ^{1}H NMR spectrum of **5.26** showed a doublet (*J* = 6 Hz) at 4.01 ppm due to the CH_2 protons and a singlet at 1.16 ppm corresponding to the *tert*-butyl protons in addition to NH and four aromatic protons (see Section 5.7.4 for details).

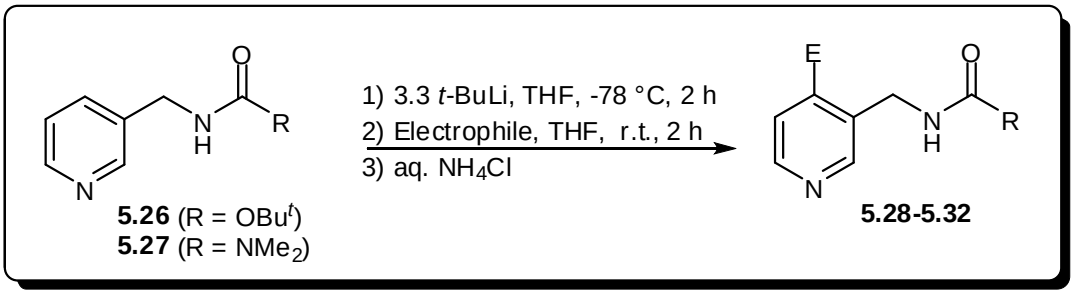
The electron-impact mass spectrum of **5.27** showed a molecular ion peak at *m/z* = 179 and the high resolution mass of this peak confirmed its formula as $C_9H_{13}N_3O$ (M). The ^{1}H NMR spectrum showed a doublet (*J* = 6 Hz) at 4.36 ppm due to the CH_2 protons, a singlet at 2.85 ppm due to NMe_2 protons, NH and four aromatic protons (see Section 5.7.5 for details).

Having successfully synthesised **5.26** and **5.27**, our attention was next turned to investigation of their lithiation followed by reactions with various electrophiles in an attempt to produce the corresponding 4-substituted derivatives.

5.5 Lithiation of and substitution of *tert*-butyl pyridine-3-ylmethylcarbamate (5.26) and *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (5.27)

Lithiations of **5.26** and **5.27** with 3.3 mole equivalents of *t*-BuLi under the conditions used for the ring substitution of **5.12** (Table 5.1; Entry 11) followed by reaction with several electrophiles (benzophenone, acetophenone, cyclohexanone and benzaldehyde) were carried out. The crude products were purified by column chromatography (silica gel; EtOAc–hexane; in 1:3 by volume), to give the corresponding substituted derivatives **5.28**–**5.32** in high yields (Table 5.3).

Table 5.3 Synthesis of **5.28–5.32** *via ortho*-lithiation and substitution of **5.26** and **527**



Products	R	Electrophile	E	Yield (%)[a]
5.28	OBu^t	Ph_2CO	$Ph_2C(OH)$	88
5.29	OBu^t	PhCOMe	PhC(OH)Me	81
5.30	OBu^t	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	84
5.31	OBu^t	PhCHO	PhCH(OH)	80
5.32	NMe_2	Ph_2CO	$Ph_2C(OH)$	66[b]

[a] Yield of the pure isolated product.
[b.] Compound **5.33** (Figure 5.9) due to addition of *t*-BuLi at C-4 of **5.27** followed by oxidation, was isolated in 5% yield

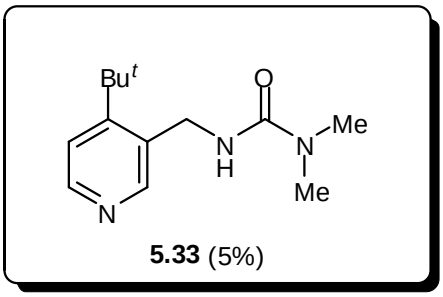
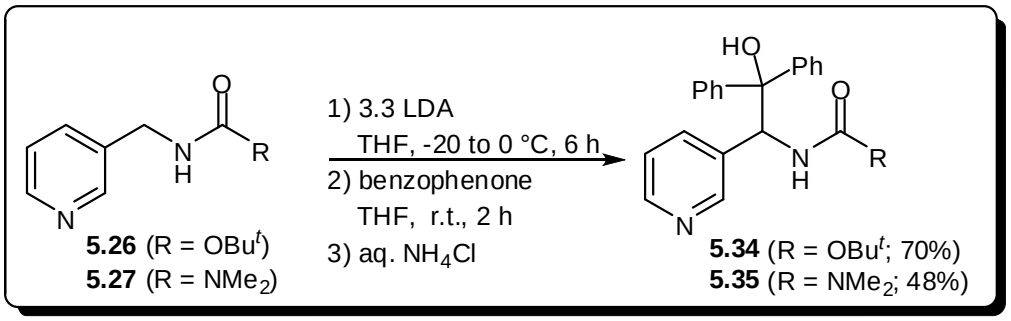


Figure 5.9 Structure of compound **5.33**

The structures of products **5.28–5.33** were confirmed by various spectroscopic techniques (see Section 5.7.6 for details). The ^1H NMR spectrum of **5.31** showed that the signals of the two hydrogens of the CH_2 group appeared as separated signals indicting that they are diastereotopic.

Finally, lithiations of **5.26** and **5.27** were attempted with LDA as the lithium reagent under similar conditions to those used for the side-chain lithiation of **5.12** (Table 5.1; Entry 9) in an attempt to produce analogous side-chain substitution

products. Indeed, lithiations of **5.26** and **5.27** with LDA followed by reactions with benzophenone as a representative electrophile gave the corresponding side-chain substitution products **5.34** and **5.35** (Scheme 5.9), isolated in 70 and 48% yields, respectively. Starting materials **5.26** (23%) and **5.27** (38%) were also recovered. Also, a polar dark material was adsorbed at the top of the chromatography column in the case of urea derivative **5.27**. This product was not identified.



Scheme 5.9 Lithiations of **5.27** and **5.27** using LDA followed by reactions with benzophenone

The structures of **5.34** and **5.35** were confirmed by the data from IR and NMR spectroscopy and mass spectrometry. Their ^{13}C NMR spectra showed that the carbons of the two phenyl groups appeared as separated signals, verifying that the phenyl groups were diastereotopic.

5.6 Conclusions

Variations in the site of lithiation have been observed with different lithiating agents in a series of *N*-acyl-3-(aminomethyl)pyridine derivatives. Ring lithiation has been achieved by the use of *t*-BuLi (3.3 mole equivalents) at −78 °C. The dilithium reagents produced *in situ* were allowed to react with various electrophiles to give the corresponding 4-substituted products in high yields. On the other hand, the reaction was regioselective towards the side-chain when LDA (3.3 mole equivalents) was used as the lithium reagent at −20 to 0 °C. A mixture of ring and side-chain substitution products, and also some product resulting from addition-oxidation was obtained when *n*-BuLi was the lithium reagent.

Two independent, convenient and simple experimental procedures have been developed for the production of ring and side-chain substitution products of such *N*-acyl-3-(aminomethyl)pyridines.

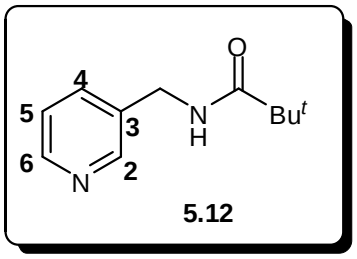
5.7 Experimental

5.7.1 General Experimental

A general experimental section outlining the instrumentation and reagents used is included in Chapter Two (Section 2.14.1).

5.7.2 Synthesis of *N*-(pyridine-3-ylmethyl)pivalamide (5.12)

To a cooled solution (0 °C) of 3-aminomethylpyridine (**5.11**; 4.32 g, 40.0 mmol) and triethylamine (6.10 g, 60.0 mmol) in DCM (50 mL) pivaloyl chloride (5.80 g, 48.0 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for 1 h and poured onto H_2O (50 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure product **5.12**.



5.12

Yield: 7.22 g (37.6 mmol, 94%); colourless oil.

IR (FT): ν_{max} = 3340, 2966, 1651, 1593, 1481, 1324, 1259, 1207, 1121 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 2 H, H-2 and H-6), 7.52 (d, *J* = 8 Hz, 1 H, H-4), 7.17 (dd, *J* = 5, 8 Hz, 1 H, H-5), 6.37 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 148.9 (s, C-2), 148.7 (d, C-6), 135.3 (s, C-3), 134.5 (d, C-4), 123.6 (d, C-5), 40.9 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

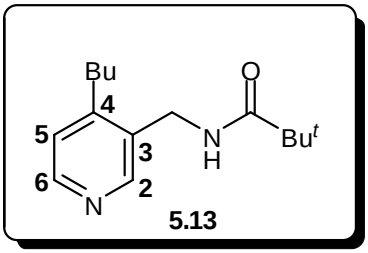
MS (APCI): *m/z* (%) = 193 (100, $[MH]^+$).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{11}H_{17}N_2O$: 193.1341; found: 193.1332.

5.7.3 Lithiation and substitution of *N*-(pyridine-3-ylmethyl)pivalamide (5.12): Synthesis of substituted derivatives 5.13, 5.15, 5.18, 5.20–5.24; general procedure

A solution of *n*-BuLi in hexane (2.75 mL, 1.6 M, 4.4 mmol), *t*-BuLi in pentane (3.47 mL, 1.9 M, 6.6 mmol) or LDA in a mixture of THF, heptane and ethyl benzene (3.30 mL, 2.0 M, 6.6 mmol) was added to a cold (-78 °C), stirred solution of **5.12** (0.38 g, 2.0 mmol) in anhydrous THF (15 mL) under N_2. The mixture was stirred at −78 °C for 2 h with *n*-BuLi or *t*-BuLi, or at –20 to 0 °C for 6 h with LDA, to ensure the complete formation of the appropriate dilithium reagent(s) after which an electrophile (6.6 mmol), in anhydrous THF (3 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h and allowed to warm up to room temperature. It was then quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure products. The reaction involving *n*-BuLi and benzophenone as electrophile gave a mixture of three products, **5.13**, **5.15** and **5.18** (Table 5.1, entry 1), but reaction involving *t*-BuLi and various electrophiles gave good yields of products **5.18** and **5.21**-**5.24** (Table 5.2) and those involving LDA and two electrophiles gave good yields of products **5.15** (Table 5.1, entry 9) and **5.25** (Scheme 5.7).

N-((4-Butylpyridin-3-yl)methyl)pivalamide (5.13)



5.13

Yield: 0.030 g (0.12 mmol, 6%) with *n*-BuLi; colourless oil.

IR (FT): ν_{max} = 3339, 2958, 1642, 1597, 1412, 1208, 1010 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 5 Hz, 1 H, H-6), 8.36 (s, 1 H, H-2), 7.06 (d, *J* = 5 Hz, 1 H, H-5), 5.72 (br., exch., 1 H, NH), 4.42 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 2.56 (t, *J* = 7 Hz, 2 H, $CH_3CH_2CH_2CH_2$), 1.51 (m, 2 H, $CH_3CH_2CH_2$), 1.33 (m, 2 H, CH_3CH_2), 1.15 [s, 9 H, $C(CH_3)_3$], 0.87 (t, *J* = 7 Hz, 3 H, CH_3).

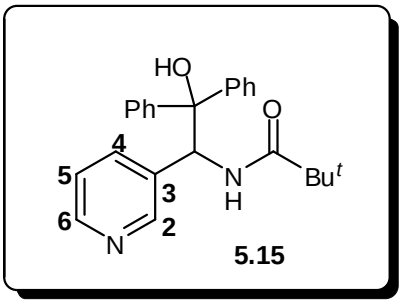
^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0 (s, C=O), 149.6 (d, C-2), 148.9 (d, C-6), 140.6 (s, C-4), 131.8 (s, C-3), 124.2 (d, C-5), 38.8 (t, CH_2NH), 38.7 [s, $C(CH_3)_3$], 32.3 [t,

$CH_3CH_2CH_2$], 31.5 (t, $CH_3CH_2CH_2CH_2$), 27.6 [q, $C(CH_3)_3$], 22.6 (t, CH_3CH_2), 13.8 (q, CH_3).

MS (EI): *m/z* (%) = 248 (53, $[M]^+$), 206 (25), 149 (29), 106 (23), 85 (100), 57 (24).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{24}N_2O$: 248.1889; found: 248.1894.

_N_-(2-Hydroxy-2,2-diphenyl-1-(pyridine-3-yl)ethyl)pivalamide (5.15)



5.15

From benzophenone (1.20 g, 6.6 mmol) using LDA; yield: 0.54 g (1.44 mmol, 72%); mp 222-224 ºC.

IR (FT): ν_{max} = 3434, 2932, 1652, 1558, 1423, 1336, 1213, 1025 cm^{-1}.

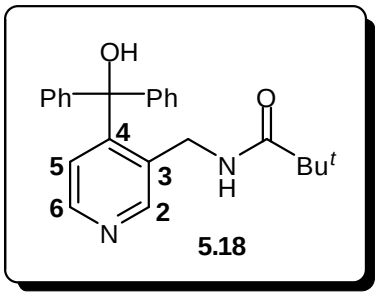
^1H NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, H-2), 7.88 (d, *J* = 5 Hz, 1 H, H-6), 7.57 (d, *J* = 8 Hz, 1 H, H-4), 7.38-6.99 (m, 10 H, 2 C_6H_5), 6.90 (dd, *J* = 5, 8 Hz, 1 H, H-5), 5.96 (d, *J* = 6 Hz, 1 H, CH), 5.22 (br., exch., 1 H, OH), 4.43 (d, *J* = 6 Hz, 1 H, NH), 0.99 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (s, C=O), 149.4 (d, C-2), 147.4 (d, C-6), 144.6, 144.1 (2 s, C-1 of C_6H_5), 137.2 (d, C-4), 135.0 (s, C-3), 128.4, 128.1 (2 d, C-3/C-5 of C_6H_5), 127.4, 127.2 (2 d, C-4 of C_6H_5), 126.2, 125.9 (2 d, C-2/C-6 of C_6H_5), 122.5 (d, C-5), 80.8 (s, COH), 57.7 (d, CH), 38.6 [s, $C(CH_3)_3$], 27.2 [q, $C(CH_3)_3$].

MS (APCI): *m/z* (%) = 416 (40, $[M + MeCNH]^+$), 375 (100, $[MH]^+$), 234 (30), 193 (35), 126 (30).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2079.

_N_-((4-(Hydroxydiphenylmethyl)pyridine-3-yl)methyl)pivalamide (5.18)



5.18

From benzophenone (1.20 g, 6.6 mmol) using *t*-BuLi; yield: 0.72 g (1.92 mmol, 96%); mp 211–213 ºC.

IR (FT): ν_{max} = 3381, 2984, 1640, 1546, 1425, 1240, 1017 cm^{-1}.

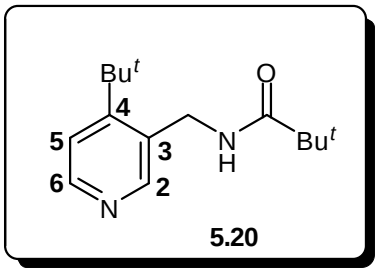
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, H-2), 8.32 (d, *J* = 5 Hz, 1 H, H-6), 7.38–7.28 (m, 11H, 10 H of 2 C_6H_5 and OH), 6.72 (br. t, *J* = 6 Hz, exch., 1 H, NH), 6.68 (d, *J* = 5 Hz, 1 H, H-5), 4.20 (d, *J* = 6 Hz, 2 H, CH_2), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0 (s, C=O), 151.2 (d, C-2), 147.1 (d, C-6), 146.8 (s, C-4), 146.0 (s, C-1 of 2 C_6H_5), 134.4 (s, C-3), 128.3 (d, C-3/C-5 of 2 C_6H_5), 127.6 (d, C-4 of 2 C_6H_5), 127.5 (d, C-2/C-6 of 2 C_6H_5), 124.1 (d, C-5), 81.7 (s, COH), 39.9 (t, CH_2), 38.5 [s, *C*$(CH_3)_3$], 27.4 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 374 (10, $[M]^+$), 358 (50), 255 (100), 179 (95).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{24}H_{26}N_2O_2$: 374.1994; found: 374.1989.

_N_-((4-*tert*-Butylpyridin-3-yl)methyl)pivalamide (5.20)



5.20

Side product from the previous reaction mixture but at higher temperature –50 °C (Table 5.1, entry 12).

Yield: 0.10 g (0.40 mmol, 20%) with *t*-BuLi; colourless oil.

IR (FT): ν_{max} = 3337, 2988, 1639, 1539, 1419, 1239, 1013 cm^{-1}.

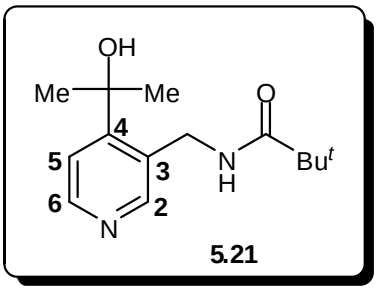
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, H-2), 8.36 (d, *J* = 5 Hz, 1 H, H-6), 7.25 (d, *J* = 5 Hz, 1 H, H-5), 5.91 (br., exch., 1 H, NH), 4.61 (d, *J* = 5 Hz, 2 H, CH_2), 1.36 [s, 9 H, $C(CH_3)_3$], 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 158.0 (s, C-4), 151.0 (d, C-2), 148.2 (d, C-6), 132.6 (s, C-4), 121.2 (d, C-5), 40.5 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 35.9 [s, $C(CH_3)$], 30.7 [q, $C(CH_3)_3$], 27.5 [q, $C(CH_3)_3$].

MS (EI): *m/z* (%) = 248 (25, $[M]^+$), 191 (33), 148 (15), 117 (15), 101 (84), 83 (100), 68 (68), 57 (96).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{24}N_2O$: 248.1889; found: 248.1891.

_N_-((4-(2-Hydroxypropan-2-yl)pyridin-3-yl)methyl)pivalamide (5.21)



From acetone (0.38 g, 6.6 mmol) using *t*-BuLi; yield: 0.45 g (1.8 mmol, 91%); colourless oil.

IR (FT): ν_{max} = 3351, 2989, 1648, 1542, 1427, 1233, 1018 cm^{-1}.

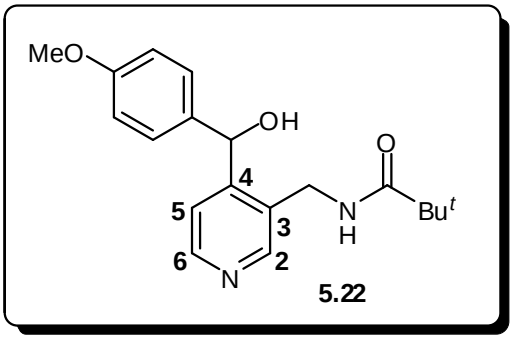
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, H-2), 8.37 (d, *J* = 5 Hz, 1 H, H-6), 7.10 (d, *J* = 5 Hz, 1 H, H-5), 6.48 (br., exch., 1 H, NH), 4.69 (d, *J* = 5 Hz, 2 H, CH_2), 3.36 (s, exch., 1 H, OH), 1.59 [s, 6 H, $C(CH_3)_2$], 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (s, C=O), 152.9 (s, C-4), 150.6 (d, C-2), 148.9 (d, C-6), 136.4 (s, C-4), 125.1 (d, C-5), 73.9 (s, COH), 40.3 (t, CH_2), 38.6 [s, $C(CH_3)_3$], 32.1 [q, $C(CH_3)_2$], 27.5 [q, $C(CH_3)_3$].

MS (EI): *m/z* (%) = 232 (50, $[M - H_2O]^+$), 217 (73), 192 (100), 174 (94), 147 (97), 118 (99), 107 (88), 92 (98), 83 (65), 65 (67).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{14}H_{20}N_2O$: 232.1576; found: 232.1581.

_N_-((4-(Hydroxy(4-methoxyphenyl)methyl)pyridin-3-yl)methyl)pivalamide (5.22)



5.22

From 4-methoxybenzaldehyde (0.90 g, 6.6 mmol) using LDA; yield: 0.58 g (1.8 mmol, 89%); colourless oil.

IR (FT): ν_{max} = 3331, 2986, 1644, 1542, 1424, 1243, 1011 cm^{-1}.

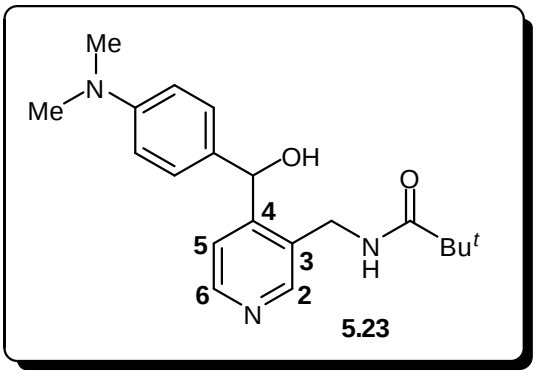
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (br. d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.40 (d, *J* = 5 Hz, 1 H, H-5), 7.17 (d, *J* = 9 Hz, 2 H, H-2 and H-6 of Ar), 6.81 (d, *J* = 9 Hz, 2 H, H-3 and H-5 of Ar), 6.87 (app. t, exch., *J* = 6 Hz, 1 H, NH), 5.96 (br. s, 1 H, C*H*OH), 4.48 (dd, *J* = 6, 15 Hz, 1 H, one H of CH_2), 4.38 (d, *J* = 6 Hz, 1 H, OH), 4.13 (dd, *J* = 6, 15 Hz, 1 H, other H of CH_2), 3.73 (s, 3 H, OCH_3), 1.03 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 159.6 (s, C-4 of Ar), 150.0 (d, C-2), 147.6 (d, C-6), 146.0 (s, C-4), 133.8 (s, C-1 of Ar), 131.6 (s, C-3), 128.4 (d, C-2/C-6 of Ar), 122.4 (d, C-5), 114.3 (d, C-2/C-6 of Ar), 72.1 (d, CHOH), 55.3 (q, OCH_3), 38.6 [s, *C*$(CH_3)_3$], 38.4 (t, CH_2), 27.4 [q, C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 327 (10, $[M-H]^+$), 267 (7), 223 (100), 118 (98), 77 (94).

HRMS (EI): *m/z* $[M-H]^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1709; found: 327.1707.

_N_-((4-((4-(Dimethylamino)phenyl)(hydroxy)methyl)pyridin-3-yl)methyl)pivalamide (5.23)



From 4-dimethylaminobenzaldehyde (0.98 g, 6.6 mmol) using *t*-BuLi; yield: 0.58 g (1.7 mmol, 85%); colourless oil.

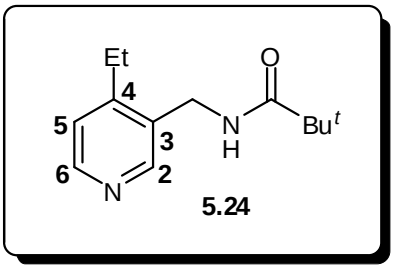
IR (FT): ν_{max} = 3328, 2977, 1640, 1589, 1429, 1248, 1015 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ =8.37 (d, *J* = 5 Hz, 1 H, H-6), 8.31 (s, 1H, H-2), 7.43 (d, *J* = 5 Hz, 1 H, H-5), 7.06 (d, *J* = 9 Hz, 2 H, H-2 and H-6 of Ar), 6.59 (d, *J* = 9 Hz, 2 H, H-3 and H-5 of Ar), 5.84 (app. t, exch., *J* = 6 Hz, 1 H, NH), 5.83 (s, 1 H, C*H*OH), 4.45 (dd, *J* = 6, 15 Hz, 1 H, one H of CH_2), 4.37 (br., 1 H, OH), 4.02 (dd, *J* = 6, 15 Hz, 1 H, other H of CH_2), 2.84 [s, 6 H, $N(CH_3)_2$], 0.95 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 150.6 (d, C-2), 150.4 (s, C-4 of Ar), 149.0 (d, C-6), 135.5 (s, C-3), 131.2 (s, C-1 of Ar), 128.2 (d, C-2/C-6 of Ar), 121.5 (d, C-5), 112.6 (d, C-3/C-5 of Ar), 72.2 (d, CHOH), 40.4 [q, $N(CH_3)_2$], 38.5 [s, *C*$(CH_3)_3$], 38.4 (t, CH_2), 27.4 [q, C(*C*$H_3)_3$].

MS (ES^+): *m/z* (%) = 392 (58, $[M+MeCNNa]^+$), 351 (19, $[M+Na]^+$), 341 (100), 329 (58, $[MH]^+$).

_N_-((4-Ethylpyridin-3-yl)methyl)pivalamide (5.24)



From iodoethane (1.03 g, 6.6 mmol) using *t*-BuLi; yield: 0.40 g (1.8 mmol, 90%); colourless oil.

IR (FT): ν_{max} = 3338, 2967, 1642, 1529, 1208, 1010 cm^{-1}.

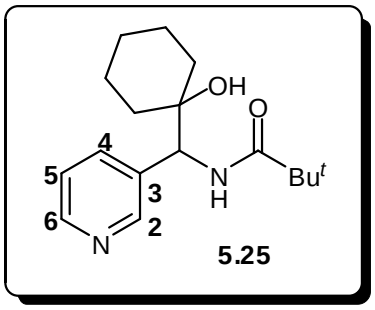
^1H NMR (500 MHz, $CDCl_3$): δ = 8.38 (br., 2 H, H-2 and H-6), 7.11 (d, *J* = 5 Hz, 1 H, H-5), 5.86 (br, exch., 1 H, NH) 4.43 (d, *J* = 6 Hz, 2 H, CH_2), 2.62 (q, *J* = 7 Hz, 2 H, CH_3CH_2), 1.18 (t, *J* = 7 Hz, 3 H, CH_3CH_2), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1 (s, C=O), 152.1 (s, C-4), 149.2 (d, C-2), 148.8 (d, C-6), 131.9 (s, C-3), 123.5 (d, C-5), 38.79 [s, $C(CH_3)_3$], 38.77 (t, CH_2), 27.6 [q, $C(CH_3)_3$], 24.7 (t, CH_3CH_2), 14.0 (q, CH_3CH_2).

MS (EI): *m/z* (%) = 220 (42, $[M]^+$), 163 (14), 135 (15), 120 (59), 107 (20), 83 (100), 77 (10), 57 (41).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1574.

_N_-((1-hydroxycyclohexyl)(pyridin-3-yl)methyl)pivalamide (5.25)



From cyclohexanone (0.64 g, 6.6 mmol) using LDA; yield: 0.44 g (1.5 mmol, 75%); colourless oil.

IR (FT): ν_{max} = 3351, 2962, 1642, 1560, 1421, 1333, 1209, 1019 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.55 (s, 1 H, H-2), 8.40 (br., 1 H, H-6), 7.60 (d, *J* = 8 Hz, 1 H, H-4), 7.21 (br., exch., 1 H, OH), 6.75 (d, *J* = 8 Hz, 1 H, H-5), 6.58 (br., exch., 1 H, NH), 4.77 (d, *J* = 8 Hz, 1 H, CH), 1.80–1.50 (m, 10 H, *c*-Hex), 1.14 [s, 9 H, $C(CH_3)_3$].

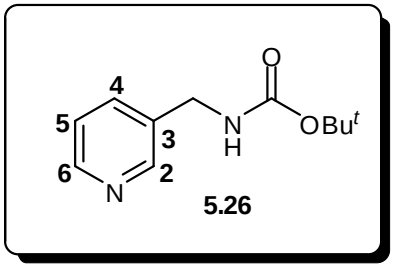
^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.5 (s, C=O), 149.2 (d, C-2), 148.3 (d, C-6), 136.3 (s, C-3), 133.1 (d, C-4), 123.3 (d, C-5), 73.2 (s, C-1 of *c*-Hex), 63.4 (d, CH), 40.8 [s, $C(CH_3)_3$], 35.9, 35.4 (2 t, C-2/C-6 of *c*-Hex), 27.5 [q, $C(CH_3)_3$], 25.3 (t, C-4 of *c*-Hex), 21.9, 21.5 (2 t, C-3/C-5 of *c*-Hex).

MS (EI): *m/z* (%) = 290 (33, $[M]^+$), 217 (55), 192 (100), 171 (91), 150 (55), 107 (99), 93 (96), 83 (98).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{26}N_2O_2$: 290.1994; found: 290.1993.

5.7.4 Synthesis of *tert*-butyl pyridine-3-ylmethyl carbamate (5.26)

To a cooled solution (0 °C) of 3-aminomethylpyridine (**5.11**; 4.32 g, 40.0 mmol) and triethylamine (6.10 g, 60.0 mmol) in DCM (50 mL) di-*tert*-butyl dicarbonate (10.50 g, 48.0 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for 1 h and poured onto H_2O (100 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure product **5.26**.



5.26

Yield: 7.70 g (37.0 mmol, 92%); colourless oil.

IR (FT): ν_{max} = 3352, 2980, 1707, 1579, 1431, 1367, 1249, 1218, 1165 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, H-2), 8.13 (d, *J* = 5 Hz, 1 H, H-6), 7.34 (d, *J* = 8 Hz, 1 H, H-4), 6.93 (dd, *J* = 5, 8 Hz, 1 H, H-5), 6.45 (br, exch., 1 H, NH), 4.01 (d, *J* = 6 Hz, 2 H, CH_2), 1.16 [s, 9 H, $C(CH_3)_3$].

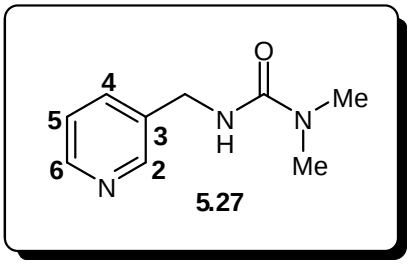
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2 (s, C=O), 148.5 (d, C-2), 148.0 (d, C-6), 135.0 (s, C-3), 134.9 (d, C-4), 123.2 (d, C-5), 79.0 [s, $C(CH_3)_3$], 41.8 (t, CH_2), 28.2 [q, $C(CH_3)_3$].

MS (EI): *m/z* (%) = 208 (5, $[M]^+$), 152 (30), 135 (20), 107 (68), 80 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{16}N_2O_2$: 208.1212; found: 208.1207.

5.7.5 Synthesis of *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (5.27)

To a cooled solution (0 °C) of 3-aminomethylpyridine (**5.11**; 4.32 g, 40.0 mmol) and triethylamine (6.10 g, 60.0 mmol) in DCM (50 mL) dimethylcarbamoyl chloride (5.20 g, 48.0 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at room temperature for 1 h and poured onto H_2O (100 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure **5.27**.



5.27

Yield: 4.37 g (24.4 mmol, 61%); reddish oil.

IR (FT): ν_{max} = 3335, 2929, 1633, 1537, 1427, 1378, 1234, 1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48-8.42 (m, 2 H, H-2 and H-6), 7.70 (d, *J* = 8 Hz, 1 H, H-4), 7.21 (dd, *J* = 5, 8 Hz, 1 H, H-5), 5.07 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 148.7 (d, C-2), 148.0 (d, C-6), 136.1 (s, C-3), 136.0 (d, C-4), 123.7 (d, C-5), 42.4 (t, CH_2), 36.3 [q, $N(CH_3)_2$].

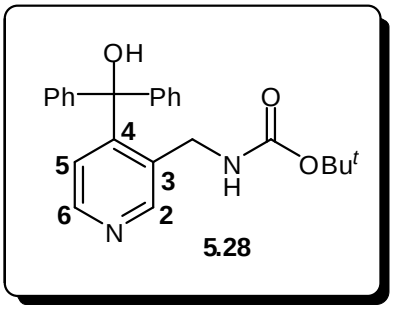
MS (EI): *m/z* (%) = 179 (100, $[M]^+$), 135 (40), 107 (45).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_{13}N_3O$: 179.1059; found: 179.1057.

5.7.6 Lithiation and substitution of *tert*-butyl pyridine-3-ylmethyl carbamate (5.26) and *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (5.27): Synthesis of substituted derivatives 5.28–5.32; general procedure

A solution of *t*-BuLi in pentane (3.47 mL, 1.9 M, 6.6 mmol) was added to a cold (-78 °C), stirred solution of **5.26** or **5.27** (2.0 mmol) in anhydrous THF (15 mL) under N_2. The mixture was stirred at −78 °C for 2 h to ensure the complete formation of the dilithium reagent, after which electrophile (6.6 mmol), in anhydrous THF (3 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h and allowed to warm up to r.t. It was then quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure products **5.28–5.32**, along with a small amount of **5.33** from the reaction of **5.27** with benzophenone.

tert-Butyl (4-(hydroxydiphenylmethyl)pyridine-3-yl)methylcarbamate (5.28)



5.28

From benzophenone (1.20 g, 6.6 mmol); yield: 0.69 g (1.77 mmol, 88%); mp 215-217 °C.

IR (FT): ν_{max} = 3447, 2980, 1692, 1591, 1445, 1369, 1214, 1076 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.45 (s, 1 H, H-2), 8.34 (d, *J* = 5 Hz, 1 H, H-6), 7.38 (s, exch., 1 H, OH), 7.36 (t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 C_6H_5), 7.31 (t, *J* = 8 Hz, 2 H, H-4 of 2 C_6H_5), 7.19 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 C_6H_5), 6.89 (br, exch., 1 H, NH), 6.54 (d, *J* = 5 Hz, 1 H, H-5), 4.07 (d, *J* = 6 Hz, 2 H, CH_2), 1.38 [s, 9 H, $C(CH_3)_3$].

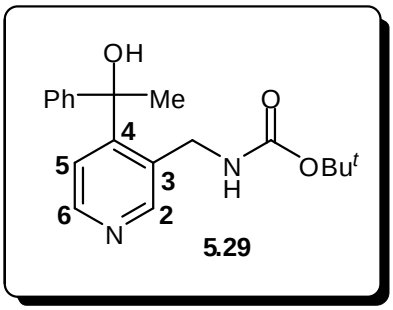
^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.2 (s, C=O), 152.9 (s, C-1 of 2 C_6H_5), 150.0 (d, C-2), 148.1 (d, C-6), 146.2 (s, C-4), 134.4 (s, C-3), 128.4 (d, C-3/C-5 of 2 C_6H_5), 127.9 (d, C-2/C-6 of 2 C_6H_5), 127.7 (d, C-4 of 2 C_6H_5), 123.4 (d, C-5), 81.7 (s, COH), 78.5 [s, *C*$(CH_3)_3$], 40.6 (t, CH_2), 28.7 [q, C(*C*$H_3)_3$].

MS (APCI): *m/z* (%) = 432 (5, [M + MeCNH]$^+$), 391 (100, [MH]$^+$), 115 (8).

HRMS (APCI): *m/z* calcd for $C_{24}H_{27}N_2O_3$ [MH]$^+$ 391.2022; found 391.2017.

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.7; H, 6.8; N, 6.9.

tert-Butyl (4-(1-hydroxy-1-phenylethyl)pyridine-3-yl)methylcarbamate (5.29)



5.29

From acetophenone (0.79 g, 6.6 mmol); yield: 0.53 g (1.62 mmol, 81%); colourless oil.

IR (FT): ν_{max} = 3352, 2979, 1686, 1581, 1449, 1391, 1267, 1166 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H-2), 8.30 (d, *J* = 5 Hz, 1 H, H-6), 7.79 (d, *J* = 8 Hz, 2 H, H-2/H-6 of C_6H_5), 7.49-7.27 (m, 4 H, H-3/H-5/H-4 of C_6H_5 and OH),

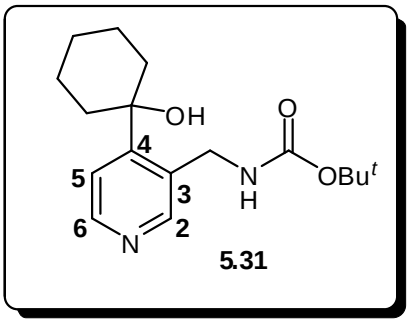
7.07 (d, *J* = 5 Hz, 1 H, H-5), 6.20 (br, exch., 1 H, NH), 4.17 (app. d, *J* = 6 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.31 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C-2), 148.1 (d, C-6), 136.9 (s, C-4), 135.1 (s, C-1 of C_6H_5), 134.9 (s, C-3), 132.9 (d, C-4 of C_6H_5), 128.4 (d, C-3/C-5 of C_6H_5), 128.1 (d, C-2/C-6 of C_6H_5), 123.3 (d, C-5), 79.1 (s, COH), 77.4 [s, *C*$(CH_3)_3$], 41.9 (t, CH_2), 28.2 [q, C(*C*$H_3)_3$], 26.3 (q, CH_3).

EI–MS: *m/z* (%) = 313 (5, $[M - CH_3]^+$), 271 (10), 210 (60), 195 (100), 180 (60), 133 (85), 83 (95).

HRMS: *m/z* $[M - CH_3]^+$ calcd for $C_{18}H_{21}N_2O_3$: 313.1552; found: 313.1555.

***tert*-Butyl (4-(1-hydroxycyclohexyl)pyridine-3-yl)methylcarbamate (5.30)**



5.31

From cyclohexanone (0.64 g, 6.6 mmol); yield: 0.49 g (1.6 mmol, 80%); colourless oil.

IR (FT): ν_{max} = 3347, 2979, 1700, 1579, 1449, 1367, 1280, 1252, 1167 cm^{-1}.

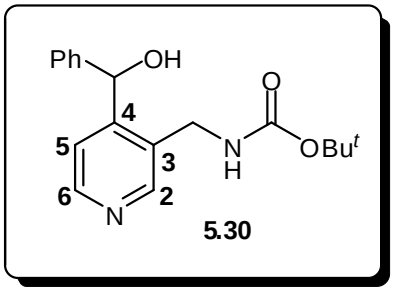
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H-2), 8.32 (d, *J* = 5 Hz, 1 H, H-6), 7.11 (d, *J* = 5 Hz, 1 H, H-5), 5.98 (br, exch., 1 H, NH), 5.98 (br, exch., 1 H, OH), 4.18 (d, *J* = 6 Hz, 2 H, CH_2), 2.25-1.44 (m, 10 H, *c*-Hex), 1.32 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C-2), 148.2 (d, C-6), 135.2 (s, C-4), 134.9 (s, C-3), 123.4 (d, C-5), 79.4 [s, *C*$(CH_3)_3$], 71.9 (s, C-1 of *c*-Hex), 43.7 (t, CH_2), 38.0(t, C-2/C-6 of *c*-Hex), 28.2 [q, C(*C*$H_3)_3$], 25.8 (t, C-4 of *c*-Hex), 21.5 (t, C-3/C-5 of *c*-Hex).

MS (EI): *m/z* (%) = 307 (100, $[MH]^+$), 250 (43), 209 (68), 194 (35), 153 (20).

HRMS (EI): *m/z* $[MH]^+$ calcd for $C_{17}H_{27}N_2O_3$: 307.2022; found: 307.2014.

***tert*-Butyl (4-(hydroxy(phenyl)methyl)pyridin-3-yl)methylcarbamate (5.31)**



5.30

From benzaldehyde (0.70 g, 6.6 mmol); yield: 0.53 g (1.62 mmol, 81%); colourless oil.

IR (FT): ν_{max} = 3344, 2969, 1688, 1580, 1454, 1388, 1265, 1161 cm^{-1}.

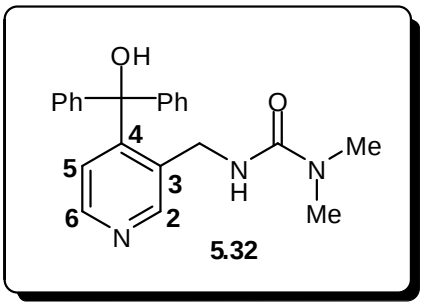
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5 Hz, 1 H, H-6), 8.33 (s, 1 H, H-2), 7.29–7.19 (m, 7 H, H-5, C_6H_5 and OH), 5.96 (s, 1 H, C*H*OH), 4.97 (br, exch., 1 H, NH), 4.27 (br. d, *J* = 14 Hz, 1 H, one H of CH_2), 4.06 (dd, *J* = 5, 14 Hz, 1 H, other H of CH_2), 1.33 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8 (s, C=O), 150.5 (d, C-2), 149.1 (d, C-6), 150.3 (s, C-4), 141.7 (s, C-1 of C_6H_5), 131.6 (s, C-3), 128.8 (d, C-3/C-5 of C_6H_5), 128.0 (d, C-4 of C_6H_5), 127.0 (d, C-2/C-6 of C_6H_5), 122.0 (d, C-5), 80.0 [s, *C*$(CH_3)_3$], 72.2 (s, COH), 39.6 (t, CH_2), 28.4 [q, C(*C*$H_3)_3$].

MS (APCI): *m/z* (%) = 315 (100, $[MH]^+$), 259 (22), 209 (9), 153 (7).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{18}H_{23}N_2O_3$: 315.1709; found: 315.1702.

***N'*-((4-(Hydroxydiphenymethyl)pyridine-3-yl)methyl)-*N*,*N*-dimethylurea (5.32)**



5.32

From benzophenone (1.20 g, 6.6 mmol); yield: 0.48 g (1.32 mmol, 66%); mp 219-221 °C.

IR (FT): ν_{max} = 3583, 2965, 1634, 1524, 1476, 1376, 1218, 1028 cm^{-1}.

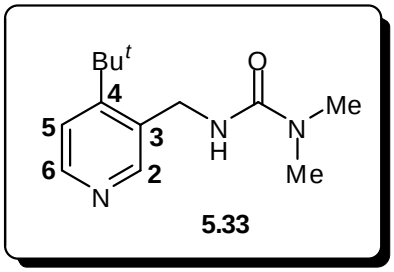
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, H-2), 8.26 (d, *J* = 5 Hz, 1 H, H-6), 7.33-7.28 (m, 11 H, 10 H of 2 C_6H_5 and OH), 6.59 (d, *J* = 5 Hz, 1 H, H-5), 5.38 (t, *J* = 6 Hz, exch., 1 H, NH), 4.12 (d, *J* = 6 Hz, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 153.6 (s, C-4), 152.1 (d, C-2), 147.8 (d, C-6), 146.7 (d, C-1 of 2 C_6H_5), 134.6 (s, C-3), 128.1 (d, C-3/C-5 of C_6H_5), 127.6 (d, C-2/C-6 of C_6H_5), 127.2 (d, C-4 of C_6H_5), 124.0 (d, C-5), 81.3 (s, COH), 41.1 (t, CH_2), 36.2 [q, $N(CH_3)_2$].

MS (EI): *m/z* (%) = 361 (10, $[M]^+$), 343 (70).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{22}H_{23}N_3O_2$: 361.1790; found: 361.1790.

***N'*-((4-*tert*-Butylpyridin-3-yl)methyl)-*N*,*N*-dimethylurea (5.33)**



5.33

Side product from the previous reaction mixture.

Yield: 0.024 g (0.10 mmol, 5%); colourless oil.

IR (FT): ν_{max} = 3341, 2972, 1632, 1521, 1469, 1230, 1023 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (s, 1 H, H-2), 8.33 (d, *J* = 5 Hz, 1 H, H-6), 7.28 (d, *J* = 5 Hz, 1 H, H-5), 4.85 (br., exch., 1 H, NH), 4.62 (d, *J* = 5 Hz, 2 H, CH_2), 2.85 [s, 6 H, $N(CH_3)_2$] 1.38 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C-4), 156.7 (s, C=O), 150.2 (d, C-2), 147.0 (d, C-6), 128.5 (s, C-3), 121.4 (d, C-5), 41.7 (t, CH_2), 36.5 [q, $N(CH_3)_2$], 36.1 [s, $C(CH_3)_3$], 30.7 [q, $C(CH_3)_3$].

MS (ES^+): *m/z* (%) = 493 (21, $[2M+Na]^+$), 299 (49, $[M+MeCNNa]^+$), 236 (100, $[MH]^+$), 191 (5).

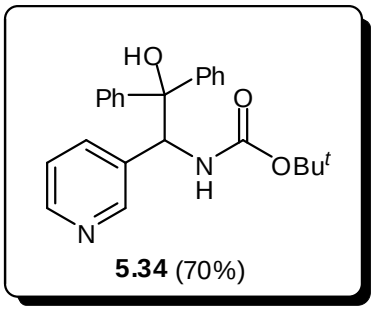
HRMS (ES^+): *m/z* $[MH]^+$ calcd for $C_{13}H_{22}N_3O$: 236.1763; found: 236.1765.

5.7.7 Lithiation and substitution of *tert*-butyl pyridine-3-ylmethyl carbamate (5.26) and *N'*-(pyridine-3-ylmethyl)-*N*,*N*-dimethylurea (5.27): Synthesis of substituted derivatives 5.34 and 5.35; general procedure

A solution of LDA in a mixture of THF, heptane and ethyl benzene (3.30 mL, 2.0 M, 6.6 mmol) was added to a cold (–20 °C), stirred solution of **5.26** (0.42 g, 2.0 mmol) or **5.27** (0.36 g, 2.0 mmol) in anhydrous THF (15 mL) under N_2. The mixture

was stirred at −20 to 0 °C for 6 h to ensure the complete formation of the dilithium reagent, after which benzophenone (1.20 g, 6.6 mmol), in anhydrous THF (3 ml) was added. The mixture was stirred for 2 h and allowed to warm up to r.t. It was then quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure products **5.34** and **5.35**.

***tert*-Butyl 2-hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethylcarbamate (5.34)**



5.34 (70%)

Yield: 0.55 g (1.4 mmol, 70%); colourless oil.

IR (FT): ν_{max} = 3357, 2931, 1693, 1541, 1423, 1374, 1224, 1061 cm^{-1}.

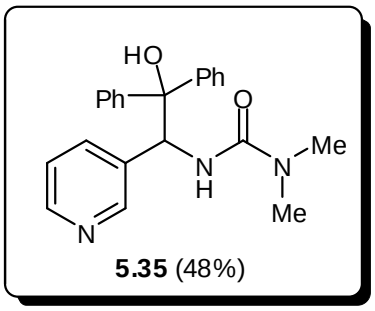
^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (br., 2 H, H-2/H-6), 7.48 (d, *J* = 8 Hz, 2 H, H-2/H-6 of one C_6H_5), 7.30 (t, *J* = 8 Hz, 2 H, H-3/H-5 of one C_6H_5), 7.26–7.20 (m, 3 H, H-4 and H-2/H-6 of other C_6H_5), 7.07–7.00 (m, 5 H, H-5 and H-3/H-5 of other C_6H_5 and H-4 of 2 C_6H_5), 6.94 (br., exch., 1 H, OH), 5.66 (d, *J* = 8 Hz, 1 H, CH), 5.59 (br., exch., 1 H, NH), 1.27 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9 (s, C=O), 149.9 (d, C-2), 148.1 (d, C-6), 144.3, 144.0 (2 s, C-1 of 2 C_6H_5), 141.3 (s, C-3), 138.0 (d, C-4), 128.5, 128.1 (2 d, C-3/C-5 of 2 C_6H_5), 127.5, 127.2 (2 d, C-4 of 2 C_6H_5), 126.3, 125.7 (2 d, C-2/C-6 of 2 C_6H_5), 122.0 (d, C-5), 90.4 (s, COH), 81.4 [s, $C(CH_3)_3$], 58.5 (d, CH), 28.3 4 [q, $C(CH_3)_3$].

MS (APCI): *m/z* (%) = 391 (8, $[MH]^+$), 193 (8), 124 (28), 83 (100).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2016.

_N'_-(2-Hydroxy-2,2-diphenyl-1-(pyridine-3-yl)ethyl)-_N_,_N_-dimethylurea (5.35)



5.35 (48%)

Yield: 0.35 g (0.97 mmol, 48%); mp 203-205 ºC.

IR (FT): ν_{max} = 3366, 2927, 1623, 1522, 1448, 1380, 1214, 1064 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1 H, H-2), 7.96 (d, *J* = 5 Hz, 1 H, H-6), 7.52 (d, *J* = 8 Hz, 1 H, H-4), 7.31-6.86 (m, 11 H, 10 H of 2 C_6H_5 and OH), 7.01 (dd, *J* = 5, 8 Hz, 1 H, H-5), 5.82 (br., exch., 1 H, NH), 5.76 (d, *J* = 6 Hz, 1 H, CH), 2.64 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (s, C=O), 149.2 (d, C-2), 146.6 (d, C-6), 144.7, 144.4 (2 s, C-1 of 2 C_6H_5), 137.8 (s, C-3), 136.4 (d, C-4), 128.5, 128.0 (2 d, C-3/C-5 of 2 C_6H_5), 127.3, 127.1 (2 d, C-4 of 2 C_6H_5), 126.5, 125.8 (2 d, C-2/C-6 of 2 C_6H_5), 122.6 (d, C-5), 80.9 (s, COH), 59.4 (d, CH), 36.1 [q, $N(CH_3)_2$].

MS (APCI): *m/z* (%) = 362 (100, $[MH]^+$), 120 (65).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{22}H_{24}N_3O_2$: 362.1869; found: 362.1874.

5.8 References

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Chapter Six

Preparation of Chiral Lewis Acid Catalysts and Their Use in Asymmetric Reactions

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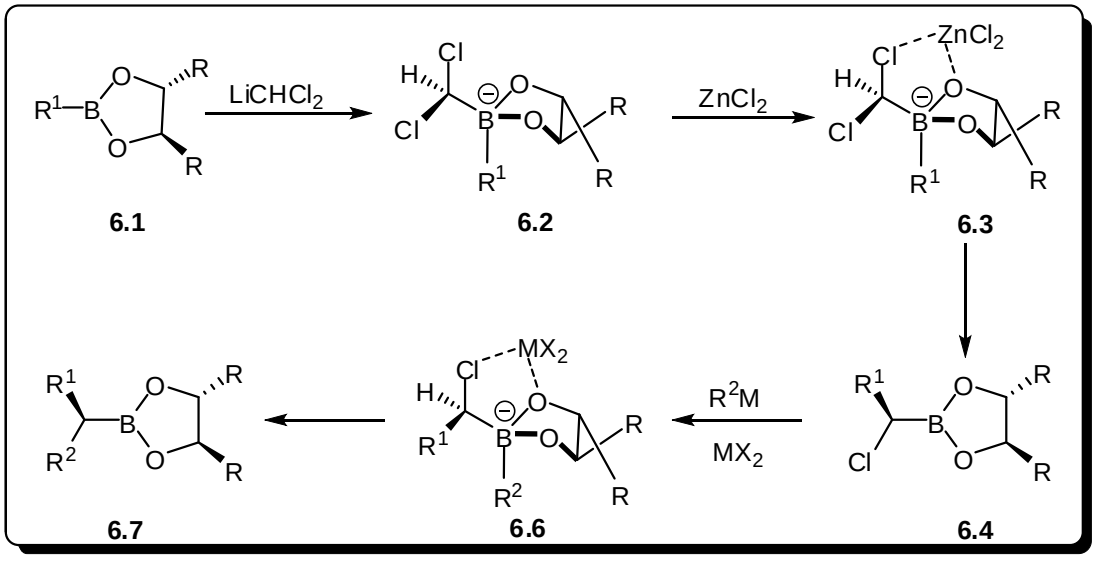
Preparation of Chiral Lewis Acid Catalysts and Their Use in Asymmetric Reactions

6.1. Introduction

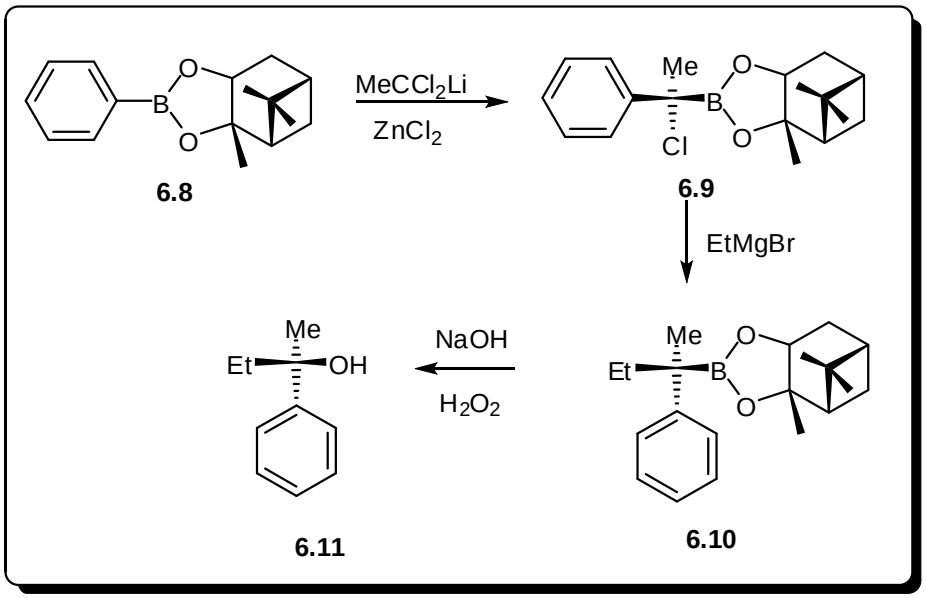
In the past several years, asymmetric catalysis and production of enantiomerically-pure substances *via* the use of chiral Lewis acids have rapidly grown and developed. Chiral compounds are important in biological processes within the human body; especially all enzymes are chiral molecules and all the natural receptors in cells prefer to bind one chiral form of molecules. Chiral compounds are also important in other areas such as drugs, medicines and catalysts.[1,2]

Matteson asymmetric homologation is a very useful process to provide state of the art stereocontrol in asymmetric synthesis as well as in geometry of unsaturated systems *via* easily synthesised reagents such as α-haloboronic esters and α,α-dihaloboronic esters.[3] Chiral alkylboronic esters **6.1** undergo nucleophilic addition of dichloromethyllithium to the electrophilic boron atom followed by rearrangement of the ate complexes **6.3** produced to give the very useful synthetic intermediate α-haloboronic esters **6.6** (Scheme 6.1), to provide access to a broad range of synthetic targets **6.7** in high yield with high level of stereocontrol.[4]



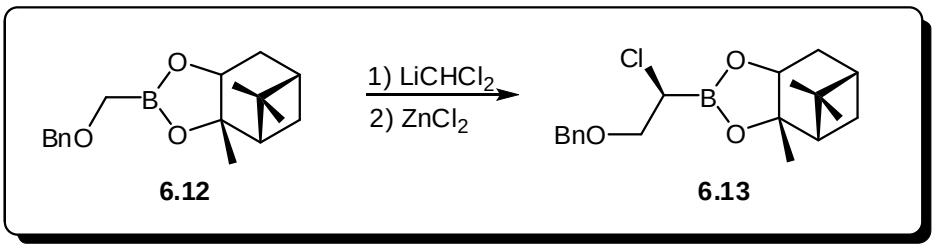
Scheme 6.1 Matteson's asymmetric homologation process

Several methods have been developed for the stereospecific conversions of compounds **6.7**, with retention of configuration, into alcohols or amines or compounds involving further C-C couplings.[5] Donald S. Matteson and Gerald D. Hurst[6] have prepared tertiary alcohols in high levels of asymmetric induction (up to 80-90% diastereomeric excess) through the reaction of (*S*)-pinanediol phenylboronates (**6.8**) with 1,1-dichloroethy1lithium generated *in situ* at –78°C followed by rearrangement of the resulting borate complex in the presence of zinc chloride at 25 °C, which resulted in chirally biased insertion of the 1-chloroethyl group into the carbon-boron bond. (*S*)-Pinanediol phenylboronate (**6.8**) produced (*S*)-pinanediol (1*S*)-(1-chloro-1-phenylethy1)boronate (**6.9**) in 92% diastereomeric excess. Non-stereospecific reaction with ethylmagnesium bromide to form (*S*)-pinanediol (1*S*)-(1-phenyl-1-methylpropy1)boronate (**6.10**) reduced the de to 88%. Peroxidic deboronation yielded (*R*)-(+)-2-phenyl-2-butanol (**6.11**) in 84% enantiomeric excess (Scheme 6.2).[6]



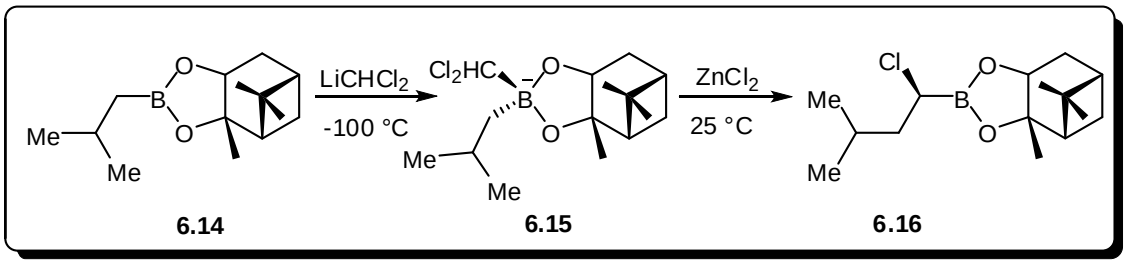
Scheme 6.2 Synthesis of tertiary alcohols **6.11** in high levels of asymmetric induction

Matteson has found that the the presence of Lewis acids such as zinc chloride in the homologation reaction is necessary in some cases. For example, no reaction occurred for (*S*)-pinanediol benzyloxymethylboronate (**6.12**) with (dichloromethyl)lithium but a good yield of the insertion product **6.13** was obtained in the presence of zinc chloride (Scheme 6.3).[7]



Scheme 6.3 Homologation reaction of (*S*)-pinanediol [(benzyloxy)methyl]boronate (**6.12**)

Also in other cases, the presence of Lewis acids is important to improve the yield and the enantiomeric excess (%ee) of α-haloalkylboronates. For example, the addition of zinc chloride in the conversion of (*S*)-pinanediol *iso*-butylboronate (**6.14**) to α-chloroboronic ester **6.16** (Scheme 6.4) increased the yield of (*S*)-pinanediol (1-chloro-3-methyl)butylboronate (**6.16**) to 90% from 15–33% and the diastereomeric excess to 99% de from 77% de.[4,7,8]

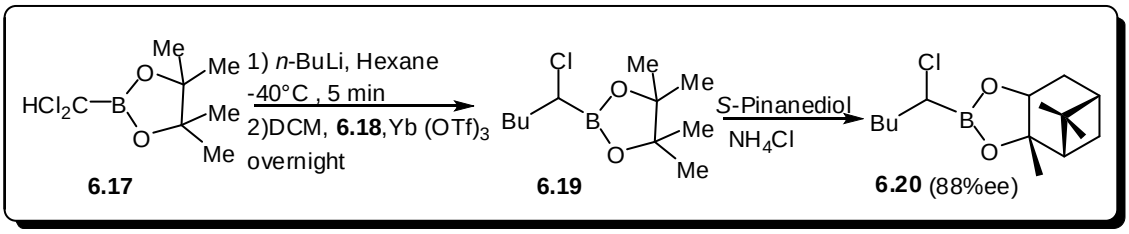


Scheme 6.4 Homologation reaction of (*S*)-pinanediol *iso*-butylboronate (**6.14**)

The addition of Lewis acids such as zinc chloride in such reactions promotes and directs the migration of the alkyl group by complexation to the less hindered oxygen atom of the boronic ester while at the same time assisting the departure of a chloride ion. The transition state (TS) (**6.3** or **6.6**, Scheme 6.1) is further stabilized by an interaction between the chloride of zinc chloride (which becomes more nucleophilic in the TS) and the C-H bond (which becomes more electrophilic in the TS as the chloride leaves) (see Scheme 6.1).[4,7,8]

In a different tactic, based on improving the enantiomeric excess percentage by adding a chiral Lewis acid catalyst, so far, only Prabhakar K. Jadhav and Hon-Wah Man[9] have carried out a Matteson-type homologation with an achiral boronic ester, namely 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6.17**, Scheme 6.5),

and an achiral reagent, but in presence of a chiral ligand *bis*-oxazoline derivative and a metal triflate (including $Yb(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Lu(OTf)_3$ as Lewis acid.[9] They obtained (*S*)-pinanediol 1-chloropentylboronate (**6.20**) in 88% diastereomeric excess as their best result by use of the chiral ligand [(–)-2,2'-isopropylidene-*bis*[(4*S*)-4-phenyl-2-oxazoline] (**6.18**, Figure 6.1)] (5 equivalents) with $Yb(OTf)_3$ (0.3 equivalents).[9]



Scheme 6.5 Using a chiral Lewis acid catalyst in Matteson's reaction

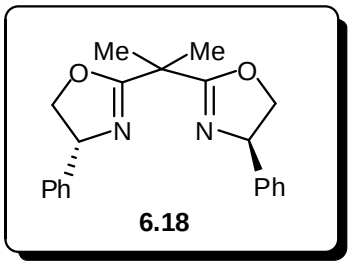


Figure 6.1 Structure of ligand **6.18**

Jadhav[9] had found that lithium chloride produced *in situ* was competing for the chiral ligand, and therefore led to some uncatalysed reaction that explained the need for the use of excess ligand in such reactions (Figure 6.2).

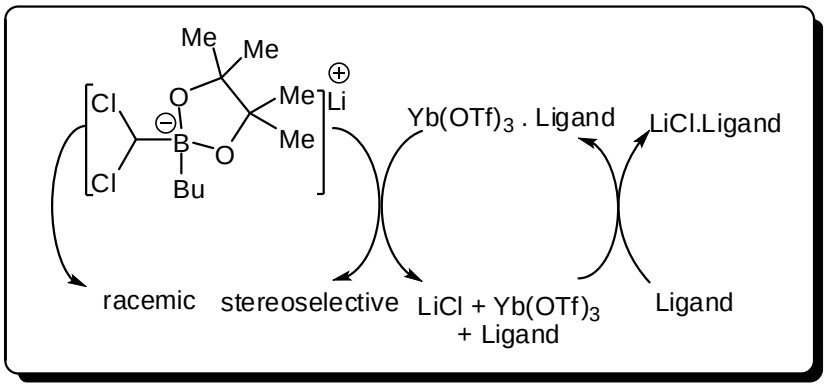


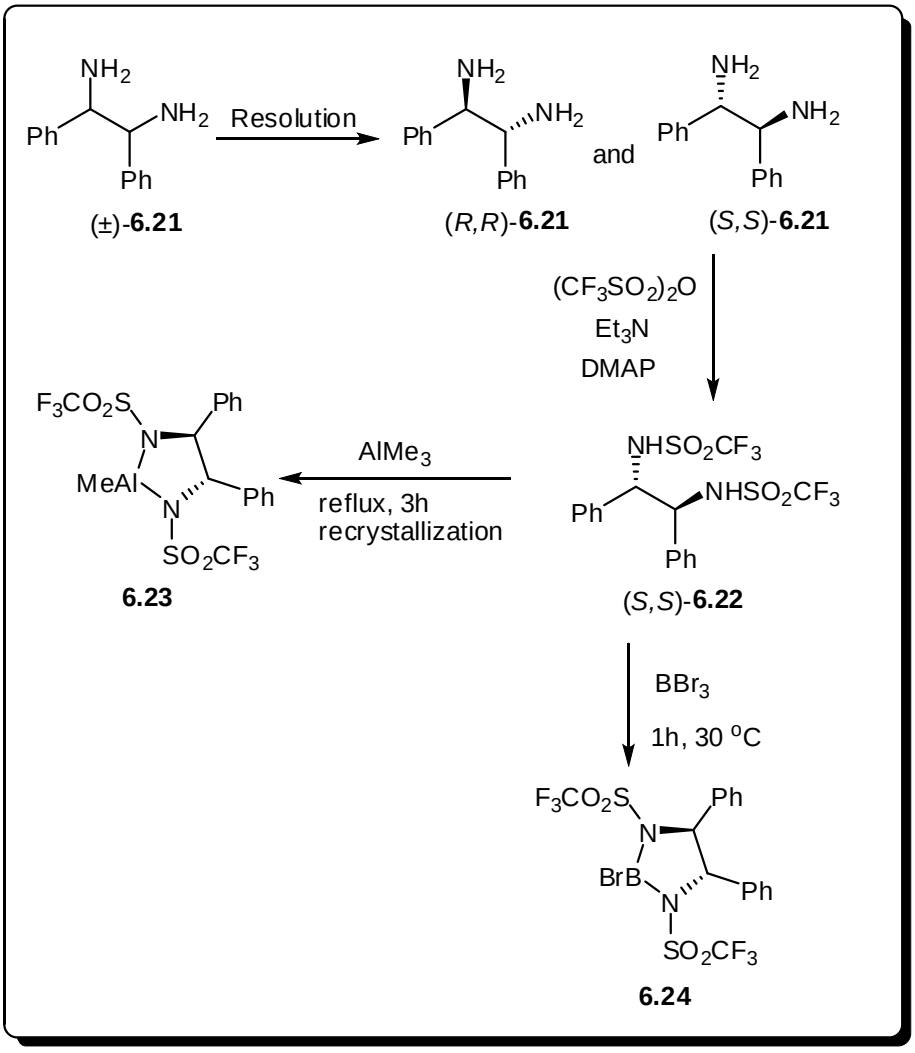
Figure 6.2 Competition for the chiral ligand between $Yb(OTf)_3$ and LiCl

In this chapter we report on the synthesis of some chiral Lewis acid catalysts and examination of their use in Matteson asymmetric homologation reactions in an attempt to improve the enantiomeric excess percentage (%ee) of the (α-chloroalkyl)boronates synthesised, which are potentially useful intermediates in organic synthesis.

6.2 Synthesis of chiral ligands

6.2.1 Synthesis of (*S,S*)-1,2-*N,N`-bis*-(trifluoromethanesulfonylamino)-1,2-diphenylethane (6.22) and chiral Lewis acid catalysts 6.23 and 6.24

Synthesis of (*S,S*)-1,2-*N,N′-bis*-(trifluoromethanesulfonylamino)-1,2-diphenylethane (**6.22**) involved two steps (Scheme 6.6). The first step involved the resolution of racemic-(±)-1,2-diphenyl-1,2-ethylenediamine (**6.21**), which was bought from Aldrich Chemical Company.



Scheme 6.6 Synthesis of chiral Lewis catalysts **6.23** and **6.24**

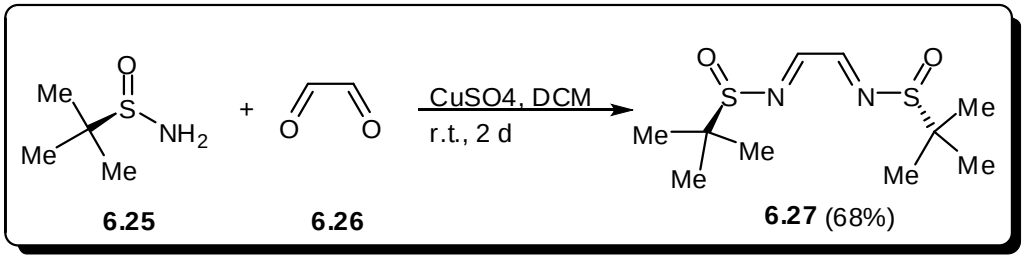
The resolution of racemic-(±)-1,2-diphenyl-1,2-ethylenediamine (**±-6.21**) was attempted[10] by its reaction with *L*-(+)-tartaric acid to produce the corresponding tartarate. The tartrate mixture was recrystallised from a mixture of EtOH and H_2O to provide a single diastereoisomer which on treatment with sodium hydroxide produced the (1*S*,2*S*)-1,2-diphenylethylenediamine (*S*,*S*-**6.21**) in 79% yield as colourless crystals. The structure of (*S*,*S*)-**6.21** was confirmed by various spectroscopic techniques (see experimental section 6.6.2.1 for details). Also, The purity of (*S*,*S*)-**6.21** was checked by polarimetry ($[\alpha]^{23}_D$: −91 (EtOH, c 0.5); [lit.[11] ($[\alpha]^{23}_D$: −91 (EtOH, c 4.6)].

Having successfully produced (*1S,2S*)-1,2-diphenylethylenediamine (*S*,*S*-**6.21**) our attention was then turned to the production of the (1*S*,2*S*)-*bis*-triflamide **6.22** in the second step. The second step involved treatment of (*S*,*S*)-**6.21** with trifluoromethanesulfonic anhydride in the presence of triethylamine as a base and 4-dimethylaminopyridine (DMAP) as a catalyst to give **6.22** in 57% yield. The structure of the (1*S*,2*S*)-*bis*-triflamide **6.22** was confirmed by various spectroscopic techniques (see experimental section 6.6.2.2 for details). Also, the purity of **6.22** was checked by the use of a polarimetry [($[\alpha]^{23}_D$: −6.7 ($CHCl_3$, c 0.1); [lit.[10] $[\alpha]^{23}_D$: −6.78 ($CHCl_3$, c 0.0277)].

The reactions of **6.22** with trimethylaluminium ($AlMe_3$) at 80 °C for 3 h or with boron tribromide at room temperature for 1 h produced the corresponding catalysts **6.23** and **6.24**. Both catalysts **6.23** and **6.24** were used directly in reactions as solutions without their physical isolation, due to their low stability.

6.2.2 (*R*,*R*)-*N*,*N*'-(ethane-1,2-diylidene)*bis*(2-methylpropane-2-sulfonamide) (6.27)

bis-Imine **6.27** was synthesised based on a literature procedure.[12] Reaction of (*R*)-*tert*-butanesulfinamide (**6.25**) with 40% aqueous glyoxal (**6.26**) in presence of anhydrous $CuSO_4$ (Scheme 6.7) at room temperature for 2 days was attempted. The residue obtained was purified by chromatography (silica gel; Et_2O–hexane, in 1:1) to give pure **6.27** in 68% yield as a pale yellow crystalline solid after recrystallization from hexane.

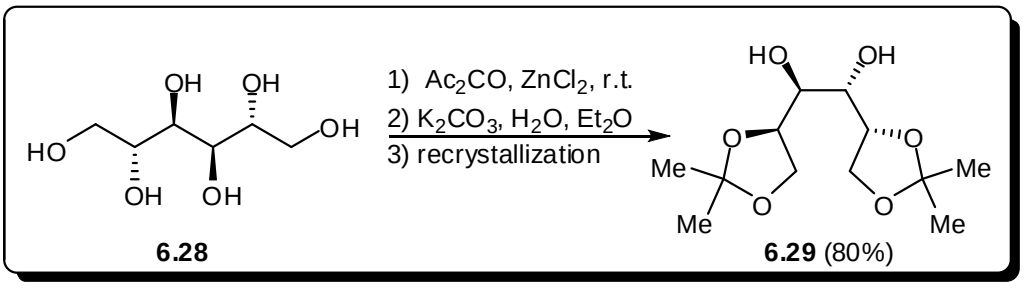


Scheme 6.7 Synthesis of chiral ligand **6.27**

The structure of the *bis*-imine **6.27** was confirmed by various spectroscopic techniques (see Section 6.6.2.5 for details). The ^{1}H NMR spectrum showed two singlet peaks at 8.39 and 1.19 ppm corresponding to two and eighteen protons, respectively. Also, the ^{13}C NMR spectrum showed three signals resonating at 159.5, 58.8 and 22.6 ppm.

6.2.3 Synthesis of (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (6.29)

The formation of a diacetal of *D*-mannitol (**6.28**) was attempted based on a literature procedure (Scheme 6.8).[13] *D*-Mannitol **6.28**), a cheap starting material, was added to a solution of anhydrous zinc chloride in dry acetone at room temperature and stirred for 4 h. The reaction mixture was poured onto a mixture of an aqueous solution of K_2CO_3 and Et_2O and vigorously stirred for 1.5 h at room temperature. The filtrate was concentrated under reduced pressure on a rotary evaporator. The white solid obtained was recrystallized from acetone to give **6.29** in 80% yield.

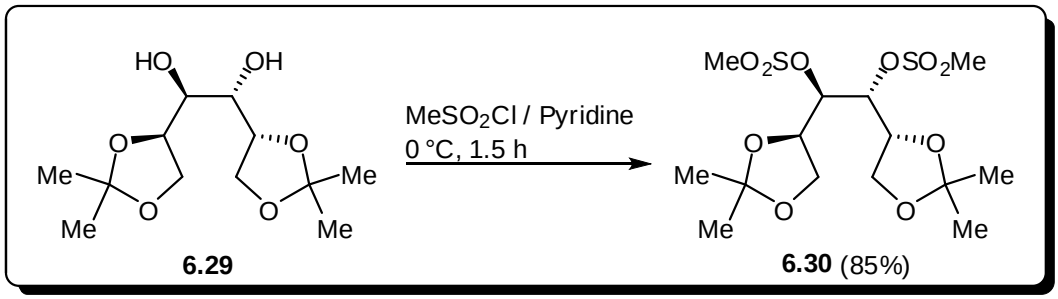


Scheme 6.8 Synthesis of the diol **6.29**

The purity of **6.29** was checked by the use of a polarimeter [($[\alpha]^{23}_D$: +6.2 ($CHCl_3$, c 0.5); [lit.[14] $[\alpha]^{23}_D$: +6±1 ($CHCl_3$, c 5)]. The structure of the diol **6.29** was confirmed by various spectroscopic techniques (see Section 6.6.2.6 for details). The ^{1}H NMR spectrum showed two singlet peaks at 1.43 and 1.37 ppm corresponding to the protons of the four CH_3 groups.

6.2.4 Synthesis of (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diyl *bis*(methanesulfonate) (6.30)

Sulfonation of diol **6.29** was attempted based on a literature procedure (Scheme 6.9),[15] using methanesulfonyl chloride in dry pyridine at 0 °C. The crude product was recrystallized from diethyl ether to give pure product **6.30** as white crystals in 85% yield. The purity of **6.30** was checked by the use of a polarimeter [($[\alpha]^{23}_D$: –5.5 ($CHCl_3$, c 0.5); [lit.[16] $[\alpha]^{23}_D$: –5 ($CHCl_3$, c 1)].



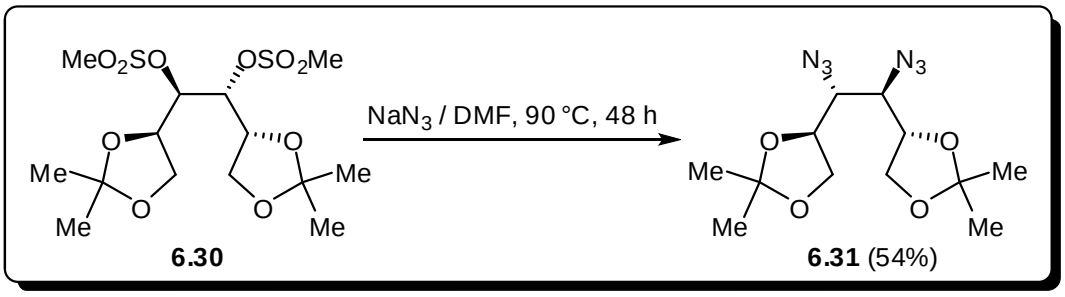
Scheme 6.9 Synthesis of the *bis*-mesylate **6.30**

The structure of the *bis*-mesylate **6.30** was confirmed by various spectroscopic techniques (see Section 6.6.2.7 for details). For example, the ^{1}H NMR spectrum showed a characteristic singlet peak that resonated at 3.11 ppm due to the six protons of the two O_2SCH_3 groups.

6.2.5 Synthesis of (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diazide (6.31)

The diazide **6.31** was synthesised by nucleophilic substitution based on a literature procedure (Scheme 6.10).[16] The reaction of *bis*-mesylate **6.30** with sodium azide was carried out in dry DMF at 90 °C for 48 h under N_2. The crude product was

purified by column chromatography (silica gel; Et_2O–hexane, in 1:5) to give the desired pure product **6.31** in moderate yield (54%) as a pale yellow oil. The purity of **6.31** was checked by the use of a polarimeter [($[\alpha]^{23}_D$: +127 ($CHCl_3$, c 0.5); [lit.[16] $[\alpha]^{23}_D$: +130 ($CHCl_3$, c 1)]. The optical activity indicated inversion of configuration compared to the corresponding *bis*-mesylate **6.30**, confirming that the S_N2 displacement had taken place.



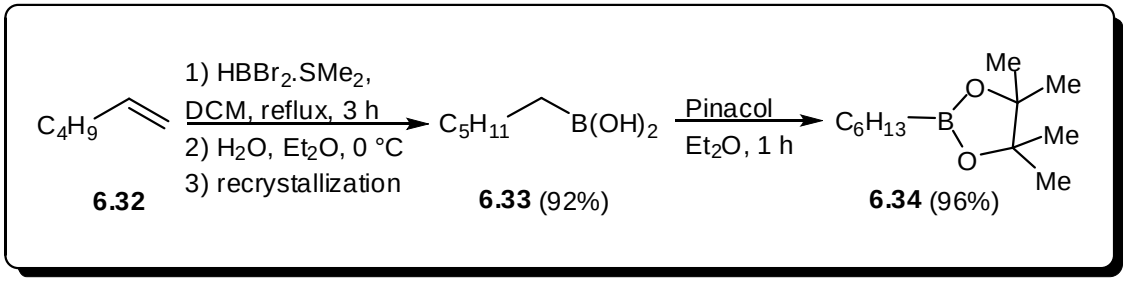
Scheme 6.9 Nucleophilic substitution of the *bis*-mesylate **6.30** with sodium azide

The structure of the diazide **6.31** was confirmed by various spectroscopic techniques (see Section 6.6.2.8 for details). The IR spectrum showed a very strong stretching band of the azide group at 2109 cm^{-1} and another stretching band for a C-N bond that resonated at 1258 cm^{-1}.

6.3 Synthesis of alkyl- and haloalkyl- boronate esters

6.3.1 Synthesis of 2-hexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.34)

Hydroboration of hex-1-ene (**6.32**) was attempted based on the procedure developed by Brown[17] (Scheme 6.10). Use of dibromoborane dimethyl sulfide complex in DCM under reflux for 3 h gave hexyldibromoborane-dimethyl sulfide complex. A solution of hexyldibromoborane-dimethyl sulfide complex in DCM was added to a mixture of H_2O and Et_2O to produce rapidly and quantitatively the corresponding boronic acid **6.33** (Scheme 6.10). Recrystallization from a mixture of hexane and acetone (9:1) gave hexylboronic acid (**6.33**) as white crystals in 92% yield.



6.32 **6.33** (92%) **6.34** (96%)

Scheme 6.10 Synthesis of pinacol hexylboronate (**6.34**)

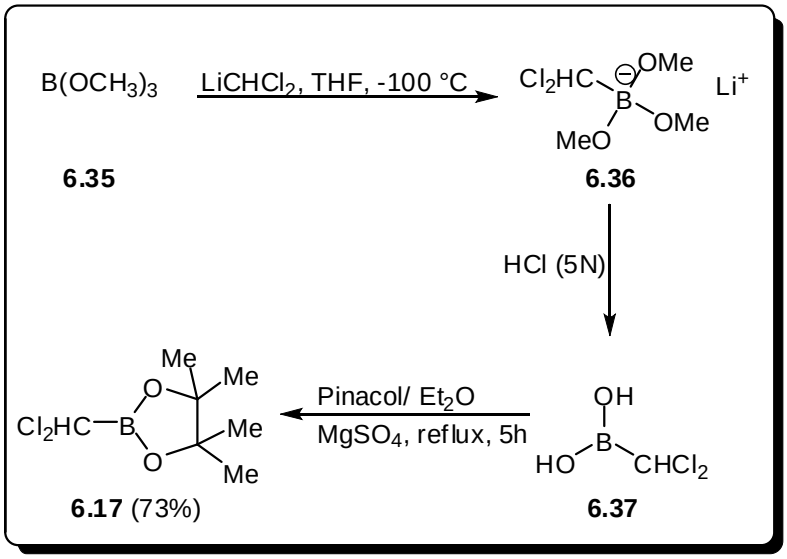
The IR spectrum of **6.33** showed a very strong band at 3411 cm^{-1} corresponding to the OH group. Also, the ^{1}H NMR spectrum showed an exchangeable singlet at 4.13 ppm due to the two OH protons (see Section 6.6.3.1 for details).

Having successfully produced the boronic acid **6.33**, our attention was next turned to its conversion to the corresponding boronate **6.34** (Scheme 6.10). Pinacol was added to a mixture of **6.33** and magnesium sulfate in Et_2O, and the mixture was stirred for 1 h at room temperature to give almost pure **6.34** in 96% yield as a colourless oil.

The ^{13}C NMR spectrum of **6.34** showed two characteristic signals that resonated at 82.8 and 24.8 ppm, corresponding to the pinacol moiety (see Section 6.6.3.2 for details).

6.3.1 Synthesis of 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.17)

The pinacol (α,α-dichloromethyl)boronate (**6.17**) was synthesised according to the steps shown in Scheme 6.11.[18] Reaction of trimethyl borate (**6.35**) with dichloromethyllithium, prepared *in situ* from the reaction of *n*-BuLi and DCM in THF at −100 °C for 30 minutes, in anhydrous THF at −100 °C, gave the corresponding borate complex **6.36**. Hydrolysis of **6.36** using hydrochloric acid (5 M) gave α,α-dichloromethylboronic acid (**6.37**) which on reaction with pinacol in Et_2O in the presence of $MgSO_4$ under reflux conditions for 5 h gave **6.17** in 73% yield (Scheme 6.11) as a colourless oil after purification by fractional distillation.



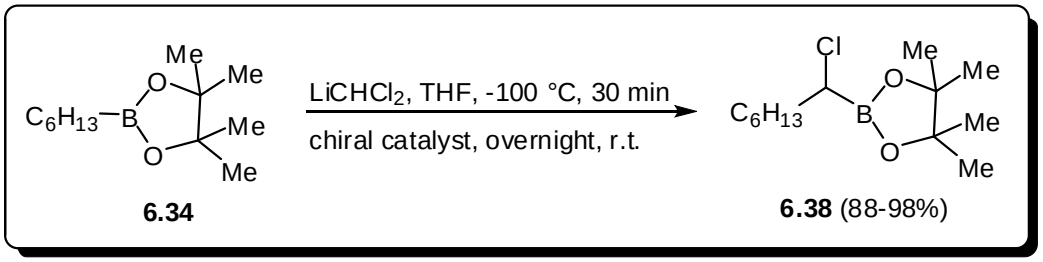
Scheme 6.11 Synthesis of pinacol (α,α-dichloromethyl)boronate (**6.17**)

The ^{1}H NMR spectrum showed two peaks that resonated at 5.27 and 1.26 ppm. Also, the ^{13}C NMR spectrum showed three peaks at 85.7, 54.1 and 24.4 ppm (see Section 6.6.3.3 for details).

Having successfully synthesised a range of chiral ligands, ligand precursors and catalysts, our attention was next turned to investigation of asymmetric synthesis reactions in the presence of such materials.

6.4 Asymmetric synthesis

Pinacol hexylboronate (**6.34**) was converted to 2-(1-chloroheptyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6.38**) on reaction with dichloromethyllithium in THF at -100 °C followed by overnight stirring at room temperature. Similar reactions were carried out in the absence and the presence of chiral Lewis acid catalysts, to produce **6.38** in 88–98% yields (Scheme 6.12) after purification by column chromatography (silica gel; DCM). The yield of **6.38** was found to be slightly affected by the type of catalyst used (Table 6.1). The structure of pinacol α-chloroheptylboronate **6.38** was confirmed by various spectroscopic techniques (see Section 6.6.6.4.1 for details).



Scheme 6.12 Synthesis of 2-(1-chloroheptyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6.38**)

Table 6.1 Synthesis of **6.38** in the presence of several chiral Lewis acid catalysts according to Scheme 6.12

Catalyst	**6.34** / ligand /metal ratio	Yield (%)
—	—	98
6.18+$Yb(OTf)_3$	1 / 2.5 / 0.3[a]	90
6.23	1 / 2.5 / 2.5[b]	90
6.24	1 / 2.5 / 2.5[c]	88

[a] A solid mixture of ligand **6.18** (Figure 6.3) and $Yb(OTf)_3$ was added to the reaction mixture.
[b] Catalyst **6.23** (Figure 6.3) was prepared from **6.22** and $AlMe_3$ then transferred to the reaction mixture.
[c] Catalyst **6.24** (Figure 6.3) was prepared from **6.22** and BBr_3 then transferred to the reaction mixture.

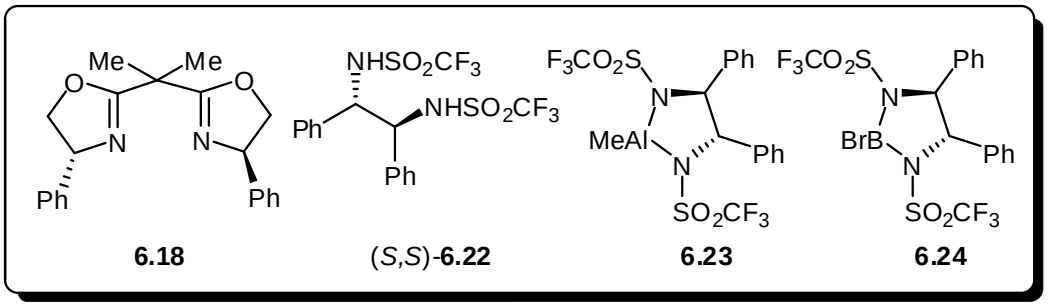
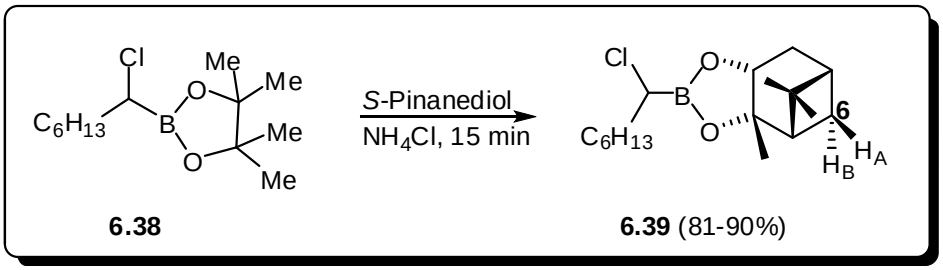


Figure 6.3 Structures of ligands **6.18** and (*S*,*S*)-**6.22** and catalysts **6.23** and **6.24**

The ^1H NMR spectrum of **6.38** showed a characteristic triplet (J = 7 Hz) which resonated at 3.35 ppm due to the CHCl proton. Also, the ^{13}C NMR spectrum showed that the CHCl carbon resonated as a doublet signal at 34.0 ppm. The presence of a

molecular ion peak at *m/z* = 260 was confirmed by the EI-mass spectrum (see Section 6.6.4.1 for details).

In order to determine the enantiomeric excess of **6.38** we attempted to replace the pinacol moiety in **6.38** by (*S*)-pinanediol in each case. Therefore, reaction of **6.38** with (*S*)-pinanediol was attempted under acidic conditions using a mixture of Et_2O and aqueous ammonium chloride at room temperature for 15 minutes according to Jadhav's procedure (Scheme 6.13).[9] (*S*)-Pinanediol (α-chloroheptyl)boronate (**6.39**) was produced in 81–90% yields (Scheme 6.13) after purification by column chromatography (silica gel; DCM).



Scheme 6.13 Synthesis of *(S)*-pinanediol (α-chloroheptyl)boronate (**6.39**)

The structure of **6.39** was confirmed by ^{1}H, ^{13}C, ^{11}B NMR, mass and IR spectra (see Section 6.6.4.2 for details) and the diastereomeric excess (%de) was calculated from the ^{1}H NMR spectrum (Table 6.2).

The electron–impact mass spectrum of **6.39** showed an intense molecular ion peak at *m/z* = 313 and the high resolution mass analysis of this peak confirmed the formula as $C_{17}H_{31}BO_2Cl$ ($[MH]^+$). The ^{1}H NMR spectrum of **6.39** showed a double doublet signal (J = 2 and 11 Hz), which resonated at 4.30 ppm, due to the CH-O proton from the *(S)*-pinanediol moiety in both diastereoisomers. Also, it showed two doublets (each J = 11 Hz) in the high field region at 1.11 and 1.10 ppm due to the H_A at the 6-position of the (*S)*-pinanediol unit for the two diastereoisomers. Thus, the diastereomeric excess (%de) was calculated from the integrations of the peaks resonating at 1.11/1.10 ppm.

Table 6.2 Synthesis of **6.39** in the presence of several chiral Lewis acid catalysts according to Scheme 6.13

Catalyst	**6.34** / ligand /metal ratio	Yield (%)	%de
—	—	90	—
6.18+$Yb(OTf)_3$	1 / 2.5 / 0.3[a]	82	4
6.23	1 / 2.5 / 2.5[b]	81	0.5
6.24	1 / 2.5 / 2.5[c]	88	0.5

[a] A solid mixture of ligand **6.18** (Figure 6.3) and $Yb(OTf)_3$ was added to the reaction mixture.
[b] Catalyst **6.23** (Figure 6.3) was prepared from **6.22** (2.5 eq) and $AlMe_3$ (2.5 eq) then transferred to the reaction mixture.
[c] Catalyst **6.24** (Figure 6.3) was prepared from **6.22** (2.5 eq) and BBr_3 (2.5 eq) then transferred to the reaction mixture.

Table 6.2 showed that the diastereomeric excess percentages obtained for **6.39** were low in all cases (0.5–4%). The reason for the low diastereomeric excess could be due to the fact that the Lewis acid coordinated to THF and inhibited its reactivity in the reaction. A similar conclusion was made earlier by Jadhav.[9]

We decided to use Jadhav's experimental design to avoid the use of donor solvents such as THF (Scheme 6.5). Therefore, we prepared pinacol (α,α-dichloromethyl)boronate (**6.17**; Figure 6.4) as mentioned in Section 6.3.1. Reaction of **6.17** with *n*-BuLi at –40 °C in hexane was attempted. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was concentrated and the residue obtained was purified by column chromatography (silica gel; DCM) to give 2-(1-chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6.19**; Figure 6.4) in 89% yield.

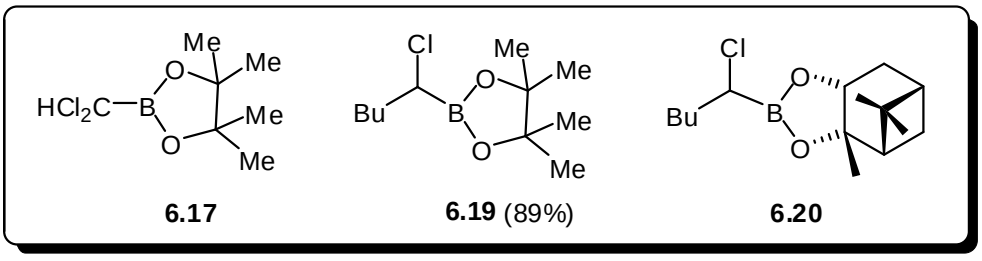


Figure 6.4 Structures of **6.17**, **6.19** and **6.20**

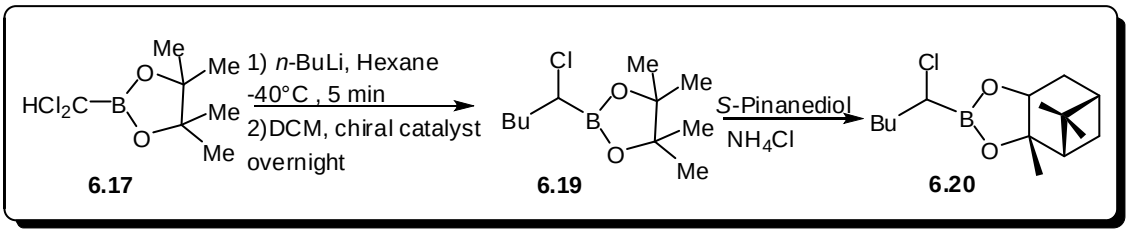
The structure of **6.19** was confirmed by ^{1}H, ^{13}C, ^{11}B NMR, mass and IR spectra (see Section 6.6.4.3 for details). The ^{1}H NMR spectrum of **6.19** showed a double doublet signal (J = 7 and 9 Hz) resonating at 3.32 ppm due to the CHCl proton. Also, it showed a multiplet in the range 1.27–1.12 ppm which represented 16 protons and a triplet (J = 7 Hz) which resonated at 0.83 ppm due to the CH_3 protons of the butyl group.

Having successfully produced **6.19** in high yield under Jadhav's conditions, our attention was then turned to its conversion to (*S*)-pinanediol (α-chloropentyl)boronate (**6.20**; Figure 6.4). Product **6.20** was produced in 90% yield under conditions similar to those used for the production of **6.39** (Scheme 6.13).

The structure of **6.20** was confirmed by ^{1}H, ^{13}C, ^{11}B NMR, mass and IR spectra (see Section 6.6.4.4 for details). The electron–impact mass spectrum of **6.20** showed a cluster of molecular ion peaks, the most intense of which was at m/z = 284, and the high resolution mass analysis of this peak confirmed the formula as $C_{15}H_{26}{}^{11}BO_2{}^{35}Cl$ ($[M]^+$). The ^{1}H NMR spectrum of **6.20** showed a double doublet (J = 2 and 9 Hz) which resonated at 4.29 ppm due to the CH–O proton from the *(S)*-pinanediol moiety. Also, it showed two doublets (each J = 11 Hz) at 1.11 and 1.10 ppm due to the H_A at the 6-position of the (*S)*-pinanediol unit for the two diastereoisomers.

Having successfully produced **6.20** in two steps starting from **6.17** in the absence of a chiral Lewis acid, our attention was next turned to the production of **6.20** under similar conditions but in the presence of chiral Lewis acids. Therefore, the conversion of **6.17** to (*S*)-pinanediol (α-chloropentyl)boronate (**6.20**) was attempted under Jadhav's conditions[9] in one-pot in the presence of various chiral Lewis acids to see what effect they could have on the stereoselectivity. Reaction of **6.17** (Scheme 6.5) with *n*-BuLi was carried out in hexane at –40 °C, for 5 minutes followed by the addition of excess DCM and chiral Lewis acid catalyst. The reaction was then allowed to warm up to room temperature and was stirred overnight. A mixture of NH_4Cl and Et_2O was added, followed by the addition of (*S*)-pinanediol (1.2 equivalents) with stirring at room temperature for 15 min. The mixture was directly worked-up and the crude product was purified by column chromatography (silica gel; DCM) to give **6.20** in 84–89% (Table 6.3). The diastereomeric excess (%de) was calculated from the ^{1}H NMR spectrum (Table 6.3).

Table 6.3 Synthesis of **6.20** in the presence of several chiral Lewis acid catalysts according to Scheme 6.5



Entry	Catalyst	**6.17** / ligand / metal ratio[a]	Yield (%)	%de
1	—	—	90	—
2	**6.18**[9]+$Yb(OTf)_3$	1 / 2.5 / 0.3	88	79
3	**6.23**[b]	1 / 2.5 / 2.5[b]	86	11
4	**6.24**[c]	1 / 2.5 / 2.5[c]	89	2.5
5	**6.22**+$Yb(OTf)_3$	1 / 2.5 / 0.3	85	16
6	**6.27**+$Yb(OTf)_3$	1 / 2.5 / 0.3	84	4
7	**6.29**+$Yb(OTf)_3$	1 / 2.5 / 0.3	89	52
8	**6.30**+$Yb(OTf)_3$	1 / 2.5 / 0.3	84	4
9	**6.31**+$Yb(OTf)_3$	1 / 2.5 / 0.3	88	2
10	**6.29**	1 / 2.5 / 0	87	46

[a] A solid mixture of the ligand and Lewis acid was added to the reaction mixture except for entries 3 and 4.
[b] Catalyst **6.23** (Figure 6.3) was prepared from **6.22** (2.5 eq) and $AlMe_3$ (2.5 eq) then transferred to the reaction mixture.
[c] Catalyst **6.24** (Figure 6.3) was prepared from **6.22** (2.5 eq) and BBr_3 (2.5 eq) then transferred to the reaction mixture.

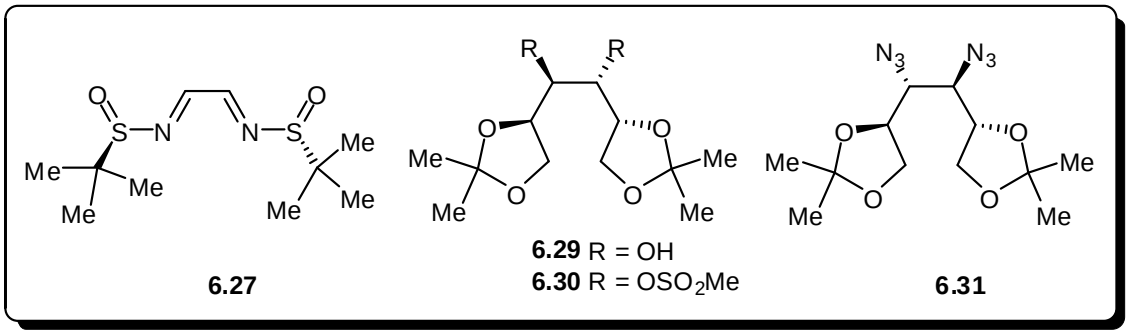


Figure 6.5 Structures of compounds **6.27** and **6.29–6.31**

From Table 6.3, it was clear that the yields were high in all cases (84–90). Also, the conditions (Jadhav's conditions[9]) seemed to be successful in allowing some streoselectivity to be achieved, which was not the case when other conditions were applied, as reported earlier (Table 6.2). Entry 2 clearly indicated that high selectivity (79 %de) was obtained under the Jadhav conditions, which is evidence that optimising the conditions had a significant effect on the selectivity of the reaction. The results in Entries 3–5 showed that $Yb(OTf)_3$ in the presence of **6.22** gave better stereoselectivity (%de = 16) than catalysts **6.23** (%de = 11) and **6.24** (%de = 2.5), which possessed a similar organic component. Therefore, $Yb(OTf)_3$ was chosen as a Lewis acid for reactions in the presence of other chiral compounds (**6.27** and **6.29**–**6.32**; Table 6.3; Entries 6–9). Very low de (4%) was obtained in the presence of **6.27**, probably because the sulfinyl group decreases the coordinating ability of the nitrogen atoms towards the Yb. The diol **6.29** gave a very good selectivity (52% de) possibly due to good coordination between the oxygen atoms and the metal.

It was expected that the bismesylate **6.30** and the diazide **6.31** would not provide high %de since they are not good at coordination with the metal, but such compounds are the precursors for the production of the diamino ligands that were initial targets for preparation. Indeed, the stereoselectivity obtained with **6.30** and **6.31** was very low (4 and 2 %de, respectively; Table 6.3; Entries 8 and 9).

In a separate piece of work carried out by a member of our research group, the effect of the number of mole equivalents of $Yb(OTf)_3$ on the %de of **6.20** in the presence of **6.18** was recently investigated. Interestingly, he found that the %de was still significant even when no Lewis acid was used. Also, he found that the selectivity dropped as the quantity of the Lewis acid increased, possibly because the lithium ion produced *in situ* could be coordinated with the ligand and act as catalyst. We have repeated such a reaction using **6.29** as the chiral ligand in the absence of Lewis acid and 46% de was seen (Table 6.3: Entry 10). No further attempts were made to try to find conditions under which the %de could be maximised because of the limited time available.

6.5 Conclusion

Various chiral compounds were prepared. Chiral catalysts were produced either as separate compounds or *in situ* by mixing one of the chiral compounds with a Lewis acid. The catalysts were tested in the Matteson homologation reaction. Some stereoselectivity (de = 2–52%) was obtained depending on the type of chiral compound and Lewis acid used. Stereoselectivity of 52% de was obtained when $Yb(OTf)_3$ was used as the Lewis acid and (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**6.29**) as the chiral ligand. However, significant (de = 46%) could be obtained with **6.29** even in the absence of the Lewis acid, which is very interesting and opens windows for further improvement.

Clearly, more work needs to be carried out to optimise the conditions to enhance the diastereomeric excess further by varying the molar equivalents of the Lewis acid. Also, investigation of the reaction with different chiral ligands having good coordination sites could be used.

6.6 Experimental

6.6.1 General Experimental

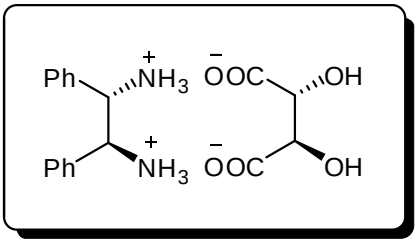
A general experimental section outlining the instrumentation and reagents used is included in Chapter Two (Section 2.14.1). The optical purity was measured on an Atago 5223 POLAX-2L Semi-Automatic Polarimeter.

6.6.2 Synthesis of chiral Lewis acid catalysts and other chiral compounds

6.6.2.1 Resolution of (±)-1,2-diphenyl-1,2-ethylenediamine (6.21)[10,11]

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the racemic-(±)-1,2-diphenyl-1,2-ethylenediamine (**6.21**; 2.0 g, 9.4 mmol) and EtOH (10 mL). The mixture was heated to 70 °C to produce a homogeneous solution and *L*-(+)-tartaric acid (1.4 g, 9.4 mmol) in EtOH (10 mL) was added. The tartrate salts precipitated immediately. The mixture was cooled to ambient temperature, the crystals were collected by filtration, washed with EtOH (2 × 10 mL) and dried under reduced pressure. The solid was mixed with hot EtOH (10 mL) and boiling H_2O was added dropwise until it dissolved. The homogeneous solution was allowed to cool

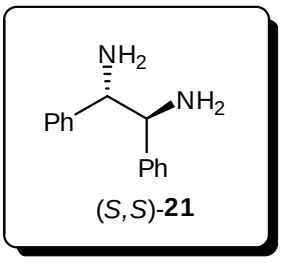
slowly to room temperature. The crystals obtained were collected by filtration, washed with EtOH (10 mL) and dried under reduced pressure. The recrystallization procedure was then repeated twice to give the tartrate salt as colourless crystals.



Yield: 1.2 g (3.3 mmol, 35%); $[\alpha]^{23}_{D}$ –10.82 (H_2O, c 0.05) [lit.[10] $[\alpha]^{23}_{D}$ −10.8 ± 0.2 (H_2O, c 1.3)].

^{1}H NMR (500 MHz, D_2O): δ =7.28–7.09 (m, 10 H, 2 C_6H_5), 4.75 (s, 2 H, 2 C*H*OH), 4.23 (s, 2 H, 2 C*H*C_6H_5).

The salt was transferred to a 50-mL, round-bottomed flask equipped with a magnetic stirring bar and suspended in H_2O (20 mL). The mixture was vigorously stirred and cooled to 0–5 °C, then aqueous sodium hydroxide (5 mL; 50%) was added dropwise followed by DCM (30 mL), and the stirring was continued for 30 min. The phases were separated, the aqueous phase was washed with DCM (2 × 15 mL) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure to give a colourless solid that was recrystallized from hexane to yield (1*S*,2*S*)-1,2-diphenylethylenediamine (*S*,*S*-**21**) in 79% yield (0.55 g, 2.6 mmol) as colourless crystals.

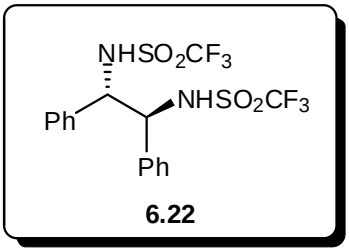


mp 49–53 °C; ($[\alpha]^{23}_{D}$: –91 (EtOH, c 0.5); [lit.[11] ($[\alpha]^{23}_{D}$: −91 (EtOH, c 4.6)].

^{1}H NMR (500 MHz, CD_3COCD_3-d_6): δ = 7.32–7.17 (m, 10 H, 2 C_6H_5), 4.21(s, 2 H, 2 CH), 2.76 (s, 4 H, 2 NH_2).

6.6.2.2 Synthesis of (*S*,*S*)-1,2-*bis*-(trifluoromethanesulfonylamino)-1,2-diphenylethane (6.22)[10]

A mixture of (1*S*,2*S*)-1,2-diphenylethylenediamine (*S*,*S*-**21**, 2.0 g, 9.4 mmol), triethylamine (2.85 g, 28.2 mmol) and 4-dimethylaminopyridine (DMAP; 0.023 g 0.19 mmol) in DCM （15 mL） was stirred to dissolve the solids, cooled to −78 °C, and trifluoromethanesulfonic anhydride (6.37 g, 22.6 mmol) was added dropwise. The cooling bath was removed and the mixture was allowed to warm to ambient temperature over 30 min. The mixture was then poured into aqueous sodium bicarbonate (4%, 2 × 20 mL), the phases were separated, and the aqueous phase was washed with DCM (2 × 20 mL). The combined organic layers were washed with hydrochloric acid (1 M, 20 mL), brine (20 mL), H_2O (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **6.22** in 57% yield (2.5 g, 5.3 mmol) as colourless crystals.



6.22

mp 213–217 °C; (Lit.[10] mp 216–219 °C), [([α]$^{23}_{D}$: –6.7 ($CHCl_3$, c 0.1); [lit.[10] [α]$^{23}_{D}$: −6.78 ($CHCl_3$, c 0.0277)].

IR (FT): ν_{max} = 3327, 2916, 2852, 1371, 1233, 1207, 1149 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20–6.91 (m, 10 H, 2 C_6H_5), 5.82 (br. s, 2 H, 2 NH), 4.72 (s, 2 H, 2 CH).

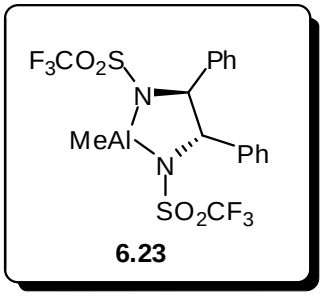
^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.5 (s, C-1 of 2 C_6H_5), 129.0 (d, C-3/C-5 of 2 C_6H_5), 128.9 (d, C-2/C-6 of 2 C_6H_5), 127.0 (d, C-4 of 2 C_6H_5), 119.3 (q, *J* = 319 Hz, 2 CF_3), 63.7 (d, 2 CH).

MS (EI): *m/z* (%) = 407 (57, $[M - CF_3]^+$), 343 (8), 328 (14), 239 (100), 104 (98), 77 (99), 68 (78).

HRMS (EI): *m/z* $[M - CF_3]^+$ calcd for $C_{15}H_{14}F_3N_2O_4S_2$: 407.0303; found: 407.0308.

6.6.2.3 Synthesis of (4*S*,5*S*)-2-methyl-4,5-diphenyl-1,3-*bis*(trifluoromethanesulfonyl)-2-aluma-1,3-diazacyclopentane (6.23)

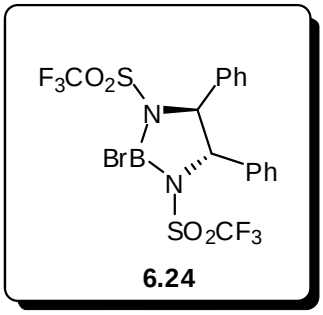
A solution of (1*S*,2*S*)-*bis*-triflamide (*S*,*S*)-**6.22** (1.2 g, 2.5 mmol) (dried at 80 °C and 1 mmHg) in dry 1,2-dichloroethane (20 mL) under N_2 was heated to 80° C with stirring to get a clear solution. The mixture was cooled to ambient temperature and treated dropwise with trimethylaluminium in toluene (2 M, 1.25 mL, 2.5 mmol). After the evolution of gases ceased, the homogeneous mixture was heated to 80 °C for 3 h. The mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and reduced pressure was maintained for an additional 30 min. The resulting solid was dissolved in dry DCM (10 mL) and used as a solution without isolation or characterisation.



6.23

6.6.2.4 Synthesis of (4*S*,5*S*)-2-bromo-4,5-diphenyl-1,3-*bis*(trifluoromethanesulfonyl)-1,3,2-diazaborolidine (6.24)

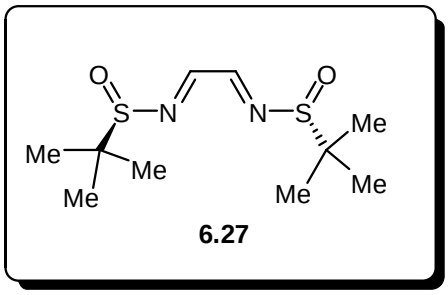
(1*S*,2*S*)-*bis*-Triflamide (*S*,*S*)-**6.22** (1.2 g, 2.5 mmol) (dried at 80 °C and 1 mm) and dry DCM (20 mL) under N_2 was heated to 80° C with stirring to get a clear solution. The mixture was cooled to ambient temperature and treated dropwise with boron tribromide in DCM (1 M, 2.5 mL, 2.5 mmol). After the evolution of gases ceased, the homogeneous mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the reduced pressure was maintained for an additional 30 min. The resulting solid was dissolved in dry DCM (10 mL) and used as a solution without isolation or characterisation.



6.24

6.6.2.5 (*R*,*R*)-*N*,*N*′-(ethane-1,2-diylidene)-*bis*(2-methylpropane-2-sulfinamide) (6.27)[12]

bis-Imine (**6.27**) was synthesised based on a literature procedure.[12] To a solution of (*R*)-*tert*-butanesulfinamide (**6.25**, 1.2 g, 10.0 mmol) in CH_2Cl_2 (40 mL) was added anhyd CuSO4 (6.4 g, 40.0 mmol) followed by 40% aqueous glyoxal (**6.26**, 0.72 mL, 5.0 mmol). The mixture was stirred at r.t. for 2 d. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed well with CH_2Cl_2. The residue obtained after removal of the solvent from the filtrate was purified by chromatography (silica gel; Et_2O–hexane, 1:1) and recrystallized from hexane to give pure **6.27** (0.94 g, 6.8 mmol, 68%) as a pale yellow crystalline solid.



6.27

mp 117–221 °C.

IR (FT): ν_{max} = 2982, 1651, 1385, 1128, 1039, 1207.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (s, 2 H, 2 CH), 1.19 [s, 18 H, 2 $C(CH_3)_3$].

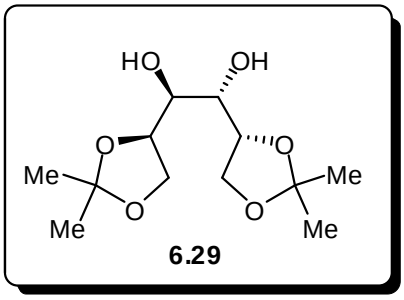
^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.5 (d, C=N), 58.8 [s, *C*$(CH_3)_3$], 22.6 [q, C(*C*$H_3)_3$].

MS (APCI): *m/z* (%) = 265 (100, $[MH]^+$), 250 (48), 209 (30), 175 (17), 115 (12).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{10}H_{21}N_2O_2S_2$: 265.1044; found: 265.1047.

6.6.2.6 Synthesis of (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (6.29)[14]

D-Mannitol (**6.28**, 10.0 g, 54.8 mmol) was added to a solution of anhydrous zinc chloride (20.0 g, 146.7 mmol) in dry acetone (200 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was poured onto a mixture of a suspension of potassium carbonate (25.0 g) in H_2O (25 mL) and Et_2O (200 mL), vigorously stirred for 1.5 h at room temperature, filtered and the zinc carbonate washed with acetone (50 mL). The filtrate was concentrated under reduced pressure on a rotary evaporator. The white solid obtained was recrystallized from acetone to give **6.29** in 80% yield (11.5 g, 43.9 mmol).



6.29

mp 119–122 °C; (Lit.[14] mp 120–122 °C), [([α]$^{23}_{D}$: +6.2 ($CHCl_3$, c 0.5); [lit.[14] [α]$^{23}_{D}$: +6±1 ($CHCl_3$, c 5)].

IR (FT): ν_{max} = 2992, 1406, 1242, 1066 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.19 (dd, *J* = 6, 12 Hz, 2 H, 2 CH-O), 4.13 (dd, *J* = 6, 8 Hz, 2 H, 2 C$H_a$$H_b$), 4.00 (dd, *J* = 6, 8 Hz, 2 H, 2 C$H_a$$H_b$), 3.75 (app. t, *J* = 6 Hz, 2 H, C*H*OH), 2.77 (d, *J* = 6 Hz, exch., 2 H, 2 OH), 1.43 (s, 6 H, 2 CH_3), 1.37 (s, 6 H, 2 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.4 [s, *C*(CH_3)$_2$], 76.3 (d, OCH), 71.2 (d, CHOH), 66.8 (t, CH_2), 26.7 (q, CH_3), 25.2 (q, CH_3).

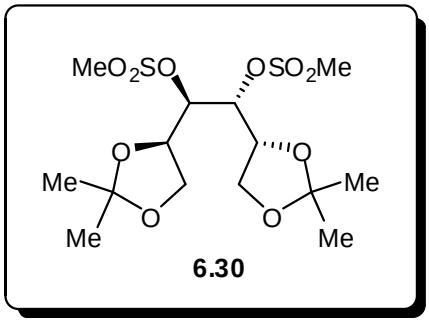
MS (APCI): *m/z* (%) = 263 (65, $[MH]^+$), 205 (53), 188 (100), 187 (27), 147 (87).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{12}H_{23}O_6$: 263.1495; found: 263.1487.

6.6.2.7 Synthesis of (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diyl *bis*(methanesulfonate) (6.30)[16]

Methanesulfonyl chloride (4.8 g, 42.2 mmol) was added to a solution of **6.29** (5.0 g, 19.1 mmol) in dry pyridine (25 mL) over a period of 15 min with stirring in an ice bath. After 1.5 h, the reaction mixture was stored in a refrigerator for 24 h. Water

(2.5 mL) was added and the mixture was stirred for 15 min. The mixture was poured into cold H_2O (50 mL) then the product was extracted with $CHCl_3$ (3 × 25 mL). The combined chloroform extracts were washed with HCl (10%, 2 × 20 mL) followed by Na_2CO_3 (5%, 40 mL), then with H_2O, then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. The crude product was recrystallized from Et_2O to give **6.30** (6.8 g, 16.2 mmol, 85 %) as white crystals.



6.30

mp 137–141 °C; (Lit.[16] mp 140–143 °C), [($[\alpha]^{23}_D$: –5.5 ($CHCl_3$, c 0.5); [lit.[16] $[\alpha]^{23}_D$: –5 ($CHCl_3$, c 1)].

IR (FT): ν_{max} = 2953, 1455, 1374, 1219 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.90 (d, *J* = 7 Hz, 2 H, 2 O_2SOCH), 4.20 (m, 2 H, 2 OCH), 4.12–4.10 (m, 4 H, 2 CH_2), 3.11 (s, 6 H, 2 SO_2CH_3), 1.37 (s, 6 H, 2 CH_3), 1.30 (s, 6 H, 2 CH_3).

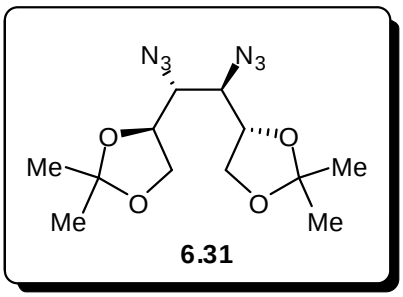
^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.2 [s, 2 $C(CH_3)_2$], 78.9 (d, 2 O_2SOCH), 73.4 (d, 2 OCH), 66.4 (t, 2 CH_2), 38.9 (q, 2 SO_2CH_3), 26.5 (q, 2 CH_3), 25.1 (q, 2 CH_3).

MS (APCI): *m/z* (%) = 419 (100, $[MH]^+$), 361 (7), 181 (5), 154 (9).

HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{14}H_{27}O_{10}S_2$: 419.1046; found: 419.1044.

6.6.2.8 (1*R*,2*R*)-1,2-*bis*((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diazide (6.31)[16]

Sodium azide (1.7 g, 26.4 mmol) was added to a solution of **6.30** (5.0 g, 12.0 mmol) in dry DMF (25 ml). The mixture was heated at 90 °C with stirring for 48 h under N_2. The reaction mixture was allowed to cool to room temperature then concentrated under reduced pressure to afford the crude azide (**6.31**) as a brown oily product. The crude product was purified by column chromatography (silica gel; Et_2O–hexane, 1:5) to give pure **6.31** in 54% yield (2.0 g, 6.5 mmol) as a pale yellow oil.



6.31

([α]$^{23}_{D}$: +127 ($CHCl_3$, c 0.5); [lit.[16] [α]$^{23}_{D}$: +130 ($CHCl_3$, c 1)].

IR (FT): ν_{max} = 2934, 2109, 1452, 1258 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.36 (dddd, *J* = 1, 3, 6, 8 Hz, 2 H, 2 CH-O), 4.06 (dd, *J* = 6, 8 Hz, 2 H, C*H*$_a$H$_b$), 3.88 (dd, *J* = 6, 8 Hz, 2 H, CH$_a$*H*$_b$), 3.32 (dd, *J* = 1, 3 Hz, 2 H, 2 CHN_3), 1.42 (s, 6 H, 2 CH_3), 1.30 (s, 6 H, 2 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.3 [s, 2 *C*$(CH_3)_2$], 75.3 (d, 2 OCH), 66.3 (t, 2 CH_2), 62.8 (d, 2 CHN_3), 26.2 (q, 2 CH_3), 25.0 (q, 2 CH_3).

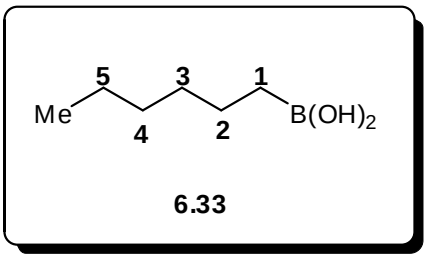
MS (EI): *m/z* (%) = 297 (5, $[M - CH_3]^+$), 269 (7), 213 (12), 183 (49), 101 (53), 84 (100), 73 (44), 59 (36).

HRMS (EI): *m/z* $[M - CH_3]^+$ calcd for $C_{11}H_{17}N_6O_4$: 297.1311; found: 297.1313.

6.6.3 Synthesis of alkyl- and haloalkyl- boronate esters

6.6.3.1 Synthesis of hexylboronic acid (6.33)[17]

A solution of $HBBr_2.SMe_2$ in DCM (1.0 M, 22.5 mL, 22.5 mmol) was added slowly *via* a syringe to a solution of hex-1-ene (**6.32**; 1.9 g, 22.4 mmol) in DCM (10 mL). The mixture was heated under reflux with stirring for 3 h. The reaction mixture was cooled to 0 °C and transferred to a stirred cold mixture of H_2O (9 mL) and Et_2O (25 mL) through a double-ended needle. The mixture was stirred for 10 min and the layers were separated. The organic layer was washed with cold H_2O (2 × 30 mL) and brine (50 mL), dried ($MgSO_4$), then evaporated under reduced pressure. The crude waxy residue obtained was recrystallised from a mixture of *n*-hexane and acetone (9:1) to give hexylboronic acid (**6.33**) in 92% yield (2.7 g, 20.7 mmol,).



6.33

mp 87–90 °C; (Lit.[17] mp 80 °C).

IR (FT): ν_{max} = 3411, 2956, 1343, 1146, 1212, 1092, 839, 777, 716 cm^{-1}.

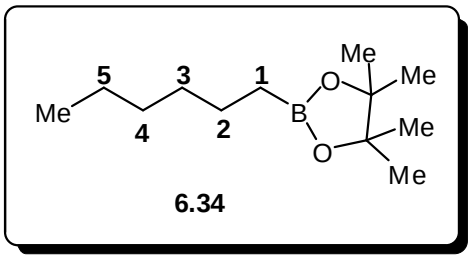
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.13 (s, exch., 2 H, 2 OH), 1.33–1.31 (m, 2 H, H-5), 1.27–1.21 (m, 6 H, H-2, H-3 and H-4), 0.83 (t, *J* = 7 Hz, 3 H, CH_3), 0.75 (t, *J* = 8 Hz, 2 H, H-1).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.1 (t, C-3), 31.7 (t, C-4), 24.4 (t, C-2), 23.3 (t, C-5), 22.6 (t, C-1), 14.2 (q, CH_3).

^{11}B NMR (160 MHz, $CDCl_3$): δ = 33.2.

6.6.3.2 Synthesis of 2-hexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.34)[17]

Pinacol (2.45 g, 20.7 mmol) was added to a mixture of hexylboronic acid (**6.33**, 2.7 g, 20.7 mmol) and $MgSO_4$ (5 g) in Et_2O (25 mL). The mixture was stirred for a 1 h at room temperature. The mixture was filtered and the filtrate was evaporated under reduced pressure to give almost pure **6.34** in 96% yield (4.2 g, 19.9 mmol) as a colourless oil.



6.34

IR (FT): ν_{max} = 2996, 1319, 1113, 1227, 805, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (m, 2 H, H-5), 1.19–1.17 (m, 18 H, H-2, H-3, H-4 and 4 × CH_3), 0.80 (t, 3 H, *J* = 8 Hz, CH_3), 0.69 (t, *J* = 8 Hz, 2 H, H-1).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 82.8 [s, 2 $C(CH_3)_2$], 32.0 (t, C-4), 31.6 (t, C-3), 24.8 [q, 2 $C(CH_3)_2$], 23.97 (t, C-2), 23.93 (t, C-5), 22.5 (t, C-1), 14.0 (q, CH_3)

^{11}B NMR (160 MHz, $CDCl_3$): δ = 34.1.

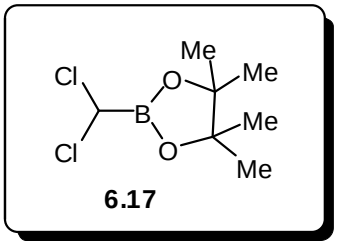
MS (EI): *m/z* (%) = 212 (2, $[M]^+$), 197 (100), 155 (50), 129 (99), 112 (95), 97 (51), 85(98).

HRMS (EI): *m/z* [M^+] calcd. for $C_{12}H_2BO_2$: 212.1901; found, 212.1898.

6.6.3.3 Synthesis of 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.17)[18]

A solution of *n*-BuLi in hexane (1.6 M, 27.5 ml, 40.0 mmol) was added dropwise to a cold (−100 °C) stirred mixture of THF (80 mL) and DCM (2.8 mL, 44.0 mmol) and the mixture was stirred for 30 min. Trimethyl borate (**6.35**; 5.0 mL, 44.0 mmol) was added in one portion. After 30 min, hydrochloric acid (5 M, 9 mL) was added to the reaction mixture. The mixture was allowed to warm up to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O, then the organic extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure on a rotary evaporator to give the crude product, which was subjected to low pressure for 1 h to get the crude dichloromethaneboronic acid (**6.37**) as a viscous colourless mass.

The crude α,α-dichloromethaneboronic acid (**6.37**) was dissolved in Et_2O (80 mL). Anhydrous magnesium sulfate (10 g) and a solution of pinacol (4.7 g, 40.0 mmol) in Et_2O (10 mL) were added. The reaction mixture was refluxed for 5 h, then filtered and concentrated under reduced pressure. The residue was distilled under low pressure to get the pinacol (α,α-dichloromethyl)boronate (**6.17**) in 73% yield (6.1 g, 29.2 mmol).



6.17

bp 50–55 °C, 1 torr; (Lit.[18] bp 52 °C, 1 torr).

IR (FT): ν_{max} = 2954, 1361, 1114, 1213, 846, 738 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.27 (s, 1 H, $CHCl_2$), 1.26 (s, 12 H, 4 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 85.7 [s, 2 $C(CH_3)_2$], 54.1 (d, $CHCl_2$), 24.4 [q, 2 $C(CH_3)_2$],).

^{11}B NMR (160 MHz, $CDCl_3$): δ = 29.0.

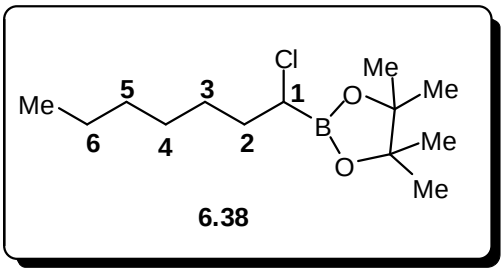
MS (EI): *m/z* (%) = 210 (25, $[M]^+$), 195 (59), 167 (23), 151 (90), 102 (89), 89 (100).

HRMS (EI): *m/z* [M^+] calcd. for $C_7H_{13}{}^{11}BO_2{}^{35}Cl_2$: 210.0386; found, 210.0388.

6.6.4 Asymmetric Reactions

6.6.4.1 Synthesis of 2-(1-chloroheptyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.38)

A solution of *n*-BuLi in hexane (1.6 M, 0.62 mL, 1.0 mmol) was added to a cold (–100 °C) stirring mixture of THF (3 mL) and DCM (0.8 mL, 1.2 mmol) and the mixture was stirred for 30 min., then pinancol hexylboronate (**6.34**; 0.21 g, 1.0 mmol) in THF (1 mL) was added. The mixture was allowed to warm up (in case of using chiral Lewis acid catalysts, the catalyst was added at –60 °C to the reaction mixture as a solution in an appropriate amount of DCM) to room temperature and stirred overnight. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; DCM) to give pure **6.38** in high yield (0.23–0.25 g, 0.88–0.98 mmol, 88–98%; See Table 6.1) as colourless oil.



6.38

IR (FT): ν_{max} = 2958, 1342, 1141, 1214, 1007, 808 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.34 (t, *J* = 7 Hz, 1 H, H-1), 1.78–1.72 (m, 2 H, H-2), 1.28–1.17 (m, 20 H, H-3, H-4, H-5, H-6 and 4 CH_3), 0.81 (appt. t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 84.3 [s, *C*$(CH_3)_2$], 34.0 (d, C-1), 31.6 (t, C-2), 28.7 (t, C-3), 27.2 (t, C-4), 24.8 (t, C-5), 24.5 [q, C(*C*$H_3)_2$], 22.5 (t, C-6), 14.0 (q, CH_3).

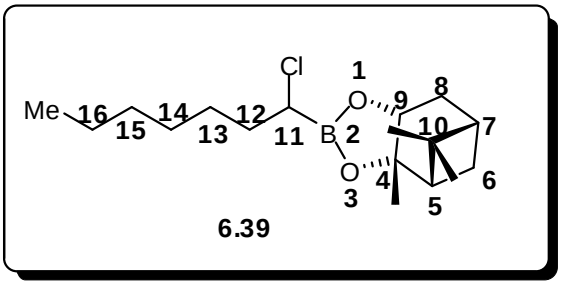
^{11}B NMR (160 MHz, $CDCl_3$): δ = 31.2.

MS (EI): *m/z* (%) = 262 (2, [M, ^{37}Cl]$^+$),260 (6, [M, ^{35}Cl]$^+$), 225 (28), 198 (20), 159 (57), 161 (23), 147 (100), 149 (29), 131 (55), 112 (35), 101 (20), 83 (49), 69 (31).

HRMS (EI): *m/z* $[MH]^+$ calcd. For $C_{13}H_{26}{}^{11}BO_2{}^{35}Cl$: 260.1707; found, 260.1705.

6.6.4.2 Synthesis of *(S)*-pinanediol (α-chloroheptyl)boronate (6.39)

Pinancol (α-chloroheptyl)boronate (**6.38**, 0.23–0.25 g, 0.88–0.98 mmol) was dissolved in a mixture of Et_2O (25 mL) and a saturated solution of NH_4Cl (20 mL). (*1S,2S,3R,5S*)-(+)-pinanediol (0.22–0.25 g, 1.3–1.5 mmol, 1.5 equivalent) in Et_2O was added and the mixture was stirred for 15 minutes. The layers were separated and the organic layer was washed with H_2O (15 mL) and brine (10 mL) then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (silica gel; DCM) to give pure **6.39** in 81–90% yield (0.22–0.27 g, 0.71–0.88 mmol) as mixture of two diastereoisomers (See Table 6.1).



6.39

IR (FT): ν_{max} = 2958, 1319, 1114, 1228, 1004, 804, 721 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.30 (dd, *J* = 2, 9 Hz, 1 H, H-9), 3.39 (m, 1 H, H-11), 2.29, 2.18 (2 m, 2 H, H-8), 2.02 (app. t, *J* = 6 Hz, 1 H, H-5), 1.89–1.72 (m, 4 H, one H of H-6, H-7 and both H of H-12), 1.43 (m, 1 H, one H of H-13), 1.33 (s, 3 H, CH_3-C-O), 1.21–1.25 [m, 10 H, other H of H-13, both H of H-14, H-15, H-16 and one CH_3 of $C(CH_3)_2$], 1.11, 1.10 (2 d, *J* = 11 Hz, 1 H, other H of H-6 in the two diastereoisomers), 0.81 (t, *J* = 7 Hz, 3 H, CH_3), 0.78 [s, 3 H, other CH_3 of $C(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 86.6 (s, C-4), 78.5 (d, C-9), 51.2 (d, C-5), 43.4 (d, C-11), 39.4 (d, C-7), 38.2 [s, C-10], 35.3 (t, C-8), 34.2 (t, C-15), 31.7 (t, C-14), 28.8 (t, C-13), 28.5 [q, one CH_3 of $C(CH_3)_2$], 27.3 (t, C-12), 27.0 [q, other CH_3 of $C(CH_3)_2$], 26.3 (t, C-6), 24.0 (t, C-16), 22.6 (q, CH_3-C-O), 14.0 (q, CH_3).

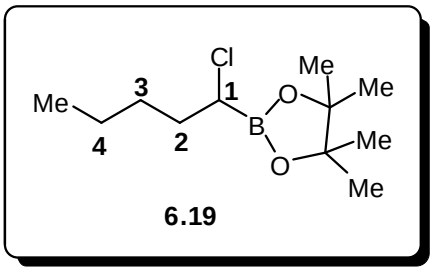
^{11}B NMR (160 MHz, $CDCl_3$): δ = 30.9.

MS (EI): *m/z* (%) = 354 (45, $[M + MeCNH]^+$), 313 (33, $[MH]^+$), 306 (25), 194 (100).

HRMS (EI): *m/z* $[MH]^+$ calcd. For $C_{17}H_{31}{}^{11}BO_2{}^{35}Cl$: 313.2106; found, 313.2101.

6.6.4.3 Synthesis of 2-(1-chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.19)[7]

A solution of *n*-BuLi in hexane (1.6 M, 0.62 mL, 1.0 mmol,) was added dropwise to a solution of pinacol (α,α-dichloromethyl)boronate (**6.17**; 0.21 g, 1.0 mmol) in dry hexane (1.5 mL) at −40 °C. The mixture was allowed to warm up and the stirring was continued overnight. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel; DCM) to give pure pinacol (α-chloropentyl)boronate (**6.19**) in 89% yield (0.2 g, 0.89 mmol) as a colourless oil.



6.19

IR (FT): ν_{max} = 2955, 1339, 1142, 1214, 1005, 801 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.32 (dd, *J* = 7, 9 Hz, 1 H, H-1), 1.77−171 (m, 2 H, H-2), 1.27−1.12 [m, 16 H, H-4, H-3 and 2 $C(CH_3)_2$], 0.83 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 84.2 [s, $C(CH_3)_2$], 33,7 (d, C-1), 29.4 (t, C-2), 24.7 (t, C-3), 24.5 [q, 2 $C(CH_3)_2$], 22.1 (t, C-4), 13.8 (q, CH_3).

^{11}B NMR (160 MHz, $CDCl_3$): δ = 31.3.

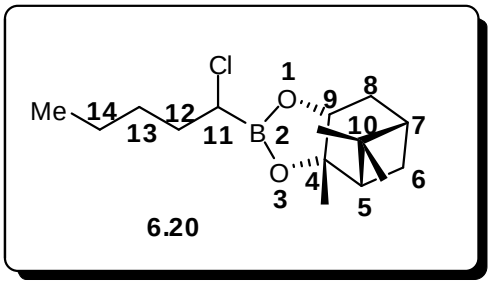
MS (EI): *m/z* (%) = 234 (4, $[M^{37}Cl]^+$), 232 (8, $[M^{35}Cl]^+$), 217 (10), 197 (19), 170 (44), 163 (40), 147 (100), 131 (91), 118 (31), 83 (55).

HRMS (EI): *m/z* $[M]^+$ calcd. For $C_{11}H_{22}BO_2{}^{35}Cl$: 232.1401; found, 232.1406.

6.6.4.4 Synthesis of (*S*)-pinanediol (α-chloropentyl)boronate (6.20)[7]

Pinacol (α-chloropentyl)boronate (**6.20**, 0.2 g, 0.89 mmol) was dissolved in a mixture of Et_2O (25 mL) and a saturated solution of NH_4Cl (20 mL). A solution of (*1S,2S,3R,5S*)-(+)-pinanediol (0.18 g, 1.1 mmol, 1.2 equivalent) in Et_2O (3 mL) was added and the mixture was stirred for 15 minutes. The layers were separated and the organic layer was washed with H_2O (15 mL) and brine (10 mL) then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product which was

purified by column chromatography (silica gel; DCM) to give pure **6.20** in 90% yield (0.23 g, 0.81 mmol).



6.20

IR (FT): ν_{max} = 2955, 1314, 1122, 1209, 1029, 805, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.29 (dd, *J* = 2, 9 Hz, 1 H, H-9), 3.39 (dd, *J* = 6, 9 Hz, 1 H, H-11), 2.29, 2.18 (2 m, 2 H, H-8), 2.02 (appt. t, *J* = 7 Hz, 1H, H-5), 1.88–1.70 (m, 4 H, one H of H-6, H-7 and both H of H-12), 1.35 (s, 3 H, CH_3-C-O), 1.30–1.25 (m, 4 H, H-13 and H-14), 1.22 [s, 3 H, one CH_3 of $C(CH_3)_2$], 1.11, 1.10 (2 d, *J* = 11 Hz, 1 H, other H of H-6 in the two diastereoisomers), 0.84 (t, *J* = 7 Hz, 3 H, CH_3), 0.77 [s, 3 H, other CH_3 of $C(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 86.6 (s, C-4), 78.5 (d, C-9), 51.2 (d, C-5), 43.2 (br., C-11), 39.4 (d, C-7), 38.2 [s, $C(CH_3)_2$], 35.3 (t, C-8), 33.9 (t, C-12), 29.5 (t, C-6), 28.4 (s, CH_3-C-O), 27.0 [q, one CH_3 of $C(CH_3)_2$], 26.3 (t, C-13), 23.9 [q, other CH_3 of $C(CH_3)_2$], 22.2 (t, C-14), 13.9 (q, CH_3).

^{11}B NMR (160 MHz, $CDCl_3$): δ = 30.9.

MS (EI): *m/z* (%) = 286 (2, $[M^{37}Cl]^+$), 284 (8, $[M^{35}Cl]^+$), 214 (69), 199 (90), 145 (100).

HRMS (EI): *m/z* $[M]^+$ calcd. For $C_{15}H_{26}{}^{11}BO_2{}^{35}Cl$: 284.1714; found, 284.1717.

6.6.4.5 Synthesis of (*S*)-pinanediol (α-chloropentyl)boronate (6.20) in one pot for the catalytic reaction (Jadhav's procedure)

A solution of *n*-BuLi in hexane (1.6 M, 0.62 mL, 1.0 mmol,) was added dropwise to a solution of pinacol (α,α-dichloromethyl)boronate (**6.17**; 0.21 g, 1.0 mmol) in dry hexane (1.5 mL) at –40 °C and the mixture was stirred for 5 min. To the mixture was added CH_2Cl_2 (20 mL), followed by either the chiral compound (2.5 equivalent) and where appropriate a separate Lewis acid (2.5 or 0.3 equivalent); in the case of solids, addition involved use of a bent tube or the solid was first dissolved in DCM. The mixture was allowed to warm to room temperature and kept overnight. The mixture was

poured onto a mixture of Et_2O (25 mL) and a saturated solution of NH_4Cl (20 mL). A solution of (*1S,2S,3R,5S*)-(+)-pinanediol (0.20 g, 1.2 mmol) in Et_2O (3 mL) was added and the mixture was stirred for 15 minutes. The layers were separated and the organic layer was washed with H_2O (15 mL) and brine (10 mL) then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography (silica gel; DCM) to give pure **6.20** in 84-89% yield (0.24-0.25 g, 0.84-0.89 mmol).

6.7 References

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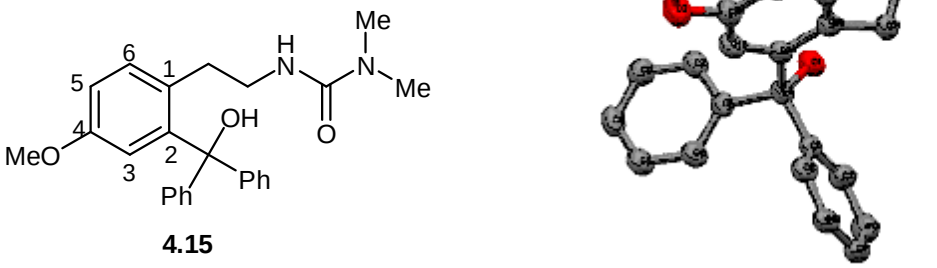
Appendix

X-Ray Data Tables

X-Ray Data Tables

Table A1: Crystal data and structure refinement for 4.15.



4.15

Identification code	ks1207t	
Empirical formula	C27 H31 N O3	
Formula weight	417.53	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 5.8703(6) Å	α= 90°.
	b = 18.294(2) Å	β= 91.561(6)°.
	c = 20.901(2) Å	γ = 90°.
Volume	2243.8(4) $Å^3$	
Z	4	
Density (calculated)	1.236 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	896	
Crystal size	0.50 x 0.03 x 0.01 mm^3	
Theta range for data collection	2.96 to 23.57°.	
Index ranges	-6<=h<=6, -20<=k<=20, -23<=l<=23	
Reflections collected	6152	
Independent reflections	3340 [R(int) = 0.1716]	
Completeness to theta = 23.57°	99.3 %	
Max. and min. transmission	0.9992 and 0.9612	

Appendix: X-Ray Data Tables

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3340 / 0 / 285
Goodness-of-fit on F^2	1.134
Final R indices [I>2sigma(I)]	R1 = 0.1183, wR2 = 0.1515
R indices (all data)	R1 = 0.2414, wR2 = 0.1838
Largest diff. peak and hole	0.251 and -0.277 e.$Å^{-3}$

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ks1207t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-6969(11)	-6512(4)	1612(3)	30(2)
C(2)	-7323(11)	-7326(4)	1765(3)	26(2)
C(3)	-5613(11)	-7679(4)	2114(3)	28(2)
C(4)	-5835(12)	-8399(4)	2320(3)	36(2)
C(5)	-7832(12)	-8774(4)	2170(3)	33(2)
C(6)	-9566(12)	-8432(4)	1826(3)	33(2)
C(7)	-9312(11)	-7711(4)	1632(3)	31(2)
C(8)	-7463(11)	-6076(4)	2225(3)	24(2)
C(9)	-5894(11)	-5607(4)	2505(3)	32(2)
C(10)	-6400(12)	-5232(4)	3058(3)	32(2)
C(11)	-8485(12)	-5323(4)	3339(3)	32(2)
C(12)	-10068(11)	-5789(4)	3062(3)	32(2)
C(13)	-9571(11)	-6159(4)	2511(3)	30(2)
C(14)	-8525(11)	-6205(4)	1049(3)	28(2)
C(15)	-8550(12)	-5373(4)	1046(3)	28(2)
C(16)	-6698(12)	-4966(4)	842(3)	37(2)
C(17)	-6804(12)	-4206(4)	869(3)	35(2)
C(18)	-8703(14)	-3847(4)	1094(3)	41(2)
C(19)	-10546(12)	-4244(4)	1280(3)	34(2)
C(20)	-10458(12)	-5002(4)	1258(3)	32(2)
C(21)	-10325(16)	-2714(4)	1422(4)	69(3)
C(22)	-7844(12)	-6457(4)	378(3)	39(2)
C(23)	-5748(13)	-7622(4)	282(3)	34(2)
C(24)	-5808(11)	-8434(4)	73(3)	30(2)
C(25)	-4471(12)	-8870(4)	592(3)	43(2)
C(26)	-8226(11)	-8741(4)	-11(3)	42(2)
C(27)	-4563(12)	-8471(4)	-562(3)	42(2)
O(1)	-4640(7)	-6384(3)	1473(2)	30(1)
O(2)	-8607(9)	-3090(3)	1093(2)	50(2)
O(3)	-3933(8)	-7333(3)	461(2)	38(1)
N(1)	-7707(10)	-7242(3)	260(2)	36(2)

Table A3. Bond lengths [Å] and angles [°] for ks1207t.

C(1)-O(1)	1.425(7)
C(1)-C(2)	1.537(9)
C(1)-C(8)	1.542(9)
C(1)-C(14)	1.573(8)
C(2)-C(3)	1.385(8)
C(2)-C(7)	1.386(9)
C(3)-C(4)	1.393(9)
C(3)-H(3)	0.9500
C(4)-C(5)	1.387(9)
C(4)-H(4)	0.9500
C(5)-C(6)	1.380(9)
C(5)-H(5)	0.9500
C(6)-C(7)	1.388(9)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(8)-C(9)	1.379(8)
C(8)-C(13)	1.398(8)
C(9)-C(10)	1.382(8)
C(9)-H(9)	0.9500
C(10)-C(11)	1.382(9)
C(10)-H(10)	0.9500
C(11)-C(12)	1.378(9)
C(11)-H(11)	0.9500
C(12)-C(13)	1.374(8)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-C(15)	1.522(9)
C(14)-C(22)	1.539(8)
C(14)-H(14)	1.0000
C(15)-C(20)	1.392(9)
C(15)-C(16)	1.395(9)
C(16)-C(17)	1.393(9)
C(16)-H(16)	0.9500
C(17)-C(18)	1.387(9)
C(17)-H(17)	0.9500
C(18)-C(19)	1.368(9)

C(18)-O(2)	1.386(8)
C(19)-C(20)	1.390(9)
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
C(21)-O(2)	1.415(8)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-N(1)	1.460(8)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-O(3)	1.237(8)
C(23)-N(1)	1.343(8)
C(23)-C(24)	1.549(9)
C(24)-C(26)	1.533(9)
C(24)-C(27)	1.534(8)
C(24)-C(25)	1.543(8)
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
O(1)-H(1)	0.8400
N(1)-H(1N)	0.8800
O(1)-C(1)-C(2)	109.8(6)
O(1)-C(1)-C(8)	106.7(5)
C(2)-C(1)-C(8)	107.4(5)
O(1)-C(1)-C(14)	109.2(5)
C(2)-C(1)-C(14)	114.9(6)
C(8)-C(1)-C(14)	108.5(5)
C(3)-C(2)-C(7)	117.5(7)
C(3)-C(2)-C(1)	117.5(6)
C(7)-C(2)-C(1)	124.7(6)
C(2)-C(3)-C(4)	122.2(7)

C(2)-C(3)-H(3)	118.9
C(4)-C(3)-H(3)	118.9
C(5)-C(4)-C(3)	118.9(7)
C(5)-C(4)-H(4)	120.6
C(3)-C(4)-H(4)	120.6
C(6)-C(5)-C(4)	120.1(7)
C(6)-C(5)-H(5)	120.0
C(4)-C(5)-H(5)	120.0
C(5)-C(6)-C(7)	119.9(7)
C(5)-C(6)-H(6)	120.0
C(7)-C(6)-H(6)	120.0
C(2)-C(7)-C(6)	121.5(7)
C(2)-C(7)-H(7)	119.3
C(6)-C(7)-H(7)	119.3
C(9)-C(8)-C(13)	118.3(6)
C(9)-C(8)-C(1)	122.5(6)
C(13)-C(8)-C(1)	119.2(6)
C(8)-C(9)-C(10)	120.5(7)
C(8)-C(9)-H(9)	119.7
C(10)-C(9)-H(9)	119.7
C(9)-C(10)-C(11)	120.6(7)
C(9)-C(10)-H(10)	119.7
C(11)-C(10)-H(10)	119.7
C(12)-C(11)-C(10)	119.4(6)
C(12)-C(11)-H(11)	120.3
C(10)-C(11)-H(11)	120.3
C(13)-C(12)-C(11)	120.1(6)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
C(12)-C(13)-C(8)	121.1(6)
C(12)-C(13)-H(13)	119.5
C(8)-C(13)-H(13)	119.5
C(15)-C(14)-C(22)	107.3(5)
C(15)-C(14)-C(1)	111.4(5)
C(22)-C(14)-C(1)	114.5(6)
C(15)-C(14)-H(14)	107.8
C(22)-C(14)-H(14)	107.8
C(1)-C(14)-H(14)	107.8

C(20)-C(15)-C(16)	118.5(7)
C(20)-C(15)-C(14)	119.6(7)
C(16)-C(15)-C(14)	121.9(7)
C(17)-C(16)-C(15)	119.0(7)
C(17)-C(16)-H(16)	120.5
C(15)-C(16)-H(16)	120.5
C(18)-C(17)-C(16)	121.6(7)
C(18)-C(17)-H(17)	119.2
C(16)-C(17)-H(17)	119.2
C(19)-C(18)-O(2)	124.3(7)
C(19)-C(18)-C(17)	119.6(7)
O(2)-C(18)-C(17)	116.1(8)
C(18)-C(19)-C(20)	119.3(7)
C(18)-C(19)-H(19)	120.3
C(20)-C(19)-H(19)	120.3
C(19)-C(20)-C(15)	121.9(7)
C(19)-C(20)-H(20)	119.0
C(15)-C(20)-H(20)	119.0
O(2)-C(21)-H(21A)	109.5
O(2)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(2)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
N(1)-C(22)-C(14)	117.7(6)
N(1)-C(22)-H(22A)	107.9
C(14)-C(22)-H(22A)	107.9
N(1)-C(22)-H(22B)	107.9
C(14)-C(22)-H(22B)	107.9
H(22A)-C(22)-H(22B)	107.2
O(3)-C(23)-N(1)	121.3(7)
O(3)-C(23)-C(24)	120.4(7)
N(1)-C(23)-C(24)	118.2(7)
C(26)-C(24)-C(27)	110.2(5)
C(26)-C(24)-C(25)	110.0(6)
C(27)-C(24)-C(25)	109.8(5)
C(26)-C(24)-C(23)	113.5(6)
C(27)-C(24)-C(23)	106.2(6)

C(25)-C(24)-C(23)	106.9(5)
C(24)-C(25)-H(25A)	109.5
C(24)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(24)-C(26)-H(26A)	109.5
C(24)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(24)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
C(24)-C(27)-H(27A)	109.5
C(24)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(24)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(1)-O(1)-H(1)	109.5
C(18)-O(2)-C(21)	117.1(6)
C(23)-N(1)-C(22)	123.6(7)
C(23)-N(1)-H(1N)	118.2
C(22)-N(1)-H(1N)	118.2

Symmetry transformations used to generate equivalent atoms:

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for ks1207t. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

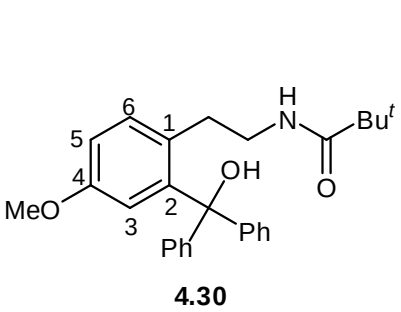
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	27(4)	36(5)	26(4)	-1(4)	0(3)	-1(4)
C(2)	22(4)	29(5)	26(4)	4(4)	2(3)	2(4)
C(3)	31(4)	25(5)	28(4)	0(4)	0(3)	-5(4)
C(4)	30(5)	45(5)	35(4)	3(4)	-1(4)	5(4)
C(5)	38(5)	24(5)	37(4)	-6(4)	7(4)	2(4)
C(6)	39(5)	26(5)	34(4)	-11(4)	-2(4)	2(4)
C(7)	31(5)	27(5)	36(4)	-3(4)	1(4)	2(4)
C(8)	29(4)	13(4)	31(4)	6(3)	9(4)	0(4)
C(9)	26(4)	26(5)	45(5)	6(4)	-1(4)	-4(4)
C(10)	45(5)	22(5)	29(4)	-4(4)	-5(4)	-2(4)
C(11)	49(5)	20(4)	27(4)	0(4)	1(4)	0(4)
C(12)	27(4)	36(5)	35(4)	6(4)	13(4)	3(4)
C(13)	23(4)	37(5)	31(4)	-1(4)	-2(3)	-5(4)
C(14)	23(4)	34(5)	28(4)	1(4)	2(3)	-2(4)
C(15)	26(4)	29(5)	30(4)	-2(4)	-7(3)	4(4)
C(16)	29(5)	38(5)	44(5)	1(4)	4(4)	5(4)
C(17)	34(5)	33(5)	38(4)	9(4)	9(4)	-1(4)
C(18)	52(6)	36(5)	36(5)	0(4)	-5(4)	6(5)
C(19)	28(5)	31(5)	45(5)	1(4)	4(4)	6(4)
C(20)	36(5)	35(5)	24(4)	11(4)	-3(4)	-8(4)
C(21)	129(9)	18(5)	61(6)	-2(4)	24(6)	9(6)
C(22)	40(5)	41(5)	35(4)	2(4)	-3(4)	6(4)
C(23)	36(5)	48(5)	18(4)	4(4)	4(4)	5(5)
C(24)	26(4)	29(5)	36(4)	-12(4)	3(4)	4(4)
C(25)	43(5)	45(5)	42(5)	5(4)	3(4)	8(4)
C(26)	33(5)	48(6)	47(5)	-20(4)	1(4)	0(4)
C(27)	48(5)	39(5)	38(4)	-11(4)	1(4)	9(4)
O(1)	24(3)	35(3)	30(3)	-1(2)	9(2)	0(2)
O(2)	67(4)	27(3)	56(4)	3(3)	13(3)	2(3)
O(3)	34(3)	40(3)	40(3)	-9(3)	-2(3)	-2(3)
N(1)	32(4)	40(4)	35(4)	-11(3)	-2(3)	8(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for ks1207t.

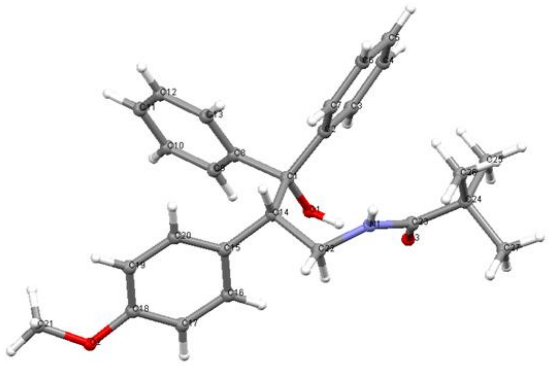
	x	y	z	U(eq)
H(3)	-4245	-7423	2216	34
H(4)	-4639	-8630	2559	44
H(5)	-8007	-9266	2304	39
H(6)	-10931	-8690	1721	40
H(7)	-10529	-7478	1404	38
H(9)	-4453	-5540	2317	38
H(10)	-5305	-4910	3246	39
H(11)	-8823	-5066	3720	38
H(12)	-11505	-5855	3252	39
H(13)	-10679	-6476	2321	36
H(14)	-10116	-6377	1119	34
H(16)	-5384	-5203	687	44
H(17)	-5546	-3927	730	41
H(19)	-11872	-4003	1424	41
H(20)	-11737	-5276	1390	38
H(21A)	-11808	-2807	1211	104
H(21B)	-10005	-2189	1418	104
H(21C)	-10351	-2888	1866	104
H(22A)	-8954	-6247	64	46
H(22B)	-6339	-6241	289	46
H(25A)	-2916	-8678	635	65
H(25B)	-4417	-9386	468	65
H(25C)	-5230	-8823	1001	65
H(26A)	-8997	-8720	399	64
H(26B)	-8148	-9250	-155	64
H(26C)	-9078	-8451	-330	64
H(27A)	-5408	-8187	-887	62
H(27B)	-4459	-8981	-701	62
H(27C)	-3026	-8268	-503	62
H(1)	-4288	-6630	1151	44
H(1N)	-8978	-7480	170	43

X-Ray Data Tables

Table A6: Crystal data and structure refinement for 4.30.



4.30



Identification code	ks1208	
Empirical formula	C27 H34 N2 O4	
Formula weight	450.56	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.382(3) Å	α= 68.507(14)°.
	b = 11.073(3) Å	β= 79.983(13)°.
	c = 12.003(3) Å	γ = 70.643(11)°.
Volume	1209.2(6) Å^3	
Z	2	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	484	
Crystal size	0.20 x 0.18 x 0.04 mm^3	
Theta range for data collection	2.26 to 26.48°.	
Index ranges	-12<=h<=10, -13<=k<=13, -14<=l<=14	
Reflections collected	6595	
Independent reflections	4692 [R(int) = 0.0560]	
Completeness to theta = 26.48°	94.0 %	
Max. and min. transmission	0.9967 and 0.9836	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4692 / 0 / 304	

Goodness-of-fit on F^2	1.170
Final R indices [I>2sigma(I)]	R1 = 0.1175, wR2 = 0.1756
R indices (all data)	R1 = 0.2074, wR2 = 0.2054
Largest diff. peak and hole	0.207 and -0.203 e.$Å^{-3}$

Table A7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ks1208. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6695(4)	2030(4)	2118(4)	36(1)
C(2)	7264(4)	2529(5)	811(4)	35(1)
C(3)	8204(5)	1679(5)	239(4)	40(1)
C(4)	8637(5)	2182(5)	-951(4)	45(1)
C(5)	8165(5)	3525(5)	-1603(4)	46(1)
C(6)	7249(5)	4399(5)	-1047(4)	46(1)
C(7)	6811(5)	3900(5)	139(4)	44(1)
C(8)	7623(5)	637(5)	2791(4)	37(1)
C(9)	7455(5)	-550(5)	2761(4)	43(1)
C(10)	8361(5)	-1803(5)	3273(4)	47(1)
C(11)	9439(5)	-1916(6)	3865(4)	54(1)
C(12)	9598(5)	-764(6)	3935(5)	58(2)
C(13)	8708(5)	505(5)	3399(4)	49(1)
C(14)	5222(4)	1962(4)	2168(4)	34(1)
C(15)	4759(5)	1914(5)	1177(4)	40(1)
C(16)	3476(5)	1755(5)	1195(4)	42(1)
C(17)	2645(5)	1630(5)	2227(4)	43(1)
C(18)	3105(5)	1665(5)	3227(4)	43(1)
C(19)	4369(5)	1833(4)	3236(4)	38(1)
C(20)	1866(5)	1544(6)	135(5)	58(2)
C(21)	4704(5)	1847(5)	4414(4)	41(1)
C(22)	3885(5)	3147(5)	4686(4)	42(1)
C(23)	3665(5)	5559(5)	3973(4)	40(1)
C(24)	5321(5)	6403(5)	2413(4)	54(1)
C(25)	3394(5)	7974(5)	3231(5)	59(2)
C(26)	596(6)	5624(6)	7156(5)	56(2)
C(27)	623(6)	5296(6)	8468(5)	71(2)
N(1)	4318(4)	4312(4)	3908(3)	40(1)
N(2)	4176(4)	6589(4)	3279(4)	45(1)
O(1)	6583(3)	3026(3)	2650(3)	42(1)
O(2)	3154(3)	1739(4)	137(3)	55(1)
O(3)	2622(3)	5729(3)	4667(3)	52(1)
O(4)	1449(4)	6475(4)	6546(3)	55(1)

Table A8. Bond lengths [Å] and angles [°] for ks1208.

C(1)-O(1)	1.430(5)
C(1)-C(8)	1.527(6)
C(1)-C(2)	1.541(6)
C(1)-C(14)	1.545(6)
C(2)-C(7)	1.391(6)
C(2)-C(3)	1.393(6)
C(3)-C(4)	1.382(6)
C(3)-H(3)	0.9500
C(4)-C(5)	1.365(7)
C(4)-H(4)	0.9500
C(5)-C(6)	1.388(6)
C(5)-H(5)	0.9500
C(6)-C(7)	1.380(6)
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(8)-C(13)	1.387(6)
C(8)-C(9)	1.396(6)
C(9)-C(10)	1.378(6)
C(9)-H(9)	0.9500
C(10)-C(11)	1.375(7)
C(10)-H(10)	0.9500
C(11)-C(12)	1.373(7)
C(11)-H(11)	0.9500
C(12)-C(13)	1.388(7)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-C(15)	1.381(6)
C(14)-C(19)	1.415(6)
C(15)-C(16)	1.396(6)
C(15)-H(15)	0.9500
C(16)-C(17)	1.371(6)
C(16)-O(2)	1.376(5)
C(17)-C(18)	1.383(6)
C(17)-H(17)	0.9500
C(18)-C(19)	1.388(6)
C(18)-H(18)	0.9500

C(19)-C(21)	1.520(6)
C(20)-O(2)	1.424(5)
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-C(22)	1.529(6)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-N(1)	1.447(5)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-O(3)	1.252(5)
C(23)-N(1)	1.346(5)
C(23)-N(2)	1.352(6)
C(24)-N(2)	1.449(6)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-N(2)	1.463(6)
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-O(4)	1.426(5)
C(26)-C(27)	1.483(7)
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
N(1)-H(1)	0.8800
O(1)-H(1A)	0.8400
O(4)-H(4A)	0.8400
O(1)-C(1)-C(8)	112.3(4)
O(1)-C(1)-C(2)	107.8(3)
C(8)-C(1)-C(2)	110.1(3)
O(1)-C(1)-C(14)	105.4(3)
C(8)-C(1)-C(14)	110.1(4)
C(2)-C(1)-C(14)	111.1(4)

C(7)-C(2)-C(3)	117.0(4)
C(7)-C(2)-C(1)	119.2(4)
C(3)-C(2)-C(1)	123.7(4)
C(4)-C(3)-C(2)	121.0(5)
C(4)-C(3)-H(3)	119.5
C(2)-C(3)-H(3)	119.5
C(5)-C(4)-C(3)	121.3(5)
C(5)-C(4)-H(4)	119.4
C(3)-C(4)-H(4)	119.4
C(4)-C(5)-C(6)	118.9(5)
C(4)-C(5)-H(5)	120.5
C(6)-C(5)-H(5)	120.5
C(7)-C(6)-C(5)	120.0(5)
C(7)-C(6)-H(6)	120.0
C(5)-C(6)-H(6)	120.0
C(6)-C(7)-C(2)	121.9(4)
C(6)-C(7)-H(7)	119.1
C(2)-C(7)-H(7)	119.1
C(13)-C(8)-C(9)	117.5(5)
C(13)-C(8)-C(1)	121.4(4)
C(9)-C(8)-C(1)	121.0(4)
C(10)-C(9)-C(8)	121.5(5)
C(10)-C(9)-H(9)	119.3
C(8)-C(9)-H(9)	119.3
C(11)-C(10)-C(9)	120.3(5)
C(11)-C(10)-H(10)	119.8
C(9)-C(10)-H(10)	119.8
C(12)-C(11)-C(10)	119.0(5)
C(12)-C(11)-H(11)	120.5
C(10)-C(11)-H(11)	120.5
C(11)-C(12)-C(13)	121.1(5)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(8)-C(13)-C(12)	120.6(5)
C(8)-C(13)-H(13)	119.7
C(12)-C(13)-H(13)	119.7
C(15)-C(14)-C(19)	118.7(4)
C(15)-C(14)-C(1)	119.4(4)

C(19)-C(14)-C(1)	121.6(4)
C(14)-C(15)-C(16)	122.1(4)
C(14)-C(15)-H(15)	118.9
C(16)-C(15)-H(15)	118.9
C(17)-C(16)-O(2)	125.2(4)
C(17)-C(16)-C(15)	119.4(5)
O(2)-C(16)-C(15)	115.4(4)
C(16)-C(17)-C(18)	118.9(5)
C(16)-C(17)-H(17)	120.6
C(18)-C(17)-H(17)	120.6
C(17)-C(18)-C(19)	123.1(4)
C(17)-C(18)-H(18)	118.4
C(19)-C(18)-H(18)	118.4
C(18)-C(19)-C(14)	117.7(4)
C(18)-C(19)-C(21)	116.0(4)
C(14)-C(19)-C(21)	126.3(4)
O(2)-C(20)-H(20A)	109.5
O(2)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(2)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(19)-C(21)-C(22)	113.0(4)
C(19)-C(21)-H(21A)	109.0
C(22)-C(21)-H(21A)	109.0
C(19)-C(21)-H(21B)	109.0
C(22)-C(21)-H(21B)	109.0
H(21A)-C(21)-H(21B)	107.8
N(1)-C(22)-C(21)	112.5(4)
N(1)-C(22)-H(22A)	109.1
C(21)-C(22)-H(22A)	109.1
N(1)-C(22)-H(22B)	109.1
C(21)-C(22)-H(22B)	109.1
H(22A)-C(22)-H(22B)	107.8
O(3)-C(23)-N(1)	119.7(4)
O(3)-C(23)-N(2)	122.3(4)
N(1)-C(23)-N(2)	118.0(4)
N(2)-C(24)-H(24A)	109.5

N(2)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
N(2)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
N(2)-C(25)-H(25A)	109.5
N(2)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
N(2)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
O(4)-C(26)-C(27)	109.0(4)
O(4)-C(26)-H(26A)	109.9
C(27)-C(26)-H(26A)	109.9
O(4)-C(26)-H(26B)	109.9
C(27)-C(26)-H(26B)	109.9
H(26A)-C(26)-H(26B)	108.3
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(26)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(23)-N(1)-C(22)	120.9(4)
C(23)-N(1)-H(1)	119.5
C(22)-N(1)-H(1)	119.5
C(23)-N(2)-C(24)	121.8(4)
C(23)-N(2)-C(25)	118.7(4)
C(24)-N(2)-C(25)	118.3(4)
C(1)-O(1)-H(1A)	109.5
C(16)-O(2)-C(20)	116.7(4)
C(26)-O(4)-H(4A)	109.5

Symmetry transformations used to generate equivalent atoms:

Table A9. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for ks1208. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	39(3)	37(3)	35(3)	-18(2)	-1(2)	-10(2)
C(2)	33(3)	44(3)	32(3)	-13(2)	-3(2)	-14(2)
C(3)	39(3)	42(3)	40(3)	-15(2)	5(2)	-16(2)
C(4)	40(3)	52(3)	44(3)	-20(3)	6(2)	-13(3)
C(5)	46(3)	62(4)	36(3)	-20(3)	6(2)	-25(3)
C(6)	50(3)	41(3)	45(3)	-11(3)	-5(3)	-14(3)
C(7)	42(3)	51(3)	41(3)	-20(3)	0(2)	-12(3)
C(8)	35(3)	38(3)	30(3)	-10(2)	6(2)	-8(2)
C(9)	39(3)	45(3)	41(3)	-12(3)	6(2)	-14(3)
C(10)	44(3)	44(3)	42(3)	-11(3)	10(3)	-8(3)
C(11)	50(4)	53(4)	37(3)	-11(3)	-1(3)	8(3)
C(12)	51(4)	75(4)	50(3)	-31(3)	-11(3)	-4(3)
C(13)	47(3)	47(3)	49(3)	-21(3)	-6(3)	-2(3)
C(14)	34(3)	32(3)	36(3)	-15(2)	-2(2)	-7(2)
C(15)	36(3)	43(3)	40(3)	-15(2)	8(2)	-15(2)
C(16)	45(3)	43(3)	38(3)	-16(2)	3(2)	-15(2)
C(17)	40(3)	44(3)	45(3)	-17(3)	3(2)	-14(2)
C(18)	48(3)	43(3)	38(3)	-14(2)	10(2)	-18(3)
C(19)	40(3)	35(3)	36(3)	-11(2)	-1(2)	-8(2)
C(20)	51(3)	77(4)	58(4)	-31(3)	-4(3)	-26(3)
C(21)	46(3)	40(3)	31(3)	-9(2)	1(2)	-11(2)
C(22)	42(3)	47(3)	34(3)	-14(2)	5(2)	-12(2)
C(23)	34(3)	49(3)	38(3)	-21(3)	-4(2)	-7(2)
C(24)	63(4)	55(3)	47(3)	-20(3)	8(3)	-24(3)
C(25)	60(4)	48(4)	70(4)	-25(3)	-10(3)	-9(3)
C(26)	56(4)	63(4)	58(4)	-27(3)	10(3)	-28(3)
C(27)	67(4)	88(5)	63(4)	-20(4)	5(3)	-39(4)
N(1)	40(2)	40(2)	38(2)	-19(2)	11(2)	-9(2)
N(2)	47(3)	38(2)	48(2)	-18(2)	1(2)	-9(2)
O(1)	34(2)	52(2)	46(2)	-26(2)	1(2)	-12(2)
O(2)	48(2)	80(3)	49(2)	-30(2)	2(2)	-28(2)
O(3)	45(2)	60(2)	52(2)	-30(2)	9(2)	-11(2)
O(4)	65(3)	66(2)	49(2)	-30(2)	9(2)	-31(2)

Table A10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ks1208.

	x	y	z	U(eq)
H(3)	8552	740	673	48
H(4)	9275	1581	-1321	54
H(5)	8458	3857	-2423	55
H(6)	6924	5340	-1483	55
H(7)	6182	4508	507	53
H(9)	6699	-493	2378	51
H(10)	8241	-2592	3217	56
H(11)	10064	-2779	4220	64
H(12)	10329	-838	4358	70
H(13)	8845	1291	3448	59
H(15)	5332	1992	461	47
H(17)	1769	1521	2256	51
H(18)	2527	1569	3941	52
H(20A)	1837	662	724	87
H(20B)	1742	1568	-665	87
H(20C)	1133	2266	345	87
H(21A)	5692	1746	4384	49
H(21B)	4516	1059	5074	49
H(22A)	2904	3325	4592	50
H(22B)	3990	3016	5530	50
H(24A)	6096	5664	2817	82
H(24B)	5585	7243	2050	82
H(24C)	5056	6175	1787	82
H(25A)	2715	8352	2625	88
H(25B)	4016	8536	3018	88
H(25C)	2928	7963	4017	88
H(26A)	927	4778	6953	67
H(26B)	-353	6094	6905	67
H(27A)	1539	4728	8728	107
H(27B)	-46	4805	8889	107
H(27C)	394	6138	8652	107
H(1)	5018	4204	3386	48
H(1A)	7368	3055	2702	63
H(4A)	1812	6306	5916	83